
# SOCIJALNA PSIHIJATRIJA – ČASOPIS HRVATSKOGA PSIHIJATRIJSKOG DRUŠTVA

# SOCIJALNA PSIHIJATRIJA – THE JOURNAL OF THE CROATIAN PSYCHIATRIC SOCIETY

**Izdavač/Publisher**
Medicinska naklada





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SOCIJALNA PSIHIJATRIJA
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The journal was established in 1973. in Zagreb, in the Clinic for Psychiatry, University Hospital Centre Zagreb, School of Medicine, Zagreb and the Editorial board headquarters are situated there as well.

Socijalna psihijatrija indeksirana je u/Socijalna psihijatrija is indexed in: SCOPUS, PsychINFO, Excerpta Medica (EMBASE), Index Copernicus, Google Scholar, EBSCO, HRČAK, CiteFactor (https://www.citefactor.org/impact-factor/impact-factor-of-journal-Socijalna-psihijatrija.php).

Izlazi četiri puta godišnje.

Godišnja pretplata za ustanove iznosi **50 €**; za pojedince **20 €**. Cijena pojedinačnog broja **10 €** (u cijenu su uključeni poštanski troškovi).
IBAN: HR2223600001101226715, Medicinska naklada, Cankarova 13, 10000 Zagreb, Hrvatska (za časopis Socijalna psihijatrija).

The Journal is published four times a year. Orders can be made through our office-address above.
The annual subscription for foreign subscriber is: for institutions **50 €**, for individuals **20 €**, and per issue **10 €** (the prizes include postage).
Payment by check at our foreign currency account:
Zagrebačka banka d.d., 10000 Zagreb, Croatia
**IBAN:** HR2223600001101226715, **SWIFT:** ZABAHR2X (for Socijalna psihijatrija).

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**Socijalna psihijatrija**

UDC 616.89
SPSIDE 53 (3) 201-316 (2025)
ISSN 2459-6140

VOL. 53 – 2025
BROJ/NUMBER 3
ZAGREB, rujan/September 2025.

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# Biopsihosocijalne odrednice post-COVID sindroma

## */ Biopsychosocial Determinants of Post-COVID Syndrome*

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Post-COVID sindrom je kompleksno stanje koje obuhvaća brojne posljedice oporavka od akutne faze infekcije COVID-19. Cilj ovog preglednog rada je biopsihosocijalnim modelom analizirati tjelesne, psihološke, kognitivne i socijalne teškoće koje pacijenti mogu doživjeti nakon otpuštanja iz bolnice, kao i njihov utjecaj na kvalitetu života pacijenata. Posebno su naglašene dugoročne posljedice liječenja u jedinicama intenzivnog liječenja (JIL) izvan konteksta pandemije COVID-19 s fokusom na sindrom postintenzivne njege (engl. *post-intensive care syndrome*, PICS) te povezanost tih posljedica s post-COVID sindromom. Pregledom literature istražena je prevalencija i priroda post-COVID simptoma te njihova sličnost sa simptomima PICS-a. Dugotrajni COVID uključuje simptome poput umora, depresije, anksioznosti i kognitivne teškoće. Psihičke smetnje često utječu na smanjenje kvalitete života, a faktori rizika uključuju dob, spol i komorbiditete. Hospitalizacija povećava rizik za post-COVID simptome, dok cjepiva smanjuju rizik od teških oblika bolesti. Dugoročne posljedice liječenja u JIL-u povezane su s PICS-om. Preživjeli pacijenti često doživljavaju post-COVID simptome i psihološke teškoće. U radu se razmatra važnost interdisciplinarnosti u liječenju ovih sindroma te ističe potreba za daljnjim istraživanjima kako bi se razvile strategije prevencije i intervencije. Nalazi ukazuju na preklapanje post-COVID sindroma i PICS-a te potrebu individualiziranih terapijskih pristupa koji uključuju medicinsku i psihološku podršku.

***/** Post-COVID syndrome is a complex condition encompassing various consequences of recovering from the acute phase of COVID-19 infection. The aim of this review article is to use the biopsychosocial model in order to analyze the physical, psychological, cognitive, and social difficulties that patients may experience after hospital discharge, as well as their impact on the patients' quality of life. Particular emphasis is placed on the long-term consequences of treatment in intensive care units (ICUs) outside the context of the COVID-19 pandemic, focusing on post-intensive care syndrome (PICS), and the association of these consequences with post-COVID syndrome. A literature review was conducted to examine the prevalence and nature of post-COVID symptoms, and their similarity to PICS symptoms. Long COVID includes symptoms such as fatigue, depression, anxiety, and cognitive difficulties. Psychological disturbances often reduce the quality of life, while the risk factors include age, sex, and comorbidities. Hospitalization increases the risk of post-COVID symptoms, while vaccination reduces the likelihood of severe disease outcomes. The long-term consequences of ICU treatment are associated with PICS. Survivors frequently experience post-COVID symptoms and psychological difficulties. This article highlights the importance of an interdisciplinary approach in treating these syndromes, and underscores the need for further research to develop prevention and intervention strategies. In conclusion, the findings indicate an overlap between post-COVID syndrome and PICS, emphasizing the need for individualized therapeutic approaches that would include medical and psychological support.*

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**KLJUČNE RIJEČI / *KEY WORDS:***
Post-COVID / *Post-COVID*
Dugotrajni COVID / *Long COVID*
Mentalno zdravlje / *Mental Health*
Sindrom postintenzivne njege / Post-intensive care syndrome - *PICS*

**TO LINK TO THIS ARTICLE:** https://doi.org/10.24869/spsih.2025.99

## UVOD

Kliničke manifestacije koronavirusa (engl. *Coronavirus Disease 2019*, COVID-19) variraju od asimptomatskih stanja do teških kliničkih slika koje su respiratorne i višeorganske (1-6). Epidemiološki podatci pokazuju da do 20 % pacijenata s COVID-19 napreduje do teškog stanja koje zahtijeva bolničko liječenje (7). Jednoj četvrtini hospitaliziranih potrebno je liječenje u jedinici intenzivnog liječenja (JIL), što u njih češće dovodi do sekundarne upale pluća, kardiovaskularnih teškoća, sepse, oštećenja bubrega, i neuroloških poremećaja (8). Stopa smrtnosti takvih bolesnika varira u rasponu od 20 do 40 % (9).

Na početku pandemije COVID-19 prevladavalo je široko rasprostranjeno mišljenje da je COVID-19 akutna infekcija koja kod većine ljudi završava oporavkom nakon 2 tjedna, a kod jednog manjeg broja, uglavnom starijih ili imunokompromitiranih ljudi, ima fatalan ishod.

Međutim, protokom vremena i sve većim brojem osoba koje su preboljele COVID-19 uvidjelo se da su mnogi tjednima ili mjesecima nakon prebolijevanja osjećali širok spektar fluktuirajućih simptoma. Potencijalni dugoročni učinci mogu uključivati višeorganske komplikacije koji se odnose na simptome središnjeg živčanog sustava, kardiovaskularne, pulmološke, hematološke, bubrežne i gastrointestinalne simptome kao i psihosocijalne posljedice, a često su prijavljivani dugotrajni umor, dispneja,

## INTRODUCTION

The clinical manifestations of coronavirus disease (COVID-19) range from asymptomatic conditions to severe clinical presentations affecting the respiratory system and multiple organs (1-6). Epidemiological data indicate that up to 20% of COVID-19 patients progress to a severe condition requiring hospitalization (7). Among hospitalized patients, one-quarter require treatment in the intensive care unit (ICU), making them more vulnerable to secondary pneumonia, cardiovascular complications, sepsis, kidney damage, and neurological disorders (8). Mortality rates among these patients range from 20% to 40% (9).

At the beginning of the COVID-19 pandemic, the prevailing belief was that COVID-19 was an acute infection that, in most cases, resolved within two weeks, while in a smaller subset of patients, mainly older adults or immunocompromised individuals, it led to fatal outcomes.

However, over time and as more people recovered from COVID-19, it became evident that many experienced a wide range of fluctuating symptoms for weeks or months after recovering from the acute phase. Potential long-term effects can include multi-organ complications affecting the central nervous system, including cardiovascular, pulmonary, hematological, renal, and gastrointestinal symptoms, as well as psychosocial consequences. Frequently reported symptoms include persistent fatigue, dys-

te bol u zglobovima i bol u prsima (10,11). Ove komplikacije manifestiraju se kao široki niz tjelesnih (npr. umor, glavobolja, dispneja, bol u mišićima, srčane abnormalnosti i anosmija) i neuroloških simptoma (npr. poremećaji spavanja, problemi s koncentracijom, kognitivno oštećenje) (1,11,12).

Osim tjelesnih, COVID je sa sobom donio i niz psiholoških posljedica uključujući depresiju, anksioznost, stres i poremećaje prilagodbe, lošiji san, povećanu uporabu psihoaktivnih tvari i povećanu uporabu antidepresiva i opioida (13-15).

Uobičajeno se za opisivanje posljedica i simptoma koji traju nakon akutnog preboljenja bolesti koriste termini dugotrajni COVID ili post-COVID. U listopadu 2021. Svjetska zdravstvena organizacija (SZO) definirala je dugotrajni COVID (engl. *long COVID*) kao stanje koje se javlja kod pojedinaca s potvrđenom ili vjerojatnom infekcijom. Teškim akutnim respiratornim sindromom koronavirus 2 (engl. *severe acute respiratory syndrome coronavirus 2,* SARS-CoV-2), obično tri mjeseca nakon pojave simptoma bolesti, traje najmanje dva mjeseca i ne može se objasniti bilo kojom alternativnom dijagnozom (16). Do sada nije postignut univerzalni konsenzus oko definicije ovog kliničkog stanja, a kao sinonimi koriste se i drugi izrazi, kao što su post-akutni COVID-19, kronični COVID-19, post-COVID-19 sindrom, dugotrajni COVID-19 sindrom i dugotrajni COVID-19. Tako smjernice Nacionalnog instituta za zdravlje i izvrsnost skrbi (NICE) navode da se termin post-COVID-19 sindrom odnosi na znakove i simptome koji se razvijaju tijekom ili nakon infekcije COVID-19, traju dulje od 12 tjedana (tri mjeseca) i nisu objašnjeni alternativnom dijagnozom (17), dakle na ono što Svjetska zdravstvena organizacija naziva dugotrajnim COVID-om. Ponekad se termin dugotrajni COVID koristi za dugotrajnu bolest koja traje od 4 do 12 tjedana nakon akutne bolesti i tijekom oporavka (npr. 18,19). U daljnjem tekstu ovog

pnea, joint pain, and chest pain (10, 11). These complications manifest as a broad spectrum of physical symptoms (e.g., fatigue, headache, dyspnea, muscle pain, cardiac abnormalities, anosmia) and neurological symptoms (e.g., sleep disturbances, concentration problems, cognitive impairment) (1, 11, 12).

Beyond physical symptoms, COVID-19 has also led to a range of psychological consequences, including depression, anxiety, stress, and adjustment disorders, poorer sleep quality, increased use of psychoactive substances, and higher consumption of antidepressants and opioids (13-15).

The terms "long COVID" or "post-COVID" are commonly used to describe the lingering consequences and symptoms following acute COVID-19 infection. In October 2021, the World Health Organization (WHO) defined long COVID as a condition occurring in individuals with confirmed or probable infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically three months after symptom onset, persisting for at least two months, and not attributable to any alternative diagnosis (16). However, a universal consensus on the definition of this clinical condition has yet to be reached, and various terms such as post-acute COVID-19, chronic COVID-19, post-COVID-19 syndrome, long COVID-19 syndrome and long COVID-19 are used interchangeably. The guidelines of the National Institute for Health and Care Excellence (NICE) thus define post-COVID-19 syndrome as the signs and symptoms that develop during or after a COVID-19 infection, persist for more than 12 weeks (three months), and cannot be explained by an alternative diagnosis (17), which aligns with what the WHO refers to as long COVID. The term long COVID is sometimes used to describe an extended illness lasting between 4 and 12 weeks after the acute infection and during recovery (e.g., 18, 19). In this article, the term post-COVID will be used,

rada korist ćemo termin post-COVID, a odnosi se na smetnje koje se javljaju kao posljedica preboljenja COVID-a.

Na početku se smatralo da se post-COVID odnosi na osobe koje su bile hospitalizirane, uključujući i one pacijente koji su bili liječeni na JIL-u, međutim novija istraživanja jasno pokazuju da ga je moguće prepoznati i kod osoba koje nisu bile hospitalizirane ili koje nisu odmah potražile liječničku skrb (20).

Dosadašnja istraživanja daju različite podatke o učestalosti i kliničkoj slici post-COVID-a.

Najčešće prijavljeni simptomi, koji se pojavljuju i kod osoba koje nisu bolovale od teških oblika COVID-19 (21,22) su umor (npr. 23-25), slabost mišića (npr. 26,27), dispnej (npr.. 28,29), teškoće spavanja (npr. 26,30), anksioznost ili depresija (npr. 21,27), smanjen kapacitet pluća (npr 24,31), teškoće pamćenja/kognitivne teškoće ("magla u mozgu") (npr. 25,27), hiposmija/anosmija (npr. 30), te nemogućnost potpune tjelesne aktivnosti ili rada. Najčešći simptom post-COVID-a je umor, neovisan o težini akutne bolesti ili prisutnosti respiratornih problema (npr. 31,32).

Jedna od ranijih meta-analiza utvrdila je da je jedan od četiri pacijenta imao neuropsihijatrijske simptome koji uključuju poremećaje spavanja, umor, anksioznost i posttraumatski stres (PTSP) nakon početka COVID-19 s približnim trajanjem praćenja od 77 dana (33). Druga meta-analiza 39 studija, uključujući preko 10 000 oboljelih, otkrila je da je 19 % ljudi s post-COVID-om prijavilo anksioznost i 8 % depresiju kao jedan od simptoma (34). Međutim, rezultati pojedinačnih istraživanja u nekim zemljama izvještavaju o puno većoj prevalenciji (npr. 42 % za tjeskobu i 41 % za loše raspoloženje u Velikoj Britaniji) (35).

Post-COVID je povezan s češćim pojavljivanjem depresije, anksioznosti, PTSP-a i smanjenog zadovoljstva životom (36), što bi se moglo djelomično pripisati dugotrajnim tjelesnim simptomima

referring to the complications arising as a consequence of recovering from COVID-19.

Post-COVID was initially thought to affect only the patients who had been hospitalized, including ICU patients. However, recent studies clearly indicate that it can also be identified in individuals who were never hospitalized or who did not seek immediate medical care (20).

The existing studies report varying prevalence rates and clinical presentations of post-COVID. The most frequently reported symptoms, found even among individuals who did not experience severe COVID-19 (21, 22), include fatigue (e.g., 23-25), muscle weakness (e.g., 26, 27), dyspnea (e.g., 28, 29), sleep disturbances (e.g., 26, 30), anxiety or depression (e.g., 21, 27), reduced lung capacity (e.g., 24, 31), memory difficulties/cognitive impairments ("brain fog") (e.g., 25, 27), hyposmia/anosmia (e.g., 30), and an inability to fully engage in physical activity or work. The most common post-COVID symptom is fatigue, regardless of the severity of the acute infection or the presence of respiratory issues (e.g., 31, 32).

One of the early meta-analyses found that one in four patients experienced neuropsychiatric symptoms such as sleep disorders, fatigue, anxiety, and post-traumatic stress disorder (PTSD) following the onset of COVID-19, with an average follow-up duration of 77 days (33). Another meta-analysis of 39 studies involving over 10 000 patients found that 19% of individuals with post-COVID reported feeling anxiety, while 8% reported depression as one of the symptoms (34). However, findings from individual studies in some countries suggested much higher prevalence rates (e.g., 42% for anxiety and 41% for low mood in Great Britain) (35).

Post-COVID has been linked to increased rates of depression, anxiety, PTSD, and reduced life satisfaction (36), which may be partially attributed to persistent physical symptoms of post-COVID (37). A study by Zhao et al. (38)

post-COVID-a (37). Istraživanje Zhaoa i suradnika (38) otkrilo je da je približno 9,6 % hospitaliziranih pacijenata koji pate od umjerene onesposobljenosti prijavljivalo probleme psihičkog zdravlja i kognitivne simptome 20 mjeseci nakon izlaska iz bolnice. Nekoliko čimbenika predviđa dugoročne tjelesne i kognitivne simptome, a uključuju dob, boravak u bolnici, spol i komorbiditete. Osobe ženskog spola, starije dobi, s više komorbiditeta i dužim boravkom u bolnici imat će viši rizik za razvoj post-COVID sindroma (4).

Iako se psihološki simptomi općenito poboljšavaju tijekom vremena, neki se mogu zadržati znatno dulje (i dulje od jedne godine) bez puno poboljšanja ili čak može doći do pogoršanja tijekom vremena (21,39). Do danas su zabilježeni dugotrajni simptomi i do dvije godine nakon infekcije (2,4).

Važno je osvrnuti se na ulogu cjepiva protiv COVID-19 u razvoju post-COVID-a. Iako cjepiva sprječavaju smrt i tešku bolest, još nije jasno mogu li spriječiti i pojavu post-COVID-a (40). Manja istraživanja pokazuju da su cjepiva AstraZeneca i Pfizer-BioNTech povezana s općenitim poboljšanjima simptoma post-COVID-a (41). Antonelli i suradnici (42) navode da su izgledi za zadržavanje simptoma 28 dana ili više nakon razvijene infekcije, iako je osoba primila cjepivo, bili otprilike dva puta manji uzimanjem dviju doza cjepiva.

Cilj ovog preglednog rada bio je analizirati tjelesne, psihološke, kognitivne i socijalne teškoće koje pacijenti koji su oboljeli od teškog COVID-19 mogu doživjeti nakon otpuštanja iz bolnice, kao i njihov utjecaj na kvalitetu života pacijenata i njihovih obitelji.

## METODOLOGIJA PRETRAŽIVANJA RADOVA

Pretraživanje literature provedeno je u bazama podataka *PubMed, Scopus* i *PsycINFO* korištenjem ključnih pojmova *post-COVID syndrome*,

found that approximately 9.6% of hospitalized patients experiencing moderate disability reported mental health problems and cognitive symptoms 20 months after being discharged from the hospital. Several factors predict long-term physical and cognitive symptoms, and they include age, hospitalization, sex, and comorbidities. Women, older adults, individuals with multiple comorbidities, and those with prolonged hospital stays are at a higher risk of developing post-COVID syndrome (4).

Although psychological symptoms generally improve over time, some may persist significantly longer (over a year) with little improvement, or may even worsen over time (21, 39). Long-term symptoms have so far been observed to last up to two years after infection (2, 4).

It is also important to consider the role of COVID-19 vaccines in the development of post-COVID. While vaccines prevent death and severe illness, it remains unclear whether they can also prevent post-COVID (40). Smaller studies suggested that the AstraZeneca and Pfizer-BioNTech vaccines are associated with overall improvements in post-COVID symptoms (41). Antonelli et al. (42) reported that the likelihood of experiencing symptoms persisting for 28 days or longer after infection, despite vaccination, was approximately halved in individuals who received two vaccine doses.

The aim of this review article was to analyze the physical, psychological, cognitive, and social difficulties that patients with severe COVID-19 may experience after hospital discharge, as well as their impact on the quality of life of the patients and their families.

## METHODOLOGY OF LITERATURE SEARCH

The literature search was conducted using the PubMed, Scopus, and PsycINFO databases, employing key terms such as *post-COVID syndrome*,

*long COVID*, *post-intensive care syndrome (PICS)*, *COVID-19 recovery*, *mental health* i *quality of life*. Obuhvaćeni su radovi objavljeni u razdoblju od 2020. do 2024. kako bi se osigurao pregled recentnih saznanja o posljedicama COVID-19 infekcije. Dvije autorice su neovisno pregledavale sažetke i naslove identificiranih radova te su na temelju relevantnosti za biopsihosocijalni model post-COVID sindroma odabrale one koji su uključeni u daljnju analizu. Posebno su naglašeni radovi koji ispituju fizičke, psihološke, kognitivne i socijalne aspekte post-COVID sindroma te njihovu povezanost sa sindromom postintenzivne njege (PICS).

Čimbenici koji pridonose pojavi psihičkih smetnji bit će prikazani iz biopsihosocijalne perspektive s fokusom na psihološke čimbenike ranjivosti. Kao jedan od čimbenika koji se posebno izdvaja jest hospitalizacija u JIL-u kao potencijalni traumatski događaj, te će biti prikazani rezultati istraživanja o psihičkim posljedicama intenzivnog liječenja pri čemu će se rezultati staviti u kontekst spoznaja o reakcijama na liječenje drugih zaraznih bolesti.

## ETIOLOŠKI ČIMBENICI PSIHIČKIH SMETNJI U POST-COVID SINDROMU

Suočavanje s COVID-om, kao i s bilo kojim drugim zdravstvenim stanjem, uključuje sve dimenzije postojanja osobe – onu biološku, potom socijalnu, te vrlo važnu psihološku dimenziju koja je u slučaju liječenja bolesti bila dodatno obilježena traumatskim situacijama hospitalizacije i boravka u JIL-u. Psihološke posljedice mogle bi se odnositi i na one osobe zaražene virusom koje su zabrinute zbog stigme (43), ishoda bolesti (44), traumatskih sjećanja na teške bolesti ili amnezije (45), psiholoških reakcija nakon zaraze COVID-19 i povezanih medicinskih intervencija (46). Međutim, na sve osobe, bez obzira jesu li zaražene virusom ili nisu, mogu utjecati iskustva povezana

*long COVID*, *post-intensive care syndrome (PICS)*, *COVID-19 recovery*, *mental health*, and *quality of life*. The review included studies published between 2020 and 2024 so as to ensure an overview of recent findings on the consequences of COVID-19 infection. Two authors independently screened the abstracts and titles of the identified studies, and selected those relevant to the biopsychosocial model of post-COVID syndrome for further analysis. Special emphasis was placed on studies examining the physical, psychological, cognitive, and social aspects of post-COVID syndrome, and their association with post-intensive care syndrome (PICS).

The factors contributing to the development of psychological difficulties will be presented from a biopsychosocial perspective, with a focus on psychological vulnerability factors. One factor that particularly stands out is hospitalization in an intensive care unit (ICU) as a potentially traumatic event. Research findings on the psychological consequences of intensive care treatment will be presented, whereby the results will be viewed in the context of the existing knowledge about responses to treatment for other infectious diseases.

## ETIOLOGICAL FACTORS OF PSYCHOLOGICAL DISTURBANCES IN POST-COVID SYNDROME

Coping with COVID-19, as with any other health condition, involves all dimensions of a person's existence – the biological, the social, and the very important psychological dimension. In the case of COVID-19 treatment, the psychological aspect was further marked by traumatic experiences of hospitalization and ICU stays. Psychological consequences may also affect individuals infected with the virus who are concerned about the stigma (43), disease outcomes (44), traumatic memories of severe illness or amnesia (45), psychological reactions after contracting COVID-19, and related medical interventions

s pandemijom uključujući socijalnu izolaciju (47), tjeskobu (48), te financijske teškoće i nezaposlenost (49). Psihički poremećaji povezani s COVID-19 vjerojatno su višefaktorski zbog kombinacije okolinskih, psihosocijalnih i bioloških čimbenika koji su rezultat ove globalne pandemije.

## Biološki čimbenici

Pretpostavlja se da je patogeneza neuropsihijatrijskih manifestacija COVID-19 uglavnom rezultat neizravnog imunološkog upalnog oštećenja središnjeg živčanog sustava (SŽS) i, hipotetski, potencijalna posljedica izravne virusne neuroinvazije (50,51). Koronavirusi, uključujući SARS-CoV-2, imaju sposobnost inficiranja SŽS-a hematogeno ili neuronski retrogradnim neuroinvazivnim putevima. Ovaj mehanizam ulaska i naknadna infekcija SŽS-a mogu objasniti visoku učestalost neuroupale koja se vidi kod pacijenata s COVID-19 (52). Ova neuroupala može rezultirati štetnim dugoročnim posljedicama, koje su povezane s neurodegenerativnim i psihijatrijskim poremećajima. Kod nekih oboljelih s post-COVID-om virus je prisutan u različitim tjelesnim organima i mjesecima nakon akutne infekcije (53,54). Također, SARS-CoV-2 može utjecati na propusnost krvno-moždane barijere što omogućuje perifernim citokinima i drugim tvarima iz krvi da prodru u SŽS i potaknu neuroupalu. Tromboembolični putevi mogu biti uzrok povećane prevalencije moždanog udara kod COVID-19, dok se "moždana magla" može razviti iz PTSP-a (51).

Dostupni dokazi ukazuju da izravni virusni encefalitis, sustavna upala, disfunkcija perifernih organa, mitohondrijska disfunkcija izazvana hipoksijom i cerebrovaskularne promjene mogu doprinijeti razvoju dugotrajnih posljedica nakon COVID-19 (55-57). Što se tiče moguće etiologije neuropsiholoških simptoma post-COVID-a, jedno objašnjenje vezano je uz

(46). However, pandemic-related experiences, including social isolation (47), anxiety (48), financial difficulties and unemployment (49), can impact all individuals regardless of whether they have contracted the virus. Psychological disorders associated with COVID-19 are likely multifactorial due to the combination of environmental, psychosocial, and biological factors resulting from this global pandemic.

## Biological factors

It is hypothesized that the pathogenesis of neuropsychiatric manifestations of COVID-19 is primarily the result of indirect immune-inflammatory damage to the central nervous system (CNS) and, hypothetically, a potential consequence of direct viral neuroinvasion (50, 51). Coronaviruses, including SARS-CoV-2, have the ability to infect the CNS via hematogenous or neuronal pathways, through retrograde neuroinvasive routes. This mechanism of entry and subsequent CNS infection may explain the high prevalence of neuroinflammation observed in COVID-19 patients (52). Such neuroinflammation can lead to harmful long-term consequences associated with neurodegenerative and psychiatric disorders. In some individuals with post-COVID syndrome, the virus remains present in various body organs for months after the acute infection (53, 54). Additionally, SARS-CoV-2 can impact the permeability of the blood-brain barrier, allowing peripheral cytokines and other blood-borne substances to enter the CNS and trigger neuroinflammation. Thromboembolic pathways may contribute to the increased prevalence of stroke in COVID-19, while "brain fog" may develop as a result of PTSD (51).

Available evidence suggests that direct viral encephalitis, systemic inflammation, peripheral organ dysfunction, hypoxia-induced mitochondrial dysfunction, and cerebrovascular changes may contribute to the development of long-term consequences after COVID-19 (55-57).

upalne procese u mozgu - cirkulirajući citokini prodiru kroz krvno-moždanu barijeru što za posljedicu može imati sniženo raspoloženje i teškoće koncentracije i pamćenja. Istraživanja ukazuju na poremećaj GABA-receptora, što se može povezati sa simptomima tjelesnog i kognitivnog umora (58).

Još je jedan važan aspekt koji treba istaknuti - mogućnost da tjelesni simptomi kao što su zaduhe i mialgija utječu na psihičko stanje oboljelih od dugotrajnih posljedica COVID-19. Ova interakcija može biti dvosmjerna: tjelesne smetnje mogu rezultirati psihičkim simptomima, dok se psihički simptomi depresije, anksioznosti i PTSP-a mogu manifestirati kao tjelesni simptomi (59).

Fernández-de-las-Peñas i suradnici (4) navode da je najznačajniji faktor rizika za razvoj post-COVID-a broj simptoma pri prijmu u bolnicu. To podupire ideju da veći teret simptoma tijekom akutne faze bolesti povećava vjerojatnost pojave post-COVID stanja (5).

Istraživanja pokazuju da žene imaju značajno veću vjerojatnost da će imati simptome post-COVID-a od muškaraca (4,6), ali samo do dobi od 60 godina nakon koje omjer postaje podjednak (60). Umor, dispneja, problemi s psihičkim zdravljem, poremećaji spavanja češće su prijavljivani kod žena (4,6), što je posljedično povezano i s nižom kvalitetom života povezanom sa zdravljem. Ostali čimbenici rizika uključuju postojeću astmu (ali nisu na nju ograničeni), prisutne komorbiditete i stariju dob (5,61).

## Socijalni čimbenici

Razmjeri patnje od kroničnih bolesti nisu jednostavno određeni težinom same bolesti, već su moderirani vanjskim i individualnim čimbenicima (62). Kako Teorija tereta liječenja postulira, nošenje s kroničnim stanjima uključuje svakodnevnu skrb s ciljem kontrole bolesti. Kako se tereti liječenja gomilaju, neki

Regarding the possible etiology of neuropsychological symptoms in post-COVID syndrome, one explanation relates to inflammatory processes in the brain – circulating cytokines penetrate the blood-brain barrier, potentially leading to low mood, concentration difficulties, and memory impairments. Research also indicates that GABA receptor dysfunction may be linked to symptoms of physical and cognitive fatigue (58).

Another important aspect to highlight is the possibility that physical symptoms, such as shortness of breath and myalgia, affect the psychological state of individuals suffering from long-term COVID-19 consequences. This interaction can be bidirectional: physical ailments may lead to psychological symptoms, while psychological symptoms such as depression, anxiety, and PTSD may manifest as physical complaints (59).

Fernández-de-las-Peñas et al. (4) observed that the most significant risk factor for developing post-COVID syndrome is the number of symptoms experienced at the time of hospital admission. This supports the idea that a higher symptom burden during the acute phase of illness increases the likelihood of developing post-COVID conditions (5).

Studies have shown that women are significantly more likely than men to experience post-COVID symptoms (4, 6), but this difference disappears after the age of 60, when the ratio becomes fairly equal (60). Symptoms such as fatigue, dyspnea, mental health issues, and sleep disturbances are more commonly reported among women (4, 6), which is consequently associated with lower health-related quality of life. Other risk factors include (but are not limited to) pre-existing asthma, as well as existing comorbidities and older age (5, 61).

## Social factors

The extent of suffering from chronic illnesses is not solely determined by the severity of the disease itself, but is also moderated by exter-

pacijenti postaju preopterećeni što dovodi do lošijih ishoda, stresa za njihove njegovatelje, i povećanja troškova zdravstvene zaštite (63). Percipirani teret post-COVID-a ukazuje na jasnu povezanost bolesti s psihičkim zdravljem pacijenata. Velik je broj čimbenika kojima se pripisuju međuodnos između stvarne težine tjelesne bolesti, zahtjeva liječenja i percepcije sposobnosti pojedinca da se prilagodi post-COVID-u (64). Prema Teoriji o teretu liječenja (63) percipirano opterećenje bolešću bolesnika s post-COVID-om može biti pojačano teškoćama u upravljanju simptomima. Medicinski troškovi (65) i financijske teškoće (66) kao posljedice pandemije COVID-19 mogu rezultirati pokušajima pacijenata da se što brže vrate na posao ignorirajući simptome post-COVID-a, čime posljedično usporavaju oporavak i dodaju teret liječenju.

Veliki je broj istraživanja usmjeren na povezanost javnozdravstvenih mjera tijekom pandemije COVID-om (kao što su karantena, socijalna izolacija i druga ograničenja osobnih sloboda) s psihičkim zdravljem utvrdila su povezanost sa simptomima depresije, tjeskobe, usamljenosti, psihosocijalnog stresa i trajne uznemirenosti (67,68). To je moguće alternativno objašnjenje za veću prevalenciju psihijatrijskih simptoma među pacijentima s post-COVID-om. Upravo veća prevalencija može biti više posljedica nametnute karantene i drugih ograničenja u smislu tjeskobe, straha, ljutnje i drugih neugodnih emocija, bez obzira na specifične aspekte infekcije COVID-19 kao što je neuroupala ili sistemska upala. Istraživanja su jasno pokazala da su oboljeli od COVID-a bili stigmatizirani i da je stigma negativno utjecala na njihovu kvalitetu života te razvijanje psihičkih smetnji (69,70). Novija istraživanja pokazuju da se slično ponavlja i s post-COVID sindromom. Oboljeli koji doživljavaju vanjsku stigmatizaciju, zabrinutost zbog razotkrivanja i internaliziranu stigmu imaju više depresivnih i anksioznih smetnji, što dodatno intenzivira

nal and individual factors (62). According to the Burden of Treatment Theory, coping with chronic conditions involves daily care aimed at disease management. As treatment burdens accumulate, some patients become overwhelmed, leading to poorer outcomes, stress for their caregivers, and increased healthcare costs (63). The perceived burden of post-COVID indicates a clear connection between the illness and the patients' mental health. Numerous factors contribute to the interplay between the actual severity of physical illness, treatment demands, and the individuals' perceived ability to adapt to post-COVID (64). Based on the Burden of Treatment Theory (63), the perceived burden of illness in post-COVID patients may be exacerbated by difficulties in managing symptoms. Medical costs (65) and financial hardships (66) resulting from the COVID-19 pandemic may lead patients to rush back to work while ignoring post-COVID symptoms, thus slowing their recovery and adding to the burden of treatment.

A large body of research has focused on the relationship between public health measures during the COVID-19 pandemic (such as quarantine, social isolation, and other restrictions on personal freedoms) and mental health. These studies have identified associations with the symptoms of depression, anxiety, loneliness, psychosocial stress, and persistent distress (67, 68). This presents an alternative explanation for the higher prevalence of psychiatric symptoms among post-COVID patients. Increased prevalence itself may be more attributable to imposed quarantine and other restrictions leading to anxiety, fear, anger, and other distressing emotions, rather than to specific aspects of COVID-19 infection, such as neuro- or systemic inflammation. Studies have clearly shown that COVID-19 patients were stigmatized, which negatively affected their quality of life and contributed to the development of mental health difficulties (69, 70). Recent studies indicate that a similar pattern is

smetnje koje sam post-COVID donosi sa sobom (71).

Za odnos post-COVID-a i psihičkog zdravlja odgovorne mogu biti i promjene koje su se dogodile zbog pandemije kao što su financijska nestabilnost, socijalna distanca i nošenje maski (72-74).

## Psihološki čimbenici

Individualni čimbenici imaju važnu ulogu u određivanju nošenja s bolešću. Prema Leventhalovom modelu samoregulacije reprezentacije bolesti pacijenta (uvjerenja o uzroku, vremenskoj liniji, posljedicama, itd.), odražavaju njihov percipirani teret i time utječu na samoregulacijska ponašanja, psihološku prilagodbu i psihičko zdravlje (75). Stoga teret bolesti koji percipiraju oboljeli od post-COVID-a, kao i od bilo koje druge kronične bolesti, može imati izravan utjecaj na njihovo psihičko zdravlje. Vjerojatno bi se izražena tjeskoba i depresija mogle pojaviti ubrzo nakon infekcije SARS-CoV-2. Međutim, prisutna je i povećana socijalna izolacija zbog dugotrajnog COVID-a i tjeskoba povezana s trajnim simptomima što može značiti da se psihološki simptomi zapravo pojavljuju tijekom i povećavaju nakon akutnog stanja infekcije među pacijentima s post-COVID-om (76,77).

Kvalitativna istraživanja pokazuju da je proživljeno iskustvo post-COVID-a vrlo različito i percipira se kao da je u suprotnosti s javnom percepcijom i službenim smjernicama za COVID-19 (78). Oboljeli opisuju niz pozitivnih i negativnih zdravstvenih iskustava.

Simptomi koje doživljavaju pacijenti s post-COVID-om variraju u težini od relativno blagih simptoma do simptoma potencijalno opasnih za život koji su zahtijevali bolničko liječenje (32). Također, takvi se simptomi izmjenjuju tijekom vremena s novim simptomima i to u različitim dijelovima tijela. Svaki je pojedinačni simptom trajao različito vrijeme,

emerging with post-COVID syndrome. Patients who experience external stigmatization, concern about disclosure, and internalized stigma, report more depressive and anxiety symptoms, further intensifying the distress already associated with post-COVID (71).

Changes brought about by the pandemic, such as financial instability, social distancing, and mask-wearing, may also play a role in the relationship between post-COVID and mental health (72-74).

## Psychological factors

Individual factors play an important role in determining how individuals cope with illness. According to Leventhal's Self-Regulation Model, patients' illness representations (beliefs about the cause, timeline, consequences, etc.) reflect their perceived burden and consequently influence their self-regulatory behaviors, psychological adjustment, and mental health (75). The burden of illness perceived by individuals with post-COVID, as with any other chronic illness, can therefore have a direct impact on their mental well-being. It is likely that pronounced anxiety and depression may emerge soon after SARS-CoV-2 infection. However, increased social isolation due to long COVID and anxiety related to persistent symptoms may indicate that psychological symptoms actually appear during and intensify after the acute phase of infection among post-COVID patients (76, 77).

Qualitative studies suggest that the experience of post-COVID varies significantly and is often perceived as being at odds with the public perception and official COVID-19 guidelines (78). Patients describe a range of both positive and negative health experiences.

The symptoms experienced by post-COVID patients range in severity, from relatively mild to potentially life-threatening symptoms requiring hospitalization (32). Additionally, such symptoms fluctuate over time, with new symptoms

ali u mnogim je slučajevima postojao kumulativni učinak. Oboljeli su opisivali kako su doživljavali sebe prije i poslije bolesti, i to unutar konteksta obitelji i posla. Navode da se često uspoređuju s osobom koja su bili prije bolesti, što neki autori objašnjavaju konceptom „uništenog identiteta", jer se identitet kakav je prije bio (zdrav, neovisan i uspješan) zbog post-COVID-a doživljava ugroženim (79).

Oboljeli su vjerovali da oporavak zahtijeva kratko razdoblje i da će se na posao vratiti u razdoblju od dva tjedna, a to su uvjerenje imali i njihovi poslodavci i okolina (79,80). Taj nesklad između očekivanja i iskustva imao je izravan učinak na psihičko i emocionalno stanje osoba s post-COVID-om i osjećaj neizvjesnosti o tome što učiniti u vezi sa svojim simptomima. Opisivali su potrebu da prilagode svoj životni stil uključujući vođenje vlastitog tempa i postavljanje realnih ciljeva kako bi sami upravljali svojim simptomima.

Osim opisanog, oboljeli su imali osjećaj stigme povezan s post-COVID-om, doživljavaju osjećaj srama i samookrivljavanje zbog simptoma i onesposobljenosti njima i izražavaju strah da bi ih poslodavci i drugi u okolini mogli stigmatizirati zbog post-COVID-a.

Ako se psihološki simptomi pojavljuju već tijekom infekcije, postavlja se pitanje utječe li njihova razina izraženosti u toj fazi na pojavu post-COVID-a, odnosno razlikuje li se među osobama koje će imati kratki oporavak od bolesti od onih s post-COVID-om.

Među istraživanjima koja se bave dugoročnim posljedicama COVID-19 tek ih je manji broj koja se bave posljedicama kod osoba koje su tijekom i zbog bolesti bile hospitalizirane s teškim ili kritičnim kliničkim slikama i liječene u jedinicama JIL-a. Unatoč sve većem znanju o COVID-19 i njegovim posljedicama još uvijek se relativno malo zna o dugotrajnim posljedicama kod osoba koje su preživjele li-

emerging in different parts of the body. Each individual symptom persists for varying durations, but in many cases, there is a cumulative effect. Patients described how they perceived themselves before and after the illness within the context of their families and work. They often compared themselves to the person they were before falling ill, which some authors explain through the concept of a "shattered identity", where their previous identity (healthy, independent, and successful) is perceived as being threatened due to post-COVID (79).

Patients believed that recovery would take only a short time and that they would return to work within two weeks, an expectation shared by their employers and social environment (79, 80). The mismatch between expectations and actual experience had a direct impact on the psychological and emotional state of individuals with post-COVID, contributing to the feeling of uncertainty about how to manage their symptoms. Many reported a need to adjust their lifestyle, including pacing themselves and setting realistic goals in order to self-manage their symptoms.

In addition to the aforementioned, individuals with post-COVID experienced stigma, feelings of shame, and self-blame related to their symptoms and disability. They also expressed fear that employers and others in their environment might stigmatize them due to their post-COVID condition.

If psychological symptoms appear during the infection itself, the question arises as to whether their severity at this stage influences the development of post-COVID, i.e. whether it is different among those who recover quickly and those who experience post-COVID.

Among studies investigating the long-term consequences of COVID-19, only few focus on the consequences among the individuals who were hospitalized with severe or critical clinical conditions and treated in intensive care units (ICUs) during the infection or due to the infection.

ječenje na JIL-u i kakve su one u odnosu na istraživanja koja se odnose na ne-COVID-19 hospitalizacije.

Iako je činjenica da osobe koje su liječene u jedinicama intenzivne skrbi često imaju simptome koji traju i nakon otpuštanja iz bolnice i koji se povezuju sa samim iskustvom hospitalizacije (81,82), pandemija COVID-19 i pojava post-COVID sindroma ponovno je u fokus vratila sindrom postintenzivne njege (engl. *post-intenzive care syndrome,* PICS).

Liječenje u JIL-u nosi sa sobom sve elemente traumatskog iskustva, no hoće li se nakon njega razviti PTSP ovisi o interakciji osobina ličnosti, vrsti traumatskih iskustava i podrške koju je osoba primala tijekom i nakon liječenja.

## DUGOROČNE POSLJEDICE LIJEČENJA U JIL-u (NEVEZANO UZ PANDEMIJU COVID-19)

Liječenje i preživljavanje pacijenata (što se podrazumijeva kao otpuštanje živih iz jedinice intenzivne njege) koji su se liječili u intenzivnim jedinicama tradicionalno se smatra mjerom uspjeha liječenja (83). Sve veća prevalencija teških i kritičnih bolesti u kombinaciji s napretkom u medicini intenzivne skrbi rezultirala je sve većim brojem pacijenata (~80-90 %) koji su preživjeli do otpusta iz bolnice (84-86). Međutim, odmicanjem od samo tradicionalnih pogleda sve je veći interes za dugoročne zdravstvene ishode osoba koje su preživjele intenzivnu njegu, što je rezultiralo pomicanjem cilja intenzivne skrbi s preživljavanja na povratak u svakodnevni život nakon kritične bolesti (87).

Prijam na intenzivno liječenje ima potencijalno dugotrajne posljedice za osobe koje su ga preživjele i njihove članove obitelji. Osobe koje su preživjele liječenje u JIL-u mogu razviti tjelesne, psihološke i/ili kognitivne teškoće koje se nazivaju i sindromom postintenzivne njege (PICS) (88-91). Tjelesni simptomi su umor i

Despite increasing knowledge about COVID-19 and its consequences, relatively little is still known about the long-term effects in survivors of ICU treatment and how these compare to the research on non-COVID-19 hospitalizations.

Although it is well established that individuals treated in intensive care units often experience persistent symptoms after hospital discharge and symptoms linked to the hospitalization experience itself (81, 82), the COVID-19 pandemic and the emergence of post-COVID syndrome have brought about a renewed attention to Post-Intensive Care Syndrome (PICS).

ICU treatment involves all elements of a traumatic experience, but whether an individual develops PTSD depends on the interaction between personality traits, the nature of the traumatic experiences, and the support received during and after treatment.

## LONG-TERM CONSEQUENCES OF ICU TREATMENT (UNRELATED TO THE COVID-19 PANDEMIC)

The treatment and survival of patients (defined as being discharged alive from the intensive care unit) who were treated in intensive care units (ICUs) have traditionally been considered a measure of treatment success (83). The increasing prevalence of severe and critical illnesses, combined with advancements in intensive care medicine, has resulted in a growing number of patients (~80–90%) surviving until hospital discharge (84–86). However, moving beyond the mere traditional perspectives, there is growing interest in the long-term health outcomes of ICU survivors, leading to a shift in the focus of intensive care from mere survival to returning to daily life after experiencing a critical illness (87).

Admission to intensive care has potentially long-term consequences for both survivors and their family members. ICU survivors may develop physical, psychological, and/or cog-

nesanica, dok kognitivni i psihijatrijski simptomi uključuju anksioznost, depresiju, teškoće pažnje i pamćenja i PTSP.

Raznolikost i ozbiljnost posljedica značajno varira u istraživanjima. Istraživanja pokazuju da 70 % osoba koje su liječene u JIL-u razvije jedan ili više simptoma PICS-a jednu godinu nakon otpusta s liječenja (92), ali i da PICS može trajati čak i 5 godina nakon izlaska iz bolnice (93-96). Šest mjeseci nakon otpusta 25 % preživjelih pati od teške onesposobljenosti, a samo se oko 55 % vratilo na posao (97). Psihološki poremećaji uključujući depresiju, anksioznost i PTSP su česti, pogađaju 55 % osoba u prvoj godini nakon otpuštanja iz JIL-a (98-100).

I za osobe koje su preživjele liječenje u JIL-a i za članove njihovih obitelji simptomi mogu imati negativan utjecaj na socijalne aspekte njihovog svakodnevnog života, kao što su povratak na posao, uloge i odgovornosti unutar obitelji i kvalitetu života (engl. *Quality of Life*, QoL) (101-103). Osim toga, iskustvo osobe koja je liječena na JIL-u razlikuje se od iskustva članova njegove obitelji, što naknadno može utjecati na njihove odnose i načine suočavanja (104).

Sve opisane posljedice PICS-a na oboljele i članove njihovih obitelji rezultiraju povećanim troškovima zdravstvene skrbi, ponovnim hospitalizacijama, nezaposlenosti, češćim posjetima liječnicima u primarnoj zdravstvenoj zaštiti i smanjenjem kvalitete života povezane sa zdravljem (105-110).

Čimbenici rizika za pojavu PICS-a nisu jasno definirani i razlikuju se u različitim studijama, no općenito su odvojeni u dvije kategorije: oni koji se odnose na već postojeće čimbenike (postojeće bolesti te komorbiditete ili psihijatrijsku anamnezu) i oni koji su povezani s JIL-om, uključujući prisutnost delirija, dozu primijenjenih sedativa, prisutnost sindroma akutnog respiratornog distresa (ARDS-a) ili sepse (111).

nitive difficulties, collectively referred to as post-intensive care syndrome (PICS) (88–91). Physical symptoms include fatigue and insomnia, while cognitive and psychiatric symptoms encompass anxiety, depression, attention and memory difficulties, and post-traumatic stress disorder (PTSD).

The variety and severity of these consequences vary significantly across studies. Research indicates that 70% of ICU-treated individuals develop one or more PICS symptoms within a year after discharge (92), and PICS can persist for up to five years post-hospitalization (93–96). Six months after discharge, 25% of survivors suffer from severe disability, and only about 55% return to work (97). Psychological disorders, including depression, anxiety, and PTSD, are common and affect 55% of individuals in the first year after ICU discharge (98–100).

For both ICU survivors and their family members, these symptoms can have a negative impact on the social aspects of daily life, such as returning to work, family roles and responsibilities, and overall quality of life (QoL) (101–103). Additionally, the experience of an ICU patient differs from that of their family members, which can subsequently affect their relationships and coping strategies (104).

The described consequences of PICS for both patients and their families result in increased healthcare costs, rehospitalizations, unemployment, more frequent visits to primary care physicians, and reduced health-related quality of life (105–110).

Risk factors for PICS have not been clearly defined and vary across studies, but they are generally categorized into two groups: those referring to pre-existing factors (such as existing illnesses, comorbidities, or a history of psychiatric disorders) and ICU-related factors, including the presence of delirium, dosage of administered sedatives, the presence of acute respiratory distress syndrome (ARDS), or sepsis (111).

## PICS I POST-COVID

Daljnjim poboljšanjem skrbi za pacijente na intenzivnoj njezi tijekom pandemije COVID 19 došlo je do povećanja broja preživjelih što je pomaknulo fokus na pitanja vezana uz dugoročne ishode. Osobe koje su preživjele teški ili kritični COVID-19 zbog kojeg su bile hospitalizirane izložene su velikom riziku razvoja PICS-a (112-115). Post-COVID simptomi, koji traju dugo nakon otpuštanja iz JIL-a, pokazuju značajno preklapanje s PICS-om i mogu pogoršati njegove simptome (116,117) (slika 1).

Kod više od 90 % pacijenata prijavljeni su simptomi koji pogađaju barem jednu glavnu PICS domenu (114).

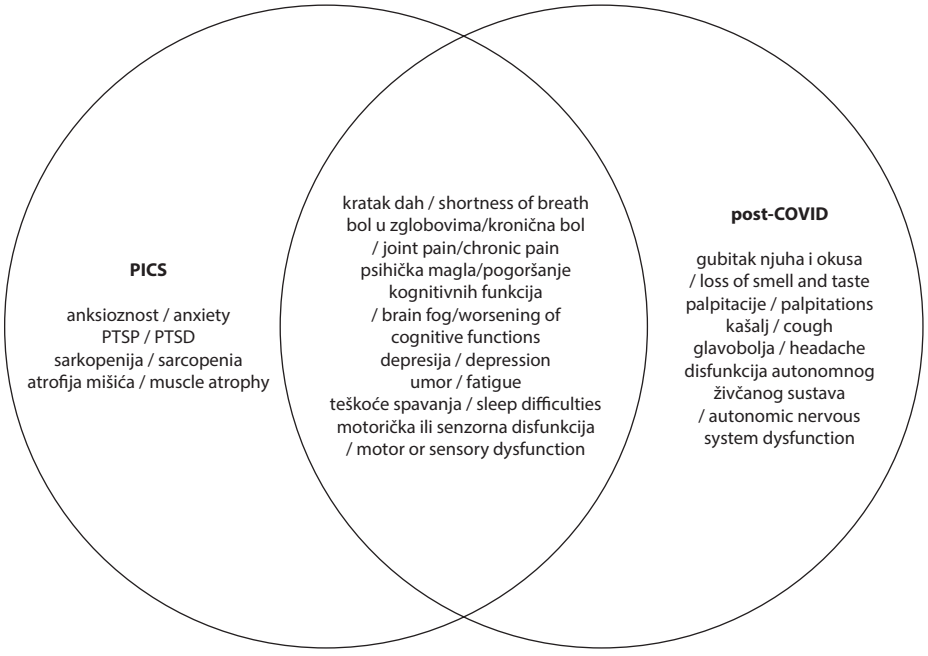
U nizozemskoj prospektivnoj kohortnoj studiji koja je uključivala procjenu 246 pacijenata jednu godinu nakon liječenja COVID-19 na intenzivnoj njezi, 74,3 % je prijavilo tjelesne simptome, 26,2 % psihičke smetnje, a 16,2 % kognitivne simptome (118). Jedan od prvih sustavnih pregleda istraživanja upućivao je na visoku prevalenciju kognitivnih poremećaja kod osoba koje su preživjele intenzivnu njegu: oko

## PICS AND POST-COVID

With further improvements in intensive care for patients during the COVID-19 pandemic, the number of survivors has increased, shifting the focus to long-term outcomes. Individuals who survived severe or critical COVID-19 that required hospitalization are at a high risk of developing PICS (112-115). Post-COVID symptoms, which persist long after discharge from the ICU, significantly overlap with PICS and may exacerbate its symptoms (116, 117) (Figure 1).

More than 90% of patients have reported symptoms affecting at least one major PICS domain (114).

In a Dutch prospective cohort study that examined 246 patients one year after ICU treatment due to COVID-19, 74.3% reported physical symptoms, 26.2% reported psychological distress, and 16.2% reported cognitive symptoms (118). One of the first systematic reviews of research pointed to a high prevalence of cognitive impairments among ICU survivors: approximately 50% to 80% of ICU survivors had




**SLIKA 1.** Preklapanje simptoma PICS-a i post-COVID-a
**FIGURE 1.** Overlapping symptoms of PICS and post-COVID

50 % do 80 % osoba koje su preživjele intenzivnu njegu imalo je kognitivna oštećenja (119). Prevalencija je bila veća kod ARDS-a preživjelih u usporedbi s mješovitim pacijentima na intenzivnoj njezi, a bila je veća i kada su se koristile objektivne mjere procjene u usporedbi sa subjektivnim samoprocjenama. Istraživanje koje se bavilo 12-mjesečnim ishodima pacijenata nakon prijmova u bolnicu zbog bolesti COVID-19 (120) utvrdilo je smanjenje kvalitete života povezane sa zdravljem (engl. *health-related quality of life*, HRQoL) nakon jedne godine i blaga do umjerena tjelesna ograničenja kod 29 % sudionika. U drugoj studiji (121) sudionici su izjavili da je umor (27 %) najizraženiji simptom 12 mjeseci nakon otpusta iz bolnice. Osobe koje su preživjele intenzivnu njegu također su prijavljivale bol kao važan simptom, a najistaknutije vrste boli su bol u zglobovima, bol u mišićima i bol u živcima (122). Sahoo i suradnici (123) izvijestili su da pacijenti smatraju liječenje u JIL-u bolnim iskustvom i kao jednu od najgorih faza svog života. Tijekom bolničkog liječenja imali su izražen strah od smrti zbog neizvjesnosti ishoda liječenja, a nakon otpusta bili su uznemireni zbog dugotrajnosti bolesti i niza psihosocijalnih negativnih posljedica (124).

U velikoj kohorti pacijenata koji su proveli u prosjeku 10 dana u JIL-u poremećaji spavanja i kognitivni poremećaji bili su dvije najčešće posljedice koje su oboljeli prijavljivali i četiri mjeseca nakon otpusta (125). Otprilike mjesec dana nakon otpusta više je od jedne trećine pacijenata prijavilo simptome akutnog stresnog poremećaja (126) ili kognitivnu disfunkciju (127), a tri mjeseca nakon akutne bolesti preživjeli su još uvijek imali narušenu kvalitetu života povezanu sa zdravljem (125,128). Šest mjeseci nakon kritičnog COVID-19 bol, nelagoda, tjeskoba ili depresija i dalje su prevladavali, za razliku od problema s pokretljivošću. Istraživanja pokazuju da je broj oboljelih koji su potpuno bez simptoma nakon liječenja u JIL-u iznimno mali. Manje od 10 % pacijenata

cognitive impairments (119). The prevalence was higher among ARDS survivors compared to mixed ICU patients, and was also higher when objective assessment measures were used compared to subjective self-assessments. A study examining 12-month outcomes in patients after COVID-19 hospitalization (120) found a decline in the health-related quality of life (HRQoL) after one year, and mild to moderate physical limitations in 29% of participants. In another study (121), participants reported fatigue (27%) as the most prominent symptom 12 months after hospital discharge. ICU survivors also reported pain as a significant symptom, with joint pain, muscle pain, and nerve pain being the most common (122). Sahoo et al. (123) reported that patients perceived ICU treatment as a painful experience and one of the worst phases of their lives. During hospitalization, they experienced intense fear of death due to uncertainty about treatment outcomes, and after discharge, they were distressed by the prolonged illness and various psychosocial negative consequences (124).

In a large cohort of patients who spent an average of 10 days in the ICU, sleep disorders and cognitive impairments were the two most common consequences, reported by the patients even four months after discharge (125). Approximately one month after discharge, more than one-third of patients reported symptoms of acute stress disorder (126) or cognitive dysfunction (127), while three months after acute illness, survivors still reported impaired health-related quality of life (125, 128). Six months after critical COVID-19, pain, discomfort, anxiety, or depression remained prevalent, as opposed to mobility problems. Studies indicate that the number of patients completely symptom-free after ICU treatment is exceptionally low. Less than 10% of patients had no PICS symptoms and were fully recovered after three months (129), suggesting a very slow clinical improvement without active and continuous post-ICU

nije imalo simptome PICS-a i bili su potpuno oporavljeni nakon tri mjeseca (129) što ukazuje na vrlo sporo poboljšanje kliničkog statusa bez aktivne i kontinuirane skrbi nakon intenzivne njege. Stvarne posljedice mogu biti podcijenjene s obzirom na kontinuiranu pristranost odabira sudionika jer manje onesposobljeni pacijenti prihvaćaju ili mogu prisustvovati u istraživanjima i dugotrajnim praćenjima.

Nekoliko istraživanja utvrdilo je da je nezaposlenost povezana s depresijom, anksioznošću i lošom kvalitetom života. Nakon povratka na posao utvrđeno je poboljšanje psihičkog zdravlja i kvalitete života, te su sudionici povratak na posao doživjeli kao znak oporavka (122). Takva koherentnost između posla i življenja smislenog života opisana je u nekoliko studija (130-132). Međutim, osobe koje su preživjele intenzivnu njegu u kvalitativnoj studiji izvještavaju da im posao više nije glavni životni prioritet i da su im socijalni odnosi postali važniji (122).

Čini se da je hospitalizacija jedan od ključnih čimbenika za prisutnost i ozbiljnost post-COVID-a. Zabilježeno je da je hospitalizacija dovela do većih ograničenja svakodnevnih životnih aktivnosti imala veći utjecaj na povratak na posao (5) i povećala rizik od dispneje, tjeskobe, mialgije i gubitka kose (7). U nekoliko sustavnih pregleda, meta-analiza i studija uspoređivano je stanje između hospitaliziranih i nehospitaliziranih pojedinaca. U takvim se studijama pokazalo da prethodno hospitalizirani pacijenti imaju veći rizik od post-COVID-19 stanja i češće pate od težih simptoma nego osobe koje nisu hospitalizirane (5,7,133-135). U jednoj od objavljenih meta-analiza prijavljena je značajna (ukupna) prevalencija post-COVID-a pri čemu je prevalencija u hospitaliziranih pacijenata bila veća (54 % (95 % CI 44-63 %)) nego u nehospitaliziranih (34 % (95 % CI 29-37 %)) (3).

Houben-Wilke i suradnici (136) proveli su *online* anketu među članovima Facebook grupe COVID pacijenata sa stalnim tegobama. Šest mjeseci nakon infekcije, depresija i anksioznost

care. The true consequences may be underestimated due to continuous selection bias, as less disabled patients accept to or can participate in research and long-term follow-ups.

Several studies have found that unemployment is associated with depression, anxiety, and poor quality of life. Returning to work was linked to improved mental health and quality of life, and participants perceived work resumption as a sign of recovery (122). Such coherence between work and living a meaningful life has been described in several studies (130-132). However, in a qualitative study, ICU survivors reported that work was no longer their main life priority and that social relationships had become more important to them (122).

Hospitalization appears to be one of the key factors for the presence and severity of post-COVID symptoms. It has been observed that hospitalization led to greater restrictions in daily life activities, had a greater impact on returning to work (5), and increased the risk of dyspnea, anxiety, myalgia, and hair loss (7). Several systematic reviews, meta-analyses, and studies have compared the conditions of hospitalized and non-hospitalized individuals. These studies have shown that previously hospitalized patients have a higher risk of post-COVID-19 syndrome and often suffer from more severe symptoms than those who were not hospitalized (5, 7, 133-135). One of the published meta-analyses reported a significant (overall) prevalence of post-COVID symptoms, whereby there was a higher prevalence in hospitalized patients (54% (95% CI 44–63%)) compared to non-hospitalized patients (34% (95% CI 29–37%)) (3).

Houben-Wilke et al. (136) conducted an online survey among members of a Facebook group for COVID patients with persistent symptoms. Six months after infection, depression and anxiety were reported in 42% and 29% of hospitalized individuals, respectively, and in 40% and 37% of non-hospitalized individuals, respectively.

zabilježene su kod 42 % i 29 % hospitaliziranih osoba te kod 40 % i 37 % nehospitaliziranih. Johnsen i suradnici (137) istraživali su pacijente s COVID-19 tri mjeseca nakon otpusta iz bolnice i pacijente koje je njihov liječnik opće prakse uputio u respiratornu ambulantu zbog postojanih simptoma post-COVID-a. Kvaliteta života povezana sa zdravljem bila je slična u obje skupine, iako je postojala tendencija nižih vrijednosti u nehospitaliziranih. Perrot i suradnici (138) usporedili su simptome post-COVID-a u tri skupine pacijenata koji su primljeni u svoju jedinicu za rehabilitaciju post-COVID-a (prosječno trajanje od 110 dana od otpusta iz bolnice): pacijenti koji nisu bili hospitalizirani, pacijenti primljeni na opći odjel i pacijenti primljeni u JIL. Utvrđeno je da je anksioznost značajno rjeđa kod pacijenata na intenzivnoj njezi (18,7 % prema 40,7-46,7 %), a depresija je bila značajno češća kod pacijenata koji nisu bili primljeni u bolnicu (37,0 % prema 17,6-26,7 %). Sukladno s time psihička komponenta upitnika o zdravstvenoj kvaliteti života SF-36 bila je niža kod pacijenata koji nisu bili liječeni u JIL-u. Međutim, tjelesna komponenta upitnika nije se razlikovala između triju skupina, a dispneja je bila podjednako učestala. Ukupno gledajući, zdravstvena kvaliteta života značajno je pogoršana kod svih oboljelih od post-COVID-a.

Veći teret samoprijavljenih simptoma kod nehospitaliziranih pojedinaca mogao bi biti posljedica njihovih različitih gledišta. Nehospitalizirane osobe smatrale su se zdravima prije i tijekom infekcije, a nakon infekcije pate od simptoma. Nasuprot tome, hospitalizirani pacijenti potencijalno su doživjeli olakšanje simptoma u vrijeme istraživanja, npr. mogli su disati samostalno i ponovno živjeti kod kuće sa svojim obiteljima. Osim toga, bili su pod strogim nadzorom, intenzivnim praćenjem i rehabilitacijom tijekom razdoblja hospitalizacije. Stoga bi stajalište hospitaliziranih pacijenata moglo biti pozitivnije, dok bi stajalište nehospitaliziranih pacijenata moglo biti negativnije.

Johnsen et al. (137) researched COVID-19 patients three months after hospital discharge, as well as patients referred by their general practitioners to a respiratory clinic due to persistent post-COVID symptoms. Health-related quality of life was similar in both groups, although there was a tendency toward lower values in non-hospitalized individuals. Perrot et al. (138) compared post-COVID symptoms in three groups of patients admitted to their post-COVID rehabilitation unit (average duration of 110 days from hospital discharge): non-hospitalized patients, patients admitted to a general ward, and ICU patients. Anxiety was significantly less common in ICU patients (18.7% vs. 40.7–46.7%), whereas depression was significantly more common in non-hospitalized patients (37.0% vs. 17.6–26.7%). Accordingly, the mental component of the SF-36 health-related quality of life questionnaire was lower in non-ICU patients. However, the physical component of the questionnaire did not differ between the three groups, and dyspnea was equally prevalent. Overall, health-related quality of life was significantly impaired in all post-COVID patients.

A higher burden of self-reported symptoms among non-hospitalized individuals could be due to their different perspectives. Non-hospitalized individuals considered themselves healthy before and during the infection, but suffered from symptoms afterward. In contrast, hospitalized patients may have experienced symptom relief by the time of the study, e.g., they were able to breathe independently and live at home with their families again. Additionally, they were under strict supervision, intensive monitoring, and rehabilitation during hospitalization. Hospitalized patients may, therefore, have had a more positive outlook, whereas non-hospitalized patients may have had a more negative perception.

Beyond ICU treatment itself, the COVID-19 pandemic had additional factors that could

Uz samo liječenje u JIL-u pandemija COVID-19 imala je i druge čimbenike koji mogu povećati psihičke smetnje, kao što su ograničenja posjeta i nedostatak direktnog kontakta i vidljivosti zdravstvenog osoblja zbog nošenja zaštitne odjeće (139).

## POVEZANOST POST-COVID-a I DRUGIH INFEKCIJA

COVID-19 je zapravo samo najnovija od mnogih drugih zaraznih bolesti koje su povezane s kroničnim posljedicama nakon oporavka od akutne faze infekcije (140). Choutk i suradnici (140) istraživali su zajedničke karakteristike između post-COVID-19-a i drugih kroničnih infektivnih sindroma i utvrdili veću prevalenciju sljedećih simptoma: netolerancija na tjelesni napor, neurokognitivno i senzorno oštećenje, perzistentni simptomi nalik gripi, poremećaj sna, mialgije i artralgije. Najveće sličnosti su s post-akutnim učincima opisanim u SARS epidemiji 2002–2004 (141) i bliskoistočnim respiratornim sindromom (engl. *Middle East Respiratory Syndrome,* MERS) koje su obje povezane s dugoročnim neuropsihijatrijskim implikacijama (142). Jedna meta-analiza pokazuje da otprilike jedna trećina preživjelih SARS-a i MERS-a ima dugotrajne psihološke posljedice kao što su anksioznost, depresija i PTSP koji traju 6 mjeseci nakon otpusta iz bolnice (143). Tijekom ranijeg izbijanja SARS-a prethodni su podatci pokazali da oboljenje od koronavirusa može rezultirati produljenim psihičkim poremećajima s dugotrajnim neuropsihijatrijskim posljedicama (144,145). Psihijatrijski simptomi koje su prijavili preživjeli od SARS-a uključuju depresiju, PTSP, opsesivno-kompulzivni poremećaj (OKP) i panični poremećaj nakon praćenja od 1 do 50 mjeseci (3,144,146).

Preklapanje kliničkih obilježja post-COVID-a s drugim postinfektivnim sindromima ukazivalo bi na uključenost zajedničkih patofizioloških

have increased psychological distress, such as visitor restrictions and the lack of direct contact and visibility of healthcare staff due to protective clothing (139).

## CONNECTION BETWEEN POST-COVID AND OTHER INFECTIONS

COVID-19 is, in fact, only the latest in a series of numerous infectious diseases associated with chronic consequences after recovery from the acute phase of infection (140). Choutk et al. (140) explored the common features between post-COVID-19 and other chronic infectious syndromes, finding a higher prevalence of the following symptoms: intolerance to physical exertion, neurocognitive and sensory impairments, persistent flu-like symptoms, sleep disturbances, myalgias, and arthralgias. The greatest similarities were observed in terms of the post-acute effects described in the SARS epidemic of 2002–2004 (141) and the Middle East Respiratory Syndrome (MERS), both of which are linked to long-term neuropsychiatric implications (142). One meta-analysis showed that approximately one-third of SARS and MERS survivors experienced long-term psychological consequences such as anxiety, depression, and PTSD, lasting six months after discharge from the hospital (143). During the earlier SARS outbreak, previous data indicated that coronavirus infection could result in prolonged psychological disorders with long-lasting neuropsychiatric consequences (144, 145). Psychiatric symptoms reported by SARS survivors include depression, PTSD, obsessive-compulsive disorder (OCD), and panic disorder after follow-ups ranging from 1 to 50 months (3, 144, 146).

The overlap of clinical features of post-COVID with other post-infectious syndromes suggests an involvement of shared pathophysiological pathways. Identifying a unique etiological model would facilitate the planning of diagnostic

kih puteva. Otkrivanje jedinstvenog etiološkog modela olakšao bi planiranje dijagnostičkih postupaka i prilagođenih tretmana (140). Trenutno je, nažalost, naše razumijevanje temeljnih patofizioloških mehanizama i etioloških čimbenika nedostatno, iako se provode obećavajuće studije (147-149).

## ISTRAŽIVANJA U HRVATSKOM KONTEKSTU

Tijekom pandemije COVID-19 u Hrvatskoj veliki su istraživački napori bili usmjereni na ispitivanje utjecaja pandemije na psihičko zdravlje različitih skupina sudionika iz opće populacije. Međutim, prema našim spoznajama broj objavljenih istraživačkih radova koji se odnose na post-COVID simptome, a provedeni su na hrvatskim pacijentima, je neznatan. Istraživački tim Klinike za plućne bolesti Jordanovac bavio se u prvom redu tjelesnim i pulmološkim simptomima post-COVID-a (150,151) . U jednom istraživanju provedenom na uzorku osoba s akutnim i post-COVID simptomima koji su uključeni u rehabilitacijski program utvrdili su da su tijekom akutne faze bolesti simptomi emocionalne uznemirenosti i anksioznosti bili povišeni, te da je došlo do pada simptoma u post-COVID fazi bolesti (151).

U jednom istraživanju provedenom na uzorku od 227 sudionika s neurološkim post-COVID-19 simptomima rezultati su pokazali da je većina oboljelih imala više simptoma, a najčešći simptomi bili su glavobolja (30 %), kognitivne tegobe (29 %), poremećaji mirisa (17 %), parestezije (16 %), kronični umor (15 %), vrtoglavica s mučninom i povraćanjem (15 %) i nesanica (11 %) (152).

U istraživanju koje je provedeno u svrhu završetka magistarskog studija, a provedeno je na 266 sudionika u pulmološkoj post–COVID ambulanti OB Dubrovnik, dobiveno je da se pacijenti najčešće žale na zaduhu (37,2 %), kašalj

procedures and tailored treatments (140). Unfortunately, our understanding of the underlying pathophysiological mechanisms and etiological factors remains insufficient, although promising studies are underway (147-149).

## RESEARCH IN THE CROATIAN CONTEXT

During the COVID-19 pandemic, significant research efforts in Croatia were focused on examining the impact of the pandemic on the mental health of various participant groups from the general population. However, to our knowledge, the number of published research papers related to post-COVID symptoms conducted on Croatian patients is insignificant. The research team at the Clinic for Pulmonary Diseases Jordanovac primarily focused on the physical and pulmonary symptoms of post-COVID (150, 151). One study conducted on a group of individuals with acute and post-COVID symptoms enrolled in a rehabilitation program found that during the acute phase of the illness, symptoms of emotional distress and anxiety were elevated, but these symptoms decreased in the post-COVID phase (151).

In a study conducted on a sample of 227 participants with neurological post-COVID-19 symptoms, the results showed that most patients had multiple symptoms, with the most common being headaches (30%), cognitive difficulties (29%), smell disorders (17%), paresthesias (16%), chronic fatigue (15%), dizziness with nausea and vomiting (15%), and insomnia (11%) (152).

In a study conducted for the completion of a master's thesis, which involved 266 participants at the post-COVID pulmonary clinic in Dubrovnik General Hospital, it was found that patients most commonly complained of shortness of breath (37.2%), cough (34.2%), muscle weakness (16.9%), and fever (15.8%) (153).

(34,2 %), mišićnu slabost (16,9 %) i febrilitet (15,8 %) (153).

## ZAKLJUČAK

Post-COVID sindrom je složeno stanje koje je praćeno tjelesnim i psihičkim smetnjama, ali i socijalnom ugroženošću u svim elementima stigmatizacije. Kako je uključena i socijalna dimenzija potrebno je provoditi istraživanja u hrvatskim uvjetima jer su naše društvene okolnosti različite u odnosu na velike zemlje iz kojih uglavnom dolaze nalazi istraživanja. No, iz svega opisanog vrlo je jasno da upravljanje post-COVID-om zahtijeva interdisciplinarnost uključujući liječnike različitih specijalnosti (opća medicina, pulmologija, kardiologija i infektologija), fizijatre, stručnjake za psihičko zdravlje, fizioterapeute, radne terapeute i socijalne radnike koji će se baviti kliničkim i psihološkim aspektima bolesti. Uz praćenje i liječenje pacijenata s post-COVID-om potrebno je osigurati rehabilitaciju i oporavak općih funkcija. Uzroci post-COVID-a su još uvijek nejasni, ali istraživanja već pokazuju da poboljšanje psihičkog stanja svakako dovodi i do boljih tjelesnih funkcija preko složenih psihoneuroimunoloških mehanizama (154,155).

## CONCLUSION

Post-COVID syndrome is a complex condition characterized by both physical and psychological disturbances, as well as social vulnerability due to all the elements of stigmatization. Considering that the social dimension is involved, it is necessary to conduct research in Croatian conditions, as our societal circumstances differ from those of large countries, where research findings mainly originate from. However, it is very clear from the above that managing post-COVID requires interdisciplinarity, involving physicians from various specialties (general medicine, pulmonology, cardiology, and infectology), physiatrists, mental health professionals, physical therapists, occupational therapists, and social workers, who must address the clinical and psychological aspects of the disease. In addition to monitoring and treating patients with post-COVID, rehabilitation and recovery of general functions must be ensured. The causes of post-COVID remain unclear, however studies have already shown that improving the psychological condition certainly leads to better physical functions through complex psychoneuroimmunological mechanisms (154, 155).

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# Pregled istraživanja o primjeni i učinkovitosti *neurofeedback* metode u liječenju depresivnog poremećaja

## */ A Review of Research on the Application and Effectiveness of the Neurofeedback Method in the Treatment of Depressive Disorder*

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Depresivni poremećaj jedna je od najranije opisanih bolesti u povijesti medicine, s dubokim utjecajem na pojedince i društvo u cjelini. Prema predviđanjima, depresija će do 2030. godine uzrokovati najveći porast troškova i opterećenja za zdravstveni sustav, tj. oni će premašiti troškove i opterećenja svih drugih bolesti i poremećaja. Standardni pristupi liječenju depresije uključuju farmakološku terapiju i psihoterapijske tehnike, dok sve više pažnje dobivaju i komplementarne metode poput *neurofeedbacka*. *Neurofeedback* je računalno podržana metoda koja prati i analizira moždanu električnu aktivnost (EEG) sa ciljem regulacije disfunkcionalnih moždanih obrazaca povezanih s depresijom. Rezultati dosadašnjih istraživanja ukazuju na značajne prednosti *neurofeedbacka*. Osobe s depresivnim poremećajem koje su bile uključene u *neurofeedback* trening pokazale su statistički značajna poboljšanja u usporedbi s kontrolnim skupinama, što ukazuje na njegovu potencijalnu učinkovitost kao dopunske terapije. Ipak, iako preliminarni rezultati obećavaju, potreban je daljnji razvoj znanstvenih studija kako bi se osigurala jasnija metodologija i bolje razumijevanje mehanizama djelovanja *neurofeedbacka*. U radu se analiziraju dosadašnja istraživanja i raspravlja o mogućnostima implementacije *neurofeedbacka* u liječenju depresije naglašavajući njegov potencijalni doprinos smanjenju simptoma depresivnog poremećaja. Iznesen je kritički osvrt na metodološka ograničenja i zaključke istraživanja te su pružene smjernice za buduća istraživanja.

*/ Depressive disorder is one of the earliest illnesses to be described in the history of medicine, with profound effects on individuals and the society as a whole. By 2030, depression is projected to cause the largest increase in health care costs and burdens, thus exceeding the costs and burdens of all other diseases and disorders. Standard approaches to the treatment of depression include pharmacological therapy and psychotherapeutic techniques, while complementary methods such as neurofeedback are also gaining increasing attention. Neurofeedback is a computer-assisted method that monitors and analyzes the electrical activity of the brain (EEG) with the aim of regulating dysfunctional brain patterns associated with depression. The results of the studies conducted so far indicate significant advantages of neurofeedback. Individuals with depressive disorder who were included in neurofeedback training showed statistically significant improvements compared to the control groups, which points to its potential effectiveness as a form of supplementary therapy. Nevertheless, although the preliminary results are promising, further scientific studies are necessary in order to provide a clearer methodology and better understanding of the mechanisms of action of neurofeedback. An analysis of the previous studies and a discussion of the possibilities for implementing neurofeedback in the treatment of depression are provided in this study, with a special emphasis on its potential contribution to reducing the symptoms of depressive disorder. A critical review of the methodological limitations and study conclusions is provided, as well as some guidelines for future research.*

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**KLJUČNE RIJEČI / *KEY WORDS***
Depresivni poremećaj / *Depressive Disorder*
EEG / *EEG*
*Neurofeedback / Neurofeedback*

**TO LINK TO THIS ARTICLE:** https://doi.org/10.24869/spsih.2025.125

## UVOD

Mentalno zdravlje sastavnica je općeg zdravlja i važan resurs za pojedinca, njegovu obitelj i društvenu zajednicu (1), a razina mentalnog zdravlja pojedinca pod utjecajem je brojnih psiholoških, socijalnih i bioloških čimbenika. Depresivni poremećaj ili depresija (lat. *deprimere* – potištenost, bezvoljnost), jedna od najranije opisanih bolesti u povijesti medicine (2), bolest je za koju se danas procjenjuje da će do 2030. godine uzrokovati najveći porast troškova i opterećenja za zdravstveni sustav u odnosu na sve druge bolesti (3, 4). Depresija je rezultat složene interakcije psiholoških i bioloških čimbenika te značajno utječe na radnu sposobnost i kvalitetu života žena i muškaraca neovisno o ekonomskom stupnju razvoja društvene zajednice. Može se javiti u bilo kojem životnom razdoblju, no najčešća je između dvadeset i pete i četrdesete godine života (2). Najznačajnije važeće klasifikacije koje se koriste za sistemsko prikazivanje depresivnog poremećaja jesu Međunarodna klasifikacija bolesti MKB-10 i Dijagnostički i statistički priručnik za mentalne poremećaje DSM-5 (5-7). Dijagnoza depresivnog poremećaja postavlja se na osnovi raspoloživih podataka (anamneza, heteroanamneza i dr.), koji između ostalog uključuju i broj simptoma, trajanje poremećaja, utjecaj poremećaja na socijalno, obiteljsko i radno funkcioniranje, diferencijalne

## INTRODUCTION

Mental health is a component of general health and an important resource for an individual, their family and the social community (1), while the level of an individual's mental health is influenced by a number of psychological, social and biological factors. Depressive disorder or depression (lat. *deprimere* – low mood, listlessness), is one of the earliest illnesses to be described in the history of medicine (2), projected to cause the largest increase in health care costs and burdens by 2030, thus exceeding all other diseases (3, 4). Depression is the result of a complex interaction of psychological and biological factors, and has a significant effect on the work capacity and quality of life of both women and men, regardless of the economic level of development of the community. It can occur at any age, but is most common between the ages of twenty-five and forty (2). The most important classifications used to systematically portray depressive disorder are the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (5-7). Depressive disorder is diagnosed based on the available data (medical history, collateral history etc.), including, among other things, the number of symptoms, duration of the disorder, its effect on the social, family and occupational functioning, differential diagnostic criteria and the circumstances in which depressive symptoms occurred (5). Despite the contem-

dijagnostičke kriterije i okolnosti pojave depresivnih simptoma (5). Unatoč suvremenim spoznajama i rastućem broju znanstvenih dokaza mehanizam nastanka depresivnog poremećaja do danas nije u potpunosti razjašnjen, ali je jasno da se radi o složenoj kliničkoj pojavi u čijoj je podlozi složeno međudjelovanje biologijskih i psihosocijalnih čimbenika. Postoji nekoliko prihvaćenih teorija koje možemo svrstati u dvije skupine: biološke i psihosocijalne teorije. Biološke teorije nude značajne doprinose u etiologiji depresivnog poremećaja, ističući čimbenike poput genetske predispozicije (8), disfunkcije neurotransmitera (9), smanjene razine moždanog neurotrofnog čimbenika (BDNF) (10,11), poremećaji u regulaciji neuropeptida poput tvari P, neuropeptida Y, kortikotropina i vazopresina (12), nedostatka vitamina B12 (13) i folata (14), disfunkcije hipotalamičko-hipofizno-adrenalne (HHA) osi (15), smanjene razine tireotropnog hormona (TSH) (16) te prisutnosti neurodegenerativnih procesa (17).

U okviru psihosocijalnih teorija ključni su sljedeći uzroci: psihodinamski čimbenici (nesvjesni konflikti, osjećaj gubitka, nisko samopoštovanje), bihevioralni čimbenici (naučena bespomoćnost), kognitivni čimbenici (negativna uvjerenja, pesimizam, iskrivljena percepcija stvarnosti), socijalni čimbenici (stresni životni događaji, gubitak bliskih osoba, nepovoljni socijalni odnosi) (18-21). Važno je naglasiti da se socijalni gubitak prepoznaje kao jedan od ključnih čimbenika u razvoju i održavanju depresivnog poremećaja.

U liječenju depresivnog poremećaja danas koristimo farmakoterapiju te različite psihoterapijske tehnike kao i elektrokonvulzivnu terapiju za rezistentnu depresiju. U okviru psihoterapije različiti psihoterapijski modaliteti jesu psihodinamska, kognitivno-bihevioralna, ekspresivna (art) terapija i dr. Iz svega navedenog jasno je da postoji potreba za istraživanjem učinaka različitih terapijskih metoda kod osoba koje boluju od depresije što će osigurati znanstve-

porary knowledge and the increasing amount of scientific evidence, the mechanism of the onset of depressive disorder has not yet been completely clarified, however, it is clearly a multifaced clinical phenomenon resulting from the complex interaction of biological and psychosocial factors. There are several accepted theories, which can be classified into two groups: biological and psychosocial theories. Biological theories offer significant contributions to the etiology of depressive disorder, highlighting the factors such as genetic predisposition (8), neurotransmitter dysfunction (9), lower levels of brain-derived neurotrophic factor (BDNF) (10, 11), dysregulation of neuropeptides such as substance P, neuropeptide Y, corticotropin and vasopressin (12), vitamin B12 (13) and folate (14) deficiency, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (15), low thyrotropic hormone (TSH) levels (16), and the presence of neurodegenerative processes (17).

Psychosocial theories highlight the following key causes: psychodynamic factors (subconscious conflicts, sense of loss, low self-esteem), behavioral factors (learned helplessness), cognitive factors (negative beliefs, pessimism, distorted perception of reality), social factors (stressful life events, loss of loved ones, unfavorable social relationships) (18-21). It should be emphasized that social loss is recognized as one of the key factors in the development and maintenance of depressive disorder.

Pharmacotherapy and various psychotherapeutic techniques are nowadays used in the treatment of depressive disorder, including electroconvulsive therapy (ECT) for resistant depression. Psychotherapy includes different psychotherapeutic modalities, such as psychodynamic, cognitive-behavioral, expressive (art) therapy, and others. It is clear from all of the above that the effects of different therapeutic methods should be studied in individuals with depression, which would ensure a scientifically-based approach to their treatment. Since this illness is becoming a growing public health issue, newer methods are also being explored. One of these methods is neurofeedback.

no utemeljen pristup njihovu liječenju. Budući da ova bolest postaje sve veći javnozdravstveni problem, istražuju se i novije metode. Jedna od tih metoda je *neurofeedback*.

*Neurofeedback* je terapijska neinvazivna metoda temeljena na praćenju električne aktivnosti mozga metodom elektroencefalografije (EEG) koja pomaže da osoba nauči modificirati moždane valove uz pomoć računalne tehnologije (22). Hammond definira *neurofeedback* kao vrstu *biofeedbacka*, odnosno kao trening moždanih valova (23). Zapravo, elektroencefalografija (EEG) u stvarnom vremenu bilježi informacije o moždanoj aktivnosti koje računalo zatim pretvara u povratne signale (vidne i/ili zvučne prikaze na ekranu). Moždani su valovi odraz specifičnih mentalnih stanja, a pojedini obrasci moždanih valova mogu biti manje ili više poželjni za određene mentalne aktivnosti pa *neurofeedbackom* učimo mozak kako da proizvede optimalne obrasce moždanih valova.

Za razumijevanje specifičnih mehanizama koji su temelj *neurofeedback* učenja prvo treba razumjeti opće teorijske i eksperimentalne osnove učenja. Dvije glavne vrste asocijativnog učenja klasično su i operantno (instrumentalno) uvjetovane. Među teorijama i modelima koji su bili predloženi kako bi objasnili učenje pomoću *neurofeedbacka* i njegove pozadinske mehanizme postoji preklapanje i kompatibilnost: npr. može se vidjeti da teorija instrumentalnog učenja djelomično oblikuje gledište koje odgovara teoriji dualnog procesa. Teorija motoričkog učenja i teorija učenja vještina također imaju neke zajedničke značajke, dok se teorija globalnog radnog prostora, koja pretpostavlja svijest o potkrepljenju (*feedback*) za učenje čini kompatibilnom s nekim oblicima teorije svijesti. Budući eksperimenti trebali bi pružiti nove uvide u valjanost navedenih teorija u *neurofeedback* učenju i izvedbi (24-27).

Početkom 2001. godine dvije stručne organizacije: *Association for Applied Psychophysiology and Biofeedback (AAPB) i International Society for Ne-*

Neurofeedback is a therapeutic, noninvasive method based on monitoring the electrical activity in the brain using electroencephalography (EEG), thus helping an individual learn how to modify the brain waves using computer technology (22). Hammond defines neurofeedback as a type of biofeedback, i.e. training of brain waves (23). In fact, electroencephalography (EEG) records information on brain activity in real time, which the computer then converts into feedback signals (visual and/or audio representations on the screen). Brain waves are a reflection of specific mental states, and individual brain wave patterns can be more or less desirable for specific metal activities, therefore neurofeedback teaches the brain how to produce the optimal brain wave patterns.

In order to understand the specific mechanisms underlying neurofeedback learning, we must first understand the general theoretical and experimental bases of learning. The two main types of associative learning are explained by classical and operant (instrumental) conditioning. There is an overlap and compatibility among the theories and models proposed for the purpose of explaining learning through neurofeedback and its underlying mechanisms, i.e. it is observable that the instrumental learning theory partially shapes the viewpoint corresponding to the dual process theory. The motor learning theory and skill acquisition theory also share some characteristics, while the global workspace theory, which assumes an awareness of feedback for learning, seems compatible with some forms of the theory of consciousness. Future experiments should provide new insights into the validity of the aforementioned theories in terms of neurofeedback learning and performance (24-27).

In early 2001, two professional organizations: *Association for Applied Psychophysiology and Biofeedback (AAPB)* and *International Society for Neuronal Regulation (ISNR)*, formed a working body tasked with developing the official standards for the methodology of research, at the same time developing the necessary conditions and forms of research for each of the 5 levels of neurofeed-

*uronal Regulation (ISNR)* osnovale su radno tijelo s ciljem razvoja službenih standarda za metodologiju istraživanja razvijajući pritom potrebne uvjete i oblike istraživanja za svaki od 5 stupnjeva učinkovitosti *neurofeedback* terapije (koje rangiraju od najniže, prve razine – nedovoljno empirijskih dokaza, sve do najviše pete razine – učinkovito i specifično). Najniže rangirani treninzi ne odražavaju slabu učinkovitost terapije, već je riječ o područjima nedovoljno istraženim da bi se izveli primjereni empirijski zaključci. Rigorozni standardi koje su donijeli AAPB i ISNR mnogo su stroži i oprezniji u zaključivanju o učinkovitosti nego mnoge dobro prihvaćene medicinske intervencije. *Neurofeedback* koji je posebno usmjeren na depresiju umjereno je podržan postojećim studijama (sve odgovaraju razini 2/5, „moguće učinkovito“) (28,29).

## METODOLOGIJA PRETRAŽIVANJA I ODABIRA LITERATURE

U cilju izrade preglednog rada o primjeni *neurofeedback* metode u liječenju depresivnog poremećaja provedena je detaljna i višefazna pretraga relevantnih znanstvenih baza podataka, stručnih časopisa i internetskih izvora. Pretraživane baze bile su: *PubMed*, *Scopus*, *Web of Science*, *PsychINFO*, *EBSCOhost*, *ScienceDirect*, *ProQuest Dissertations and Theses* te nacionalna baza Hrčak. Ove baze su odabrane zbog svoje reputacije u području biomedicine, psihologije i neuroznanosti, kao i dostupnosti recenziranih radova iz područja primjene *neurofeedbacka* u psihijatriji. Osim toga, ciljano su pretraženi i stručni časopisi s fokusom na *neurofeedback* poput: *Journal of Neurotherapy, Neuropsychobiology, Applied Psychophysiology and Biofeedback i Frontiers in Behavioral Neuroscience.*

Pretraživanje je provedeno u razdoblju od listopada do prosinca 2024. godine, a uključivalo je radove objavljene od 1997. do 2024. godine. Ključne riječi korištene pri pretraživa-

back therapy effectiveness (ranked from the lowest, Level 1 – “not empirically supported”, to the highest, Level 5 – “efficacious and specific”). The lowest ranking trainings do not indicate a low efficiency of the treatment, but represent areas that have not been explored enough to enable drawing appropriate empirical conclusions. The rigorous standards set by the AAPB and ISNR are much stricter and more cautious in their conclusions about efficacy than many other well-accepted medical interventions. Neurofeedback specifically focused on depression is moderately supported by the existing studies (all of which correspond to Level 2/5, “possibly efficacious”) (28, 29).

## SEARCH METHODOLOGY AND LITERATURE SELECTION

A detailed multiphase search of the relevant scientific databases, professional journals and internet sources was conducted for the purpose of preparing this review article on the application of the neurofeedback method in the treatment of depressive disorder. The following databases were searched: *PubMed*, *Scopus*, *Web of Science*, *PsycINFO*, *EBSCOhost*, *ScienceDirect*, *ProQuest Dissertations and Theses*, as well as the national database Hrčak. These databases were selected based on their reputation in the field of biomedicine, psychology and neuroscience, as well as the availability of reviewed papers in the field of neurofeedback application in psychiatry. In addition, a targeted search focusing on neurofeedback was conducted in the following professional journals: *Journal of Neurotherapy, Neuropsychobiology, Applied Psychophysiology and Biofeedback,* and *Frontiers in Behavioral Neuroscience.*

The search was conducted in the period from October to December 2024, and included papers published from 1997 to 2024. The key words used during the search included combinations in both Croatian and English: *elektroencefalogram*, *neurofeedback, depresivni poremećaj* (in English: electroencephalogram, neurofeedback, depression). The inclusion criteria involved the following: papers

nju uključivale su kombinacije na hrvatskom i engleskom jeziku: elektroencefalogram, *neurofeedback,* depresivni poremećaj (na engleskom jeziku: *electroencephalogram*, *neurofeedback*, *depression*). Kriteriji uključivanja obuhvaćali su: radove koji se bave primjenom EEG *neurofeedback* metode u liječenju depresivnog poremećaja, istraživanja provedena na ljudima (kliničke studije, prikazi slučajeva, probna istraživanja) te radove s dostupnim punim tekstom. Kriteriji isključivanja odnosili su se na: radove koji se primarno bave drugim poremećajima bez jasne poveznice s depresijom, te radove u kojima se *neurofeedback* spominje, ali nije primijenjen u terapijskom kontekstu liječenja depresije.

Konačan broj radova uključenih u analizu iznosio je 34, a obuhvaćaju znanstvene članke, poglavlja iz stručnih knjiga i specijalistički rad.

## *NEUROFEDBACK* I DEPRESIVNI POREMEĆAJ

Baehr, Rosenfeld i Baehr među prvima su prikazali dvije studije slučaja na depresivnim pacijentima. U navedenim prikazima slučaja navode da prethodno trogodišnje liječenje medikamentnom terapijom i psihoterapijom kod pacijenata nije dovelo do poboljšanja. U procesu liječenja uz medikamentnu terapiju i psihoterapiju autori uvode i *neurofeedback* trening alfa asimetrije u kojem pokušavaju povećati razliku u aktivaciji lijevog i desnog frontalnog režnja. Elektrode su bile smještene na F3 i F4 položaje u odnosu na referentno smještenu Cz poziciju. Ovu (vlastitu) metodu nazivaju ALAY (od *alpha asymmetry*), a uvode i indeks alfa asimetrije (veći od nule ukazuje na višu zastupljenost desnostrane alfa frekvencije, odnosno nižu aktivaciju desnog u odnosu na lijevo frontalno moždano područje što se povezuje sa smanjenjem neugodnih emocija). Ispitanici su dolazili jednom do dva puta/tjedan na *neurofeedback* trening nakon čega su bili uključeni u pola sata psihoterapije. Tijekom *neurofeedbacka*

exploring the application of the EEG neurofeedback method in the treatment of depressive disorder, studies conducted on people (clinical studies, case studies, trial studies) and papers with full text available. The exclusion criteria were the following: papers primarily examining other disorders without a clear connection to depression; and papers mentioning neurofeedback, but without applying it in the therapeutic context of depression treatment.

The final number of papers included in the analysis was 34, and included scientific papers, chapters from expert books and a specialist paper.

## NEUROFEEDBACK AND DEPRESSIVE DISORDER

Baehr, Rosenfeld and Baehr were among the first to present two case studies on depressive patients. In these case studies, they reported that previous three-year treatments with medication therapy and psychotherapy did not lead to improvements in the patients. In the process of treatment with medication therapy and psychotherapy, the authors also introduced alpha asymmetry neurofeedback training in an attempt to increase the difference in the activation of the left and right frontal lobes. The electrodes were positioned at F3 and F4, relative to the reference position Cz. They called this (their own) method ALAY (alpha asymmetry), and also introduced the alpha asymmetry index (greater than zero indicates higher alpha frequency on the right side, i.e. lower activation of the right frontal brain area as opposed to the left, which is associated with fewer unpleasant emotions). The respondents underwent neurofeedback training one/two times per week, followed by a half hour of psychotherapy. In the course of neurofeedback, the goal was to learn how to increase the alpha asymmetry index above zero (when the alpha asymmetry index was above zero, the respondent would get a confirmation, i.e. a reinforcing sound, vibration or image change on the screen confirming that they managed to increase their alpha asymmetry index

cilj je bio naučiti povisiti indeks alfa asimetrije iznad nule (kada bi indeks alfa asimetrije bio iznad nule, ispitanik bi dobio potvrdu odnosno potkrepljenje zvukom, vibracijom ili promjenom slike na ekranu što bi bila potvrda da je uspio povisiti indeks alfa asimetrije iznad nule). *Neurofeedback* trening trajao je od 34 do 36 susreta tijekom razdoblja od dvije godine. Rezultati su pokazali nižu razinu depresije na svim kliničkim mjernim ljestvicama. Ponovno EEG mjerenje nakon pet mjeseci za jednu pacijenticu pokazalo je da su se naučene promjene u EEG frontalnoj asimetriji zadržale. Druga pacijentica nije bila dostupna. Autori su zaključili kako je *neurofeedback* tretman učinkovit dodatak psihoterapiji u liječenju depresije (30).

U svom su sljedećem radu Baehr i suradnici koristili *neurofeedback* kao dodatni tretman za depresiju uz prisutnost psihoterapije i medikamentne terapije. Izvijestili su da je četvero od šest ispitanika pokazalo poboljšanje na tri mjere Beckova upitnika depresije (BDI), Minnesota multifazičnom inventaru ličnosti (MMPI-2) te indeksu alfa asimetrije. Dva ispitanika nisu zadovoljila sve kriterije, jedan je ispitanik razvio nuspojave na lijekove, dok je kod drugoga bio prisutan trend smanjenja simptoma. Autori navode kako *neurofeedback* tretman nije uspješan kod svih sudionika te predlažu daljnja istraživanja s kontrolnim skupinama. *Neurofeedback* metodu autori predlažu kao dodatnu metodu liječenja, uz medikamentnu terapiju i psihoterapiju, a nikako ne kao jedini tretmanski izbor kod depresije (31).

Studija slučaja Hammonda uvodi novi postupak *neurofeedbacka* pod nazivom Roshi. Autor smatra da i drugi protokoli, osim ALAY-a, mogu mijenjati učinke alfa frontalne asimetrije i na taj način smanjiti simptome depresije. Postupak Roschi sastoji se od jačanja frekvencija beta valova te istovremenog inhibiranja alfa i *theta* frekvencija. Ispitanik je bio uključen u 12 *neurofeedback* treninga s elektrodama smještenim na F3 i F4 referentno u odnosu na Cz te 13 *neurofeedback* treninga s elektrodama smješte-

above zero). The neurofeedback training included 34 to 36 meetings over a period of two years. The results showed lower levels of depression on all clinical measurement scales. Repeated EEG measurements conducted on a female patient five months later showed that the learned changes in the EEG frontal asymmetry were maintained. The other patient was not available. The authors concluded that neurofeedback was an efficient addition to psychotherapy for the treatment of depression (30).

In their following paper, Baehr et al. used neurofeedback as a supplementary treatment for depression in addition to psychotherapy and medication. They reported that four out of the six respondents showed improvement on three items of the Beck Depression Inventory, the Minnesota Multiphasic Personality Inventory (MMPI-2) and the alpha asymmetry index. Two respondents did not meet all of the criteria, one developed side effects to medication, while another presented with a trend of symptom reduction. The authors stated that the neurofeedback treatment was not successful in all participants, and proposed further research which would include control groups. The authors suggested neurofeedback as a supplementary treatment method in addition to medication and psychotherapy, but certainly not as the only treatment for depression (31).

The case study conducted by Hammond introduced a new neurofeedback procedure, entitled Roshi. The author believed that other protocols, beside ALAY, could change the effects of frontal alpha asymmetry and thus reduce the symptoms of depression. The Roshi procedure consists of increasing the frequencies of beta brainwaves, while simultaneously inhibiting the alpha and theta frequencies. The respondent was included in 12 sessions of neurofeedback training, with electrodes positioned at F3 and F4, relative to the reference position Cz, and 13 sessions of neurofeedback training with electrodes positioned at C3 and C4. The results indicated reduced symptoms on the BDI depression scale, from 21 to 2 after four months of undergoing neurofeedback training. However, since the sample consisted of only one

nim na C3 i C4. Rezultati ukazuju na smanjenje pojave simptoma na BDI ljestvici za depresiju s 21 na 2 nakon četiri mjeseca *neurofeedback* treninga. Međutim, budući da je u uzorku bila samo 1 osoba, ti nalazi ne mogu reprezentativno predstavljati učinak metode (32).

Pet godina kasnije Hammond je koristio protokol korekcije alfa asimetrije za 9 Amerikanaca s teškom depresijom, ali nije prikazao srednje vrijednosti ili standardne devijacije, što znači da ovi nalazi također ne mogu reprezentativno predstavljati učinak metode. Sudionici s depresivnim poremećajem otpornim na medikamentnu terapiju bili su uključeni u *neurofeedback* terapiju tijekom 20 susreta po pola sata. Osam je pacijenata završilo trening bez druge psihoterapije. Sedam od osam pacijenata postiglo je značajna poboljšanja (na ljestvici depresije MMPI), a jedan je pacijent nakon pet susreta odustao. Autor zaključuje kako tretman depresije postupkom Roshi dovodi do smanjenja simptoma depresivnog poremećaja te predlaže daljnja kontrolirana eksperimentalna istraživanja (33).

Prvi kvantitativni EEG (*quantitative* EEG, qEEG) kao smjernicu u *neurofeedback* treningu kod depresije opisali su Walker, Lawson i Kozlowski u prikazu dvije studije slučaja. U prvom prikazu ispitanica je bila uključena u 16 *neurofeedback* treninga trenirajući beta 12 – 15Hz i snižavajući *theta* vrijednosti na C3 lokaciji. Nakon završenog treninga i poslije dvije godine ispitanica više nije imala depresivne simptome. U drugom prikazu slučaja ispitaniku koji se liječio od bipolarnog afektivnog poremećaja mijenjali su nekoliko *neurofeedback* protokola. Nakon treninga autor navodi kako su se kod ispitanika smanjili simptomi anksioznosti, iritabilnosti, ljutnje i depresivnosti, no ne navodi na koji način su promjene izmjerene. Pacijentov QEEG zapis nakon *neurofeedback* tretmana pokazao je promjene. Autor zaključuje kako QEEG može pomoći u određivanju individualnih protokola te na taj način ubrzati oporavak od depresivnog poremećaja (34).

individual, these results cannot represent the effect of the method (32).

Five years later, Hammond used the alpha asymmetry correction protocol on a sample of 9 Americans with severe depression, but did not present medium values or standard deviations, meaning that these findings could not represent the effect of the method either. Participants with treatment-resistant depression were included in neurofeedback therapy encompassing 20 half-hour sessions. Eight patients completed the training without other psychotherapy. Seven out of eight patients experienced significant improvement (on the MMPI depression scale), while one patient dropped out after five sessions. The author concluded that depression treatment with the Roshi procedure leads to a reduction of depressive symptoms, and suggested further controlled experimental research to be conducted (33).

The first quantitative EEG (qEEG) as a guideline for neurofeedback training in depression was described by Walker, Lawson and Kozlowski in their two case studies. In the first study, the female respondent underwent 16 sessions of neurofeedback training, training beta at 12 – 15Hz and lowering theta values at C3 location. After completing the training and after two years, the respondent no longer exhibited depressive symptoms. In the second case study, several different neurofeedback protocols were applied on a patient who was treated for bipolar affective disorder. After training, the author stated that the patient experienced fewer symptoms of anxiety, irritability, anger and depression, but he did not state in which manner the changes were measured. Changes were observable on the patient's QEEG report after the neurofeedback treatment. The author concluded that QEEG could assist in determining the individual protocols, and in this way accelerate recovery in depressive disorder (34).

Dias and van Deusen provided an overview of the neurofeedback protocols for depression, with a suggestion of a new, their own, protocol. The protocol focused on the symptoms presented by the

Pregled *neurofeedback* protokola za depresiju, uz prijedlog novog vlastitog protokola prikazuju Dias i van Deusen. Protokol je bio usmjeren na simptome koje je ispitanik pokazivao s obzirom na QEEG mjerenje. Autori predlažu spajanje dosadašnjih protokola alfa asimetrije te *theta* – beta omjer na lijevom prefrontalnom korteksu. Povećavali su desnostranu alfa asimetriju (koja je bila usmjerena na povećanje pozitivnog ponašanja) i lijevostrani prefrontalni beta – *theta* omjer (koji je usmjeren na poboljšanje kognitivnih i motivacijskih funkcija), a smanjivali su visoku betu u prefrontalnom korteksu (usmjerenu na smanjivanje anksioznosti). Istraživanje je provedeno tijekom 10 *neurofeedback* treninga u trajanju od sat vremena, a istovremeno su se primjenjivala sva tri *neurofeedback* kriterija na F3 i F4 smještaju elektroda. Potkrepljujući zvuk čuo se kada su bila zadovoljena sva tri kriterija. Upitnik samoprocjene depresivnog stanja ispitanik je ispunjavao nakon svakog *neurofeedback* treninga. Novi protokol, prema riječima autora, bio je djelomično uspješan: uspjeh da se zadrže sva tri *neurofeedback* kriterija porastao je s početnih 15 % na 26 % na kraju tretmana, dok je smanjenje simptoma u odgovorima na upitnik samoprocjene iznosilo 43 %. Rezultat u upitniku samoprocjene zadržao se jedan mjesec nakon istraživanja. Autori predlažu povećanje broja *neurofeedback* tretmana (35).

Ghosh, Jahan i Singh prikazali su primjenu *neurofeedback* tretmana kod 39-godišnjeg ispitanika iz Indije koji se liječio od ovisnosti o alkoholu, anksioznosti i depresivnosti. Prije uključivanja u *neurofeedback* trening ispitanik je podučen o progresivnom treningu opuštanja kako bi se naučio samostalno opustiti bez podrške terapeuta. Ispitanik je bio uključen u 10 *neurofeedback* treninga u trajanju od 40 minuta. Sam protokol *neurofeedback* treninga u radu nije bio opisan. Autori primjećuju trend smanjenja simptoma na upitnicima anksioznosti i depresivnosti (BDI je inicijalno iznosio 23, finalno 19) te poboljšanje rezultata na kognirespondent in regard to the QEEG measurement. The authors suggested merging the previous alpha asymmetry protocols and the theta-beta ratio in the left prefrontal cortex. They increased the alpha asymmetry on the right side (which aimed at increasing positive behavior) and the theta-beta ratio in the left prefrontal cortex (aimed at improving the cognitive and motivational functions), and decreased the high beta activity in the prefrontal cortex (aimed at reducing anxiety). The study was conducted over 10 one-hour neurofeedback training sessions, and all three neurofeedback criteria were simultaneously applied at F3 and F4 electrode positions. A reinforcing sound was played when all three criteria were met. The patient filled out the depression self-assessment questionnaire after every neurofeedback training session. According to the authors, the new protocol, was a partial success: the success rate in maintaining all three neurofeedback criteria increased from the starting 15% to 26% at the end of the treatment, while the self-assessment questionnaire showed a 43% symptom decrease. The self-assessment questionnaire results were maintained for one month after the study. The authors suggested increasing the number of neurofeedback treatments (35).

Ghosh, Jahan and Singh observed the application of neurofeedback treatment on a 39-year-old patient from India, who was being treated for alcohol addiction, anxiety and depression. Before starting the neurofeedback training sessions, the respondent was taught progressive relaxation training in order to learn how to relax on his own, without support from the therapist. The respondent underwent ten 40-minute neurofeedback training sessions. The neurofeedback training protocol was not described in the paper. The authors observed a trend of symptom reduction on the anxiety and depression questionnaires (BDI initially amounted to 23, and finally to 19), as well as an improvement in the cognitive test results. The respondent also significantly reduced his alcohol consumption. Based on the graphs of the arithmetic means of alpha, theta, and beta frequencies, the authors observed lower frequen-

tivnim testovima. Ispitanik je također značajno smanjio konzumaciju alkohola. Na temelju grafova aritmetičkih sredina alfa, *theta* i beta frekvencija autori su primijetili snižavanje frekvencija tijekom 10 susreta pa zaključuju kako je *neurofeedback* tretman imao važnu ulogu u pacijentovu oporavku i predlažu daljnja istraživanja na većem uzorku i s pacijentima koji pate od drugih psihijatrijskih poremećaja (36).

Posljedice alfa frontalnog *neurofeedbacka* na depresiju ispitivala je Nazarian u svojoj doktorskoj disertaciji. Istraživanje je na početku uključivalo 19 sudionika. Ispitanici su trebali biti uključeni u 36 *neurofeedback* treninga triput/tjedan u trajanju od pola sata (elektrode su bile postavljene na F3 i F4, a referentno na Cz). Zadatak ispitanika bio je povisiti glasnoću tona tijekom tretmana, a ton se javljao kada su ispitanici uspjeli povisiti desnostranu alfa aktivnost, što bi podrazumijevalo jaču lijevostranu frontalnu aktivaciju (s obzirom da su alfa snaga i kortikalna aktivnost obrnuto povezane). U studiju je bilo uključeno 19 ispitanika. Autorica navodi kako je 12 ispitanika odustalo unutar prvih 12 susreta, ostali ispitanici prošli su *neurofeedback* trening, ali je odustajanje ispitanika značajno utjecalo na izvorni nacrt istraživanja. Mjerni instrumenti, Beckov upitnik depresije (BDI), Hamiltonova ljestvica depresivnosti (HAM-D), Penn State upitnik zabrinutosti (*Penn State Worry Questionnaire*) te *Inventar depresivne simptomatologije*, primjenjivali su se svaka dva tjedna. Ni kod jednog od 7 sudionika nije dobivena statistički značajna povezanost frontalne EEG asimetrije i rezultata na mjernim instrumentima (r nije prelazio 0.38, $p > 0.05$). Inventar depresivne simptomatologije nije pokazao značajno smanjenje simptoma ($F(6,30) = 2,11$, $p > 0,05$), dok je BDI pokazao statistički značajno smanjenje simptoma ($F(5,25) = 6,95$, $p < 0,05$). Autorica je provjeravala utjecaj *neurofeedback* treninga na promjenu u frontalnoj asimetriji, no nisu dobiveni statistički značajni rezultati (svi $p > 0,05$).

cies over 10 sessions, and therefore concluded that the neurofeedback treatment had a significant role in the patient's recovery, suggesting further research to be conducted on a larger sample and with patients suffering from other psychiatric disorders (36).

The effects of frontal alpha neurofeedback on depression were studied by Nazarian in her doctoral dissertation. The study initially involved 19 participants. They were intended to undergo 36 neurofeedback training sessions three times a week, each lasting half an hour (the electrodes were positioned at F3 and F4, relative to the reference position Cz). The respondents' task was to increase the sound volume during the treatment, and the sound was played when the respondents managed to increase the alpha activity on the right side, which would imply a stronger left frontal activation (given that alpha power and cortical activity are inversely related). A total of 19 respondents took part in the study. The author stated that 12 respondents dropped out during the first 12 sessions, while the other respondents underwent neurofeedback training. However, the withdrawal of respondents had a significant impact on the original research design. The measuring instruments, the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Penn State Worry Questionnaire and the Inventory for Depressive Symptomatology were applied every two weeks. No statistically significant association between frontal EEG asymmetry and psychometric results was obtained in any of the 7 participants (r never exceeded 0.38, $p > 0.05$). The Inventory for Depressive Symptomatology showed no significant symptom reduction ($F(6.30) = 2.11$, $p > 0.05$), while the BDI showed statistically significant symptom reduction ($F(5.25) = 6.95$, $p < 0.05$). The author examined the effect of neurofeedback training on the change in frontal asymmetry, however no statistically significant results were obtained (all at $p > 0.05$). The assumption is that statistically significant results were not obtained due to a small number of respondents, while the significant reduction in BDI can be explained by other factors, and not only by

Pretpostavka je da je uzrok rezultata koji nisu statistički značajni bio mali broj ispitanika, a značajno smanjenje na BDI može se objasniti i drugim čimbenicima, a ne samo *neurofeedback* treningom. Na primjer, ispitanici su navodili kako se tijekom *neurofeedback* treninga osjećaju opušteno te da im se sviđa podržavajući pristup tijekom istraživanja. Zapaženo je da nakon 18 *neurofeedback* treninga krivulja pozitivno potkrepljujućih zvukova nije došla do kritične vrijednosti odnosno ispitanici nisu naučili što povisuje ton (svi $p > 0.05$), što kod depresivnih sudionika može biti obeshrabrujuće. Rezultati ovog istraživanja ne podupiru povezanost promjena raspoloženja ispitanika i promjena u alfa frontalnoj asimetriji (37).

Choi i suradnici primijenili su protokol korekcije alfa asimetrije kako bi izmjerili učinke *neurofeedbacka* na depresiju. Istraživanje su proveli na 24 ispitanika koja su bila podijeljena u kontrolnu i eksperimentalnu skupinu. Tijekom pet tjedana u eksperimentalnoj skupini primjenjivan je *neurofeedback* trening dva put/tjedan, dok je u kontrolnoj skupini primjenjivan trening placebo psihoterapije. Cilj je *neurofeedback* treninga bio da ispitanici održavaju kontinuitet klasične glazbe koja se javljala kada bi individualni indeks frontalne alfa asimetrije bio veći od nule, što označava smanjenje neugodnih emocija. Elektrodama su mjerili frontalnu alfa asimetriju na lokacijama F3 i F4 te referentno na Cz. Koristili su upitnike samoprocjene i procjenu kognitivnog funkcioniranja. U eksperimentalnoj skupini dobivena je statistički značajna razlika u indeksu alfa frontalne asimetrije prije i poslije treninga, tj. povećanju desnostrane frontalne alfa snage. Prosječna razina depresivnih simptoma prije primjene *neurofeedbacka* u ovoj studiji bila je 22,75 (SD = 12,35), a nakon primjene *neurofeedbacka* razina simptoma pala je na prosjek od 9,08 (SD = 6,92). Veličina učinka ovog smanjenja bila je $d = -1,32$ što je pokazatelj vrlo velikog učinka, a smanjenje je bilo statistički značajno pri $p < 0,001$. U kontrolnoj

neurofeedback training. For example, the respondents stated that they felt relaxed during neurofeedback training sessions, and that they liked the supportive approach provided in the course of the research. It was observed that after 18 neurofeedback training sessions the curve of positive reinforcing sounds did not reach a critical value, i.e. the respondents did not learn what raised the tone (all at $p > 0.05$), which can be discouraging in depressed participants. The results of this study did not support a connection between the respondents' mood changes and changes in the frontal alpha asymmetry (37).

Choi et al. applied the alpha asymmetry correction protocol in order to measure the effects of neurofeedback on depression. The study was conducted on 24 respondents, divided into a control and an experimental group. In the course of five weeks, neurofeedback training was applied in the experimental group two times a week, while placebo psychotherapy training was conducted in the control group. The goal of neurofeedback training was for the respondents to maintain the continuity of classical music which played when the individual frontal alpha asymmetry index was greater than zero, signifying reduced unpleasant emotions. Electrodes were used to measure the frontal alpha asymmetry on locations F3 and F4, and relative to Cz. They used self-assessment questionnaires and cognitive functioning assessment. A statistically significant difference was obtained in the experimental group in terms of the frontal alpha asymmetry index before and after training sessions, i.e. an increase of alpha power in the right frontal region. The average level of depressive symptoms before neurofeedback application in this study amounted to 22.75 (SD = 12.35), while after neurofeedback application the symptom level decreased to an average 9.08 (SD = 6.92). The size of the effect of this reduction amounted to $d = -1.32$, indicating a very high effect, and the reduction was statistically relevant at $p < 0.001$. No statistically significant differences were found in the control group before and after training sessions, and the authors did not provide any specific data. Furthermore,

skupini nisu pronađene statistički značajne razlike prije i poslije treninga, a autori u radu ne iznose konkretne podatke. Također, u retestiranju nakon mjesec dana nije došlo do promjena fizioloških, kliničkih i kognitivnih mjera u odnosu na rezultate poslije tretmana, što autori smatraju pokazateljem da su se nastale promjene zadržale. Ova studija ukazuje na mogućnost da bi EEG *biofeedback* mogao biti obećavajući alternativni tretman za depresivne pacijente kod kojih je zbog nuspojava otežano standardno farmakološko liječenje. Autori naglašavaju da bi studija s dovoljno velikim uzorkom i placebom kontroliranim dizajnom te ponovljenim ispitivanjima potvrdila valjanost asimetričnog *neurofeedback* treninga (38).

Peeters i suradnici proveli su istraživanje na devet ispitanika s teškim depresivnim poremećajem (*major depressive disorder*). Ispitanici su bili uključeni u 30 *neurofeedback* treninga s ciljem smanjivanja frontalne alfa asimetrije, a elektrode su bile smještene na položaje F3 i F4. Prije svakog treninga primijenjen je *Kratki upitnik depresivnosti* (QIDS-SR16). Upitnik QIDS-SR16 (*Quick Inventory of Depressive Symptomatology – Self-Report*, 16) alat je za samoprocjenu depresije. Razvili su ga John Rush i suradnici, a koristi se za brzo mjerenje težine depresivnih simptoma. Za analizu frontalne alfa asimetrije korištena je višerazinska regresijska analiza kojom je utvrđeno značajno sniženje prosječnih rezultata u frontalnoj alfa asimetriji tijekom 30 tretmana ($p < 0,01$). Prosječni rezultati u upitniku depresivnosti QIDS-SR16 bili su značajno sniženi ($p < 0,05$) nakon 30 tretmana te su bili povezani s padom u alfa asimetriji ($p < 0,001$). Autori su ispitali i promjene u alfa asimetriji tijekom jednog *neurofeedback* tretmana i prikazali kako alfa asimetrija ima značajan linearni i kvadratični učinak, tj. pada do pete minute treninga (od ukupno osam minuta) nakon čega ponovno počinje polagano rasti. Na kraju svih *neurofeedback* tretmana jedan sudionik izvijestio je o pozitivnom odgovoru na *neurofeedback* in retesting after a month, there were no changes to the physiological, clinical and cognitive measures in relation to the results obtained after the treatment, which the authors considered to be an indication that the changes were maintained. This study points to the possibility that EEG biofeedback could be a promising alternative treatment for depressed patients who due to side effects experience difficulty when receiving standard pharmacological treatment. The authors highlighted that a study with a large enough sample and a placebo-controlled design and repeated testing would confirm the validity of asymmetry neurofeedback training (38).

Peeters et al. conducted a study on nine respondents suffering from major depressive disorder. The respondents underwent 30 neurofeedback training sessions with the aim of reducing frontal alpha asymmetry, and the electrodes were positioned at F3 and F4. The Quick Inventory of Depressive Symptomatology – Self-Report, 16 (QIDS-SR16) was applied before every training session. The QIDS-SR16 is a tool used for the self-assessment of depression. It was developed by John Rush et al., with the aim to quickly assess the severity of depressive symptoms. A multilevel regression analysis was used to analyze the frontal alpha asymmetry, determining a significant reduction of average frontal alpha asymmetry scores in the course of 30 treatments ($p < 0.01$). The average scores in the QIDS-SR16 depression questionnaire were significantly lower ($p < 0.05$) after 30 treatments, and were associated with a decrease in alpha asymmetry ($p < 0.001$). The authors also examined the changes in alpha asymmetry during one neurofeedback treatment, and presented that alpha asymmetry has a significant linear and quadratic effect, i.e. it decreases until the fifth minute of training (out of eight minutes in total), after which it starts to slowly increase again. Upon the completion of all neurofeedback treatments, one participant reported having a positive response to the neurofeedback treatment, four experienced a remission of depressive symptoms, two had dropped out during the treatment, and the remaining two did not

tretman, četvero ih je izvijestilo o remisiji depresivnih simptoma, dvoje ih je odustalo tijekom tretmana, dok preostalih dvoje nisu imali nikakav pomak u razini depresivnih simptoma. Autori zaključuju kako je *neurofeedback* bio djelomično uspješan tretman depresivnosti. Kako je istraživanje bilo ograničeno malim brojem sudionika te nekontroliranim metodološkim čimbenicima, predlažu provođenje novog istraživanja s većim brojem sudionika raspoređenih slučajnom raspodjelom u eksperimentalnu i kontrolnu skupinu (39).

Temeljna ideja treninga asimetrije korištena je i u istraživanju Cheona i suradnika. Autori su proveli istraživanje s ciljem ispitivanja utjecaja *neurofeedback* tretmana na promjene u izraženosti depresivnih simptoma i EEG pokazatelja kod pacijenata s depresivnim poremećajem. U istraživanju je sudjelovalo dvadeset ispitanika koji su *neurofeedback* trening provodili dva do tri put/tjedan tijekom razdoblja od dva mjeseca. Protokol tretmana obuhvaćao je 30-minutni trening beta aktivnosti na F3 lokaciji te regulaciju alfa/*theta* omjera na Pz lokaciji u istom trajanju. Za procjenu učinkovitosti tretmana korišteni su *Globalni indeks težine kliničkog stanja* (*Clinical Global Impression-Severity*, CGI-S) te Hamiltonova i Beckova ljestvica za procjenu anksioznosti i depresije. Mjere su prikupljene prije početka tretmana, nakon četiri tjedna te nakon završetka intervencije. Rezultati su pokazali statistički značajno smanjenje simptoma depresije i anksioznosti na svim upitničkim ljestvicama već nakon četiri tjedna, a poboljšanje se nastavilo do kraja tretmana. Navode ograničenja provedenog istraživanja: mali broj ispitanika, izostanak kontrolne skupine i izostanak dugoročnog praćenja ispitanika (40).

Mennella i suradnici primijenili su Alpha protokol korekcije asimetrije kako bi izmjerili učinke *neurofeedbacka* na smanjenje depresije u uzorku od 16 odraslih osoba koristeći BDI mjeru depresije. Srednja vrijednost depresije prije primjene *neurofeedbacka* u ovoj studiji bila je 9,75

experience any shift in the depressive symptom levels. The authors concluded that neurofeedback was partially successful in treating depression. Since the study was limited by a small number of participants and uncontrolled methodological factors, they proposed conducting a new study with a larger number of participants who would be placed into experimental and control groups by random assignment (39).

The fundamental idea of asymmetry training was also used in a study conducted by Cheon et al. The authors conducted the study in order to examine the effects of neurofeedback treatments on the changes in the severity of depressive symptoms and EEG indicators in patients with depressive disorder. A total of 20 respondents took part in the study, and they underwent feedback training sessions two to three times a week over a period of two months. The treatment protocol encompassed 30-minute training of beta activity at F3, and regulation of the alpha/theta ratio at Pz location in the same duration. The Clinical Global Impression-Severity (CGI-S) scale and Hamilton and Beck's scales for anxiety and depression assessment were used to verify the effectiveness of the treatment. The measures were collected before the treatment started, then after four weeks, and finally after the intervention had ended. The results showed a statistically significant reduction of depression and anxiety symptoms in all questionnaire scales after four weeks already, while the improvement continued until the end of the treatment. They listed the following limitations of the conducted study: a small number of respondents, lack of control group and lack of long-term follow-ups of the respondents (40).

Manella et al. applied the alpha asymmetry correction protocol in order to measure the effects of neurofeedback on the reduction of depressive symptoms on a sample of 16 adults by using the BDI depression measure. The mean value of depressive symptoms before neurofeedback application in this study amounted to 9.75 (SD = 12.38); while after neurofeedback application the symptom level decreased to an average 6.00 (SD = 7.90). The size of the effect of this drop

(SD = 12,38); nakon primjene *neurofeedbacka* depresija je pala na prosjek od 6,00 (SD = 7,90). Veličina učinka ovog pada bila je d = -0,35, što ukazuje na mali učinak, a pad je bio statistički značajan pri p < 0,05. Studija Mennella i sur. stoga je poduprla tvrdnju da *neurofeedback* smanjuje depresiju (41). Sažetci istraživanja zadnjih pet godina prikazani su u tablici 1.

Grin-Yatsenko i suradnici predstavili su tri studije slučaja u kojima su procijenili učinke infra-niskog *neurofeedbacka* na depresiju. Jedna sudionica i dva sudionika pokazivali su simptome depresivnog poremećaja; nitko se nije obratio liječniku niti je uzimao lijekove protiv depresije. Osnovno istraživanje sastojalo se od ljestvica za ocjenjivanje depresije: Montgomery-Åsbergova ljestvica za ocjenjivanje depresije (MADRS), Hamiltonova ljestvica depresije (HAM-D) i Beckov upitnik depresije (BDI). ILF-*Neurofeedback* korišten je pozicioniranjem elektrode na T4 – P4 i T4 – Fp2 tijekom prvih susreta; naknadno su dodane elektrode na T4 – amounted to d = -0.35, indicating a very small effect, and the drop was statistically relevant at p < 0.05. The study by Mennella et al., therefore, confirmed the hypothesis that the use of neurofeedback reduces depression (41). Summaries of the studies conducted in the last five years are presented in Table 1.

Grin-Yatsenko et al. presented three case studies in which they estimated the effects of infra-low neurofeedback on depression. One female and two male participants presented symptoms of depressive disorder; none had gone to a doctor or taken antidepressant medications. The basic research consisted of the following depression assessment scales: the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HAM-D) and the Beck Depression Inventory (BDI). ILF-neurofeedback was used by positioning the electrodes at T4 – P4 and T4 – Fp2 in the first sessions; electrodes were additionally added at T4 – T3 and T3 – Fp1. After 20 neurofeedback training sessions, each lasting between 30 to 45 minutes, all three pa-

**TABLICA 1.** Prikaz sažetaka istraživanja (ukupno 6 studija) o učinkovitosti *neurofeedback* tretmana kod depresivnog poremećaja objavljenih unutar posljednjih 10 godina (2019-2021).
**TABLE 1.** Summaries of the studies (6 studies in total) on the effectiveness of neurofeedback treatment in depressive disorder, published within the last 10 years (2019-2021).

| Autor / Author | NF protokol / NF protocol | Uzorak / Sample | Mjerni instrument / Measuring instrument | Inicijalno NF / Initial NF M (SD) | Finalno NF / Final NF M (SD) |
|---|---|---|---|---|---|
| Wang et al. (42) | Alfa asimetrija / Alpha asymmetry | 24 | BDI | 30.25 (8.39) | 19.83 (12.02) |
| Takamura et al. (43) | rftMRI-NF | 6 | BDI | 28.70 (8.57) | 17.20 (6.12) |
| Yu et al. (44) | 10-11 Hz povećanje aktivnosti na *Fp1 i Fp2* / 10-11 Hz activity increase at Fp1 and Fp2 | 14 | BDI | 24.90 (8.25) | 16.80 (9.24) |
| Zotev et al. (45) | rtfMRI-EEG-NF | E = 18<br>K = 8 | POMS | 15.40 (14.00) | 7.75 (10.10) |
| Hariss et al. (46) | Nespecifični *neurofeedback* / Nonspecific neurofeedback | 11 | BDI | 10.55 (9.66) | 5.64 (6.86) |
| Hou et al. (47) | Alfa asimetrija / Alpha asymmetry Lijevi parijetalni režanj / Left parietal lobe | 13 | BDI | 20.23 (0.47) | 12.08 (7.33) |
| Hou et al. (47) | Alfa asimetrija / Alpha asymmetry Desni parijetalni režanj / Right parietal lobe | 13 | BDI | 17.69 (7.24) | 10.31 (5.98) |

Legenda: rtfMRI-EEG-NF (*real-time fMRI and EEG neurofeedback*) – *neurofeedback* u stvarnom vremenu temeljen na istodobnom snimanju funkcionalne magnetske rezonancije i elektroencefalografije. POMS (*Profile of Mood States*) – Profil stanja raspoloženja.
/ Legend: rtfMRI-EEG-NF (*real-time fMRI and EEG neurofeedback*) – neurofeedback in real time, based on a simultaneous recording of functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG). POMS – Profile of Mood States

T3 i T3 – Fp1. Nakon 20 *neurofeedback* treninga, svakog u trajanju od 30 do 45 minuta, sva tri pacijenta pokazala su poboljšanje raspoloženja i vještina samoorganizacije, smanjenu anksioznost, kao i povećanu emocionalnu stabilnost i otpornost. Posebno se promijenio rezultat profila depresije slučajeva A i B tijekom drugog testiranja pri čemu su se sve ljestvice poboljšale za najmanje 90 %, a slučaj C pokazao je poboljšanje od najmanje 70 %. Rezultat profila depresije za sva tri sudionika nije ukazivao na depresiju i poboljšanja su bila stabilna godinu dana nakon početka ILF *neurofeedback* terapije. Prema autorima, ova je studija također pokazala da je trening doveo do promjene u moždanoj aktivnosti, posebno do smanjenja *theta* aktivnosti u frontalnim i središnjim područjima u pasivnim stanjima (48). I drugi rad Grin-Yatsenka i suradnika pokazao je pozitivne učinke ILF-treninga na 8 ispitanika sa širokim popisom simptoma (umor, depresivno raspoloženje, simptomi unutarnje napetosti, promjene raspoloženja, glavobolja, problemi sa spavanjem, smanjena pozornost i slabo radno pamćenje). Elektrode su postavljene na T4 – P4, T4 – T3 i, naknadno, T4 – Fp2 i T3 – Fp1. Nakon 20 ILF-*neurofeedback* treninga svi su sudionici prijavili poboljšanje svog stanja: smanjenje unutarnje napetosti, reaktivnosti na stresne čimbenike, stabilnost raspoloženja, poboljšanu svijest o tijelu i prostoru, povećanje razine energije i kognitivnih performansi (49). Na temelju prikazanih studija moguće je sagledati glavne prednosti, ali i metodološka ograničenja primjene *neurofeedback* metode kod depresije.

## RASPRAVA

*Neurofeedback* je relativno nova metoda koja se sve češće primjenjuje u liječenju psihičkih poremećaja. Ovu je metodu putem znanstvenih istraživanja važno približiti stručnoj, ali i široj javnosti. Cilj ove rasprave jest pružiti novi doprinos razumijevanju i primjeni *neurofeedback* metode u kliničkom kontekstu.

tients showed improvements in terms of their moods and self-organization skills, as well as reduced anxiety and improved emotional stability and resilience. The results of depression profiles in the A and B cases particularly changed in the second testing, whereby all scales showed an improvement of at least 90%, while case C showed an improvement of at least 70%. The depression profile results in all three participants did not indicate depression, and the improvements were stable a year after starting the ILF neurofeedback therapy. According to the authors, this study also showed that the training led to changes in the brain activity, particularly to a reduction of theta activity in the frontal and central areas of the brain in passive states (48). Another paper written by Grin-Yatsenka et al. presented positive effects of the ILF training on eight respondents with a wide range of symptoms (fatigue, depressive mood, internal tension symptoms, mood changes, headaches, difficulty sleeping, reduced attention and poor working memory). The electrodes were positioned at T4 – P4, T4 – T3, and subsequently at T4 – Fp2 and T3 – Fp1. After 20 ILF-neurofeedback training sessions, all the participants reported improvements in their conditions: lower internal tension, reactivity to stressors, mood stability, improved body and spatial awareness, increased energy levels and cognitive performances (49). Based on the presented studies, it is possible to review the main advantages, as well as the methodological limitations, of applying the neurofeedback method in depression treatment.

## DISCUSSION

Neurofeedback is a relatively new method, which is increasingly being used in the treatment of mental disorders. It is important to present this method to the professional, but also wider public, through scientific research. The aim of this discussion is to provide a new contribution to the understanding and application of the neurofeedback method in the clinical context.

Jedan od glavnih problema s kojim se istraživači suočavaju jest osipanje sudionika u istraživačkom uzorku. U svojoj doktorskoj disertaciji Nazarian detaljno opisuje ovu pojavu. Od planiranih 138 ispitanika samo ih je 19 započelo *neurofeedback* trening, dok je svega 6 ispitanika dovršilo eksperiment. *Neurofeedback* zahtijeva visoku razinu motivacije, redovitost i ustrajnost, što je izazov i razlog osipanja ispitanika. U konkretnom istraživanju, uzorak od 60 ispitanika skupljao se tijekom pet godina. Kako navodi Nazarian, mnogi su sudionici odustali jer nisu razumjeli kako metoda djeluje, a zahtijevala je znatan vremenski angažman.

Pojednostavljenje terminologije i jasnija komunikacija mogli bi pomoći u povećanju zadržavanja sudionika tijekom tretmana. Uz obrazovanje, i dob sudionika može imati ulogu – mlađe osobe, sklonije tehnologiji, potencijalno su motiviranije i rjeđe odustaju od tretmana.

Prva istraživanja o *neurofeedbacku* bila su uglavnom prikazi slučajeva. Premda ograničena metodološki, pružila su vrijedan kvalitativni uvid u iskustva korisnika. Sudionici su najčešće imali depresivni poremećaj, često u komorbiditetu s drugim stanjima, poput anksioznosti, bipolarnog poremećaja, alkoholizma ili posljedica moždanog udara. Takvi slučajevi otežavaju donošenje zaključaka o učinkovitosti metode kod izolirane depresije.

Escolano i sur. navode da čak 80 % osoba s depresijom ima i anksiozni poremećaj, dok drugi autori uopće ne navode podatke o komorbiditetima ili navode da su ih isključili. Zbog toga je u istraživanjima nužno sustavno ispitivati i jasno prikazivati komorbiditete.

U literaturi se uočava velika raznolikost u kriterijima uključivanja i isključivanja sudionika. Neki autori isključuju sudionike zbog lijevorukosti, prisutnosti organskih oštećenja, istodobne farmakoterapije ili uključivanja u psihoterapiju što otežava međusobnu usporedbu

One of the main problems for researchers is the dropout of participants in the research sample. In her doctoral dissertation, Nazarian describes this phenomenon in detail. Out of the planned 138 respondents, only 19 started their neurofeedback training, while a mere 6 of them finished the experiment. Neurofeedback requires a high level of motivation, regularity and persistence, which represents a challenge and is the reason for the participant dropouts. In this specific study, a sample of 60 respondents was collected over a period of five years. According to Nazarian, many participants dropped out because they did not understand the functioning of the method, and it required a significant time commitment.

Simplifying the terminology and ensuring clearer communication could help increase participants' retention during the treatment. In addition to education, the participants' age could also play a role – younger individuals, more inclined to technology, are potentially more motivated and less likely to give up on the treatment.

The first neurofeedback studies were mainly case studies. Although they were methodologically limited, they offered a valuable qualitative insight into the users' experiences. The participants most often suffered from depressive disorder, often in comorbidity with other conditions such as anxiety, bipolar disorder, alcoholism or consequences of a stroke. Such cases make it difficult to draw conclusions in regard to the effectiveness of the method in isolated depression.

Escolano et al. observed that as many as 80% of patients with depression also suffered from anxiety disorder, while other authors did not present any data on comorbidities or stated that they had excluded them. Due to the aforementioned, it is necessary to conduct systemic research and provide a clear presentation of comorbidities in the studies.

There is a great variety of inclusion and exclusion criteria for the participants in the literature. Some authors exclude participants due to left-handedness, presence of organic defects, concomitant pharmacotherapy or inclusion in psychotherapy,

rezultata. Broj *neurofeedback* treninga varira od 5 do 30, a trajanje se kreće od 15 do 60 minuta. U prosjeku, istraživanja uključuju 15 tretmana, a Peeters i suradnici među rijetkima su koristili maksimalnih 30 tretmana. U ovom istraživanju sudionici su prošli 15 treninga u trajanju od 20 minuta. Postavlja se pitanje optimalnog broja i trajanja tretmana kako bi se postigli značajni učinci. Iako neka istraživanja ukazuju da je potrebno barem 20 seansi, ovo područje ostaje nedovoljno istraženo.

Gotovo sva istraživanja koriste samoprocjenske mjere poput ljestvica BDI i MADRS. Iako korisne, one su podložne subjektivnosti i nedostatku objektivizacije.

Primijenjeni *neurofeedback* protokoli međusobno se značajno razlikuju – od protokola temeljenih na frontalnoj alfa asimetriji, preko funkcionalne magnetske rezonancije u stvarnom vremenu (fMRI *neurofeedback*) do treninga u infra-niskim frekvencijama (ILF). Ova raznolikost otežava sistemsku analizu učinkovitosti metode. Zbog toga APA i dalje navodi da je razina učinkovitosti *neurofeedbacka* u tretmanu depresije od 2 do 5 („možda učinkovito“). To ne znači da *neurofeedback* nije učinkovit, već da su potrebna dodatna istraživanja s kontrolnim skupinama.

Batail i suradnici ističu kako većina istraživanja ne izvještava o procesima koji dovode do kliničke učinkovitosti niti o učenju koje se odvija tijekom treninga. Gaume i suradnici predlažu sveobuhvatan, transdisciplinaran model istraživanja mehanizama *neurofeedbacka* uključujući biomedicinsku, inženjersku, psihološku i neuroznanstvenu perspektivu.

Određena istraživanja ukazuju na potencijalnu učinkovitost *neurofeedbacka* u kombinaciji s psihoterapijom, no za takve tvrdnje nedostaje dovoljno znanstvenih dokaza.

U Hrvatskoj se *neurofeedback* trening može provoditi u zdravstvenim ustanovama i brojnim privatnim praksama. Na tržištu postoji

which makes it difficult to compare results. The number of neurofeedback training sessions varies from 5 to 30, and the duration spans from 15 to 60 minutes. The studies, on average, include 15 treatments, and Peeters et al. were among the rare ones who used the maximum 30 treatments. In this study, the participants underwent 15 training sessions, each lasting 20 minutes. The question arises as to the optimal number and duration of treatments necessary to achieve significant effects. Although some studies indicate that at least 20 sessions are necessary, this area remains underexplored.

Almost all studies use self-assessment measures such as the BDI and MADRS scales. Although useful, they are often subjective and lack objectivization.

The applied neurofeedback protocols differ significantly – from protocols based on frontal alpha asymmetry, through functional magnetic resonance imaging in real time (fMRI neurofeedback) to infra-low frequency training. This diversity makes it difficult to systematically analyze the effectiveness of the method. For this reason, APA still states that the effectiveness level of neurofeedback in depression treatment ranges from 2 to 5 (“possibly efficacious”). This does not mean that neurofeedback is not effective, but that additional research that would include control groups is necessary.

Batail et al. emphasized that most studies report neither on the processes leading to clinical effectiveness, nor on the learning processes that develop during the training. Gaume et al. proposed a comprehensive, transdisciplinary model for neurofeedback mechanism research, including biomedical, engineering, psychological and neuroscientific perspectives.

Certain studies pointed to a potential effectiveness of neurofeedback in combination with psychotherapy, however there is insufficient evidence for such claims.

In Croatia, neurofeedback training can be conducted in medical institutions and numerous

više od 15 različitih softverskih rješenja. Istraživači koriste različite uređaje – od komercijalno dostupnih, jednostavnih za korištenje, ali s lošijom kvalitetom signala – do sofisticiranijih koji zahtijevaju dodatnu kalibraciju. Ramirez i suradnici preporučuju upotrebu naprednijih uređaja u budućim istraživanjima. Do danas nije provedena komparativna studija u kojoj bi se usporedila kvaliteta tih uređaja.

Pitanje postavljanja kriterija za kritične vrijednosti povratnih informacija također je važno. Upute koje sudionici dobivaju tijekom tretmana značajno se razlikuju – od preciznih zadataka (npr. „podignite stupac“) do sugestivnih uputa („opustite se“). Peeters i suradnici zaključuju da mentalne strategije poput opuštanja nisu učinkovite u povećanju željene moždane aktivnosti. Ovo područje ostaje nedovoljno istraženo i zaslužuje veću pažnju u budućim istraživanjima. Autori također opisuju da su se sudionici, ovisno i izvedbi, tijekom tretmana osjećali istovremeno kompetentno i frustrirano.

## ZAKLJUČAK

*Neurofeedback* se čini obećavajućom metodom u liječenju depresivnog poremećaja, no postoje značajne metodološke prepreke koje otežavaju generalizaciju rezultata i precizno određivanje njegove učinkovitosti. Glavni izazovi u istraživanju *neurofeedback* metode uključuju visoku stopu osipanja sudionika, različite kriterije uključivanja i isključivanja ispitanika te heterogenost *neurofeedback* protokola i uređaja. Unatoč sve većem broju istraživanja i dalje nisu jasno definirani optimalni parametri poput broja i trajanja *neurofeedback* treninga, što otežava formuliranje jasnih smjernica za kliničku primjenu.

Buduća istraživanja trebala bi se usmjeriti na poboljšanje eksperimentalnog dizajna, povećanje reprezentativnosti uzoraka, standardizaciju protokola i objektivizaciju mjernih instrume-

medical private practices. There are more than 15 different software solutions in the market. The researchers use various devices – from commercially available, simple to use devices which, however, have poorer signal quality – to more sophisticated ones that require additional calibration. Ramirez et al. recommended the use of more advanced devices in future research. No comparative studies have been conducted so far to compare the quality of these devices.

The issue of setting the criteria for the critical values of feedback is also important. The instructions that the participants receive during treatment also significantly vary – from precise tasks (e.g. “raise the column”) to suggestive instructions (“relax”). Peeters et al. concluded that mental strategies such as relaxation were not effective in increasing the desired brain activity. This area remains insufficiently researched and deserves more attention in future research. The authors also described that, depending on their performance, the participants felt both competent and frustrated during the treatment.

## CONCLUSION

Neurofeedback appears to be a promising method in the treatment of depressive disorder, however there are significant methodological obstacles that hinder the generalization of results and a precise determination of its effectiveness. The main challenges in researching the neurofeedback method include high participant dropout rates, different inclusion and exclusion criteria for the respondents, and a heterogeneity of neurofeedback protocols and devices. Despite an increasing number of studies, the optimal parameters such as the number and duration of neurofeedback training sessions have still not been defined, which makes it difficult to formulate clear guidelines for clinical application.

Future studies should focus on improving the experimental design, increasing the representativeness of the samples, standardizing the protocols, and objectivizing the measuring instruments.

nata. Također, važno je dublje istražiti učinkovitost mentalnih strategija koje ispitanici koriste tijekom *neurofeedback* treninga te njihov utjecaj na terapijske ishode. Konačno, iako postoje preliminarni dokazi o učinkovitosti *neurofeedback* metode u kombinaciji s drugim terapijama, potrebno je daljnje istraživanje kako bi se razvili optimalni tretmanski modeli temeljeni na znanstvenim dokazima.

Unatoč opisanim ograničenjima, rezultati znanstvenih studija ukazuju da *neurofeedback* predstavlja perspektivnu metodu koja može utjecati na smanjenje depresivne simptomatologije. S obzirom na tehnološki napredak *neurofeedback* uređaja (biosenzori) u bliskoj budućnosti može se očekivati i veliki napredak u razvoju ove metode te bi se intervencije mogle dosljednije integrirati u dosadašnje metode liječenja depresivnog poremećaja. Daljnji razvoj sofisticiranijih sustava za obradu neuroloških signala, primjena umjetne inteligencije u analizi podataka te optimizacija personaliziranih *neurofeedback* protokola mogli bi značajno povećati efikasnost i preciznost ove metode. Osim toga, povećana dostupnost *neurofeedback* tehnologije u kliničkim i istraživačkim postavkama mogla bi olakšati provođenje longitudinalnih studija, što bi doprinijelo boljem razumijevanju dugoročnih ishoda primjene *neurofeedbacka* u liječenju depresivnog poremećaja. Integracija *neurofeedbacka* s drugim terapijskim modalitetima, poput kognitivno-bihevioralne terapije ili farmakoterapije, mogla bi dovesti do sinergijskog učinka i poboljšanja terapijskih rezultata kod pacijenata s depresijom.

Ovaj rad doprinosi boljem razumijevanju trenutnog stanja istraživanja te može poslužiti kao temelj za buduća istraživanja usmjerena na standardizaciju i kliničku primjenu *neurofeedbacka* u cilju smanjenja simptoma depresivnog poremećaja.

Furthermore, it is important to further investigate the effectiveness of mental strategies used by the respondents in the course of neurofeedback training, as well as their influence on the therapeutic outcomes. Finally, although there is preliminary evidence on the effectiveness of the neurofeedback method in combination with other therapies, further research is required in order to develop the optimal treatment models based on scientific evidence.

Despite the described limitations, the results of scientific studies indicate that neurofeedback represents a perspective method that could have an effect on reducing depressive symptomatology. Considering the technological improvements of neurofeedback devices (biosensors), great developments to this method can be expected in the future, and interventions could thus be integrated more consistently into the current methods of depressive disorder treatment. Further developments of more sophisticated neurological signal processing systems, application of artificial intelligence in data analysis and optimization of personalized neurofeedback protocols, could significantly increase the effectiveness and precision of this method. In addition, increased availability of neurofeedback technology in clinical and research settings could facilitate the implementation of longitudinal studies, thus contributing to a better understanding of the long-term outcomes of neurofeedback application in the treatment of depressive disorder. An integration of neurofeedback with other therapeutic modalities, such as cognitive-behavioral therapy or pharmacotherapy, could lead to synergistic effects and improved therapeutic outcomes in patients with depression.

This paper contributes to a better understanding of the current state of research and can serve as a basis for future research aimed at the standardization and clinical application of neurofeedback for the purpose of reducing the symptoms of depressive disorder.

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# Neinvazivne metode stimulacije mozga u liječenju poremećaja kockanja: narativni pregled

## */ Non-Invasive Brain Stimulation Methods in the Treatment of Gambling Disorder: A Narrative Review*

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Poremećaj kockanja sve se češće promatra u kontekstu bihevioralnih ovisnosti zbog kliničkih i neurobioloških sličnosti sa zloporabom supstancija, a neinvazivne metode stimulacije mozga (NIBS) poput repetitivne transkranijalne magnetske stimulacije (rTMS), thetaburst stimulacije (cTBS) i transkranijalne stimulacije istosmjernom strujom (tDCS) istražuju se kao potencijalne terapijske opcije. Cilj ovog rada bio je prikazati postojeću literaturu o primjeni NIBS-a u liječenju poremećaja kockanja te analizirati njihov učinak na žudnju, impulzivnost, kognitivne funkcije i druge sekundarne ishode. Provedena je pretraga baze PubMed u listopadu 2024. Uključeno je 13 istraživanja različitog dizajna, koja su ispitivala NIBS kod osoba s poremećajem kockanja ili zdravih ispitanika u zadatcima povezanima s kockanjem. Najčešće korištena metoda bila je rTMS nad lijevim dorzolateralnim prefrontalnim korteksom (DLPFC) pri čemu pri čemu je većina istraživanja izvijestila o smanjenju žudnje za kockanjem. Učinci na ponašanje i funkcionalne ishode bili su manje dosljedni. Sekundarni ishodi, poput učinka za depresivnost, anksioznost, impulzivnost i kvalitetu sna zabilježeni su samo u dijelu studija.Iako preliminarni, rezultati ukazuju da NIBS može imati terapijsku vrijednost u liječenju poremećaja kockanja. Dostupni dokazi su još uvijek ograničeni zbog male veličine uzoraka, kratkog trajanja praćenja i heterogenih protokola.

*/ Gambling disorder is increasingly viewed within the context of behavioral addictions due to its clinical and neurobiological similarities with substance use disorders. Non-invasive brain stimulation (NIBS) methods, such as repetitive transcranial magnetic stimulation (rTMS), continuous theta burst stimulation (cTBS), and transcranial direct current stimulation (tDCS), are being explored as potential therapeutic options. This narrative review aims to present the existing literature on the application of NIBS in the treatment of gambling disorder and to analyze its effects on craving, impulsive behavior, cognitive functions, and other secondary outcomes. A PubMed database search was conducted in October 2024. Thirteen studies of various designs were included, examining the use of NIBS in individuals with gambling disorder or in healthy participants performing gambling-related tasks. The most commonly used method was rTMS over the left dorsolateral prefrontal cortex (DLPFC), with most studies reporting a reduction in gambling craving. Effects on behavior and functional outcomes were less consistent. Secondary outcomes, such as the effects on depressive symptoms, anxiety, impulsive behavior, and sleep quality, were reported in only a subset of studies. Although preliminary, the findings suggest that NIBS may have therapeutic value in the treatment of gambling disorder. The available evidence remains limited due to small sample sizes, short follow-up durations, and heterogeneous protocols.*

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**KLJUČNE RIJEČI /** ***KEY WORDS:***
Kockanje / *Gambling*
Neinvazivna stimulacija mozga / *Noninvasive Brain Stimulation*
Transkranijalna magnetska stimulacija / *Transcranial Magnetic Stimulation*
Žudnja / *Craving*
Impulzivnost / *Impulsive Behavior*



**TO LINK TO THIS ARTICLE:** https://doi.org/10.24869/spsih.2025.146

# UVOD

## Osnovni pojmovi i koncept poremećaja kockanja

Poremećaj kockanja se u MKB-10 pod nazivom „patološko kockanje“ uvrštavao u poremećaje navika i kontrole impulsa. Porastom dokaza kako je neurobiologija poremećaja kockanja slična poremećajima ovisnosti i izlaskom novog Dijagnostičkog i statističkog priručnika za duševne poremećaje (DSM-5), poremećaj kockanja je svrstan zajedno s ovisnostima (1). Sukladno tome, i u Međunarodnoj klasifikaciji bolesti, 11 izdanje (MKB-11) je kao poremećaj kockanja (6C50) svrstan u bihevioralne ovisnosti(2).

Uzevši u obzir obje klasifikacije, klinička obilježja poremećaja obuhvaćaju: gubitak kontrole koji se odnosi na povećanje količine novca potrošenog za kockanje i neuspješne pokušaje prestanka kockanja; simptome sustezanja; iskazivanje razdražljivog raspoloženja pri pokušaju smanjenja ili prestanka kockanja; zanemarivanje drugih područja života uz laganje kako bi se prikrilo kockanje i oslanjanje na druge za osiguranje novca što rezultira gubitkom značajnih odnosa ili zaposlenja (1,2).

Žudnja je kao ključna karakteristika ovisnosti uključena u DSM-5 kao dijagnostički kriterij za poremećaje ovisnosti, odražavajući rastući broj istraživanja te teme. Žudnja se manifestira kao

# INTRODUCTION

## Basic concepts and the framework of gambling disorder

Gambling disorder was classified among habit and impulse control disorders in the ICD-10, under the term “pathological gambling”. With growing evidence of neurobiological similarities between gambling disorder and substance use disorders, and following the publication of the new Diagnostic and Statistical Manual of Mental Disorders (DSM-5), gambling disorder was classified together with addictions (1). Accordingly, it was categorized under behavioral addictions as gambling disorder (6C50) in the 11th edition of the International Classification of Diseases (ICD-11) (2).

Taking both classifications into account, the clinical features of the disorder include the following: loss of control, reflected in increasing amounts of money spent on gambling and unsuccessful attempts to stop; withdrawal symptoms; irritability when attempting to reduce or cease gambling; neglect of other areas of life with lying to conceal gambling behavior and reliance on others for financial support, which may result in the loss of significant relationships or employment (1, 2).

Craving, as a key characteristic of addiction, was included as a diagnostic criterion for substance use disorders in the DSM-5, reflecting

neodgodiva potreba konzumacije sredstva ovisnosti, bilo zbog njegovih poželjnih učinaka ili kako bi se izbjegle negativne emocije nastale prestankom upotrebe (3). Žudnja može biti potaknuta specifičnim okidačima koji mogu biti vanjski ili unutarnji (4). Iako su dijagnostički kriteriji za poremećaj kockanja u DSM-5 modelirani prema onima za ovisnosti, žudnja nije uvrštena kao kriterij koji treba postojati za postavljanje dijagnoze poremećaja kockanja (5).

Korištenjem supstancija koje izazivaju ovisnost dolazi do povećanog oslobađanja dopamina u ključnim moždanim područjima poput nukleusa akumbensa i ventralnog strijatuma (6). Kontinuirana stimulacija dopaminskih puteva nagrade uzrokuje plastične promjene povećavajući osjetljivost na sredstvo ovisnosti i s njim povezane podražaje (7). Ovi podražaji aktiviraju prefrontalni korteks (PFC), uključujući dorzolateralni prefrontalni korteks (DLPFC), prednji cingularni girus i medijalni orbitofrontalni korteks(8). Neuroslikovna istraživanja su pokazala kako se područje inzule također aktivira kod žudnje za kokainom i nikotinom (9), a literaturni podatci sugeriraju da žudnja prethodi recidivu (10).

S neurobiološke strane su brojna istraživanja pokušala razjasniti mehanizam koji stoji iza nastanka poremećaja kockanja, ali konsenzus još uvijek nije postignut. Teorija o dostupnosti dopaminskog transportera sugerira da je kod osoba s poremećajem kockanja zabilježena smanjena dostupnost dopaminskog transportera u strijatumu. Navodi se i potencijalno obrnuti odnos između dostupnosti strijalnog dopaminskog transportera i broja dana provedenih u kockanju (11).

## Kognitivne funkcije u poremećaju kockanja

Impulzivnost koja se definira kao tendencija brzog djelovanja bez prethodnog promišljanja smatra se znakom smanjene kognitivne kon-

the growing body of research on this topic. Craving manifests as an urgent need to consume the addictive substance, either due to its desirable effects or to avoid negative emotions arising from its cessation (3). Craving can be triggered by specific cues, which may be either external or internal (4). Although the diagnostic criteria for gambling disorder in the DSM-5 are modeled after those for substance use disorders, craving is not included as a required criterion for the diagnosis of gambling disorder (5).

The use of addictive substances leads to increased dopamine release in key brain areas such as the nucleus accumbens and ventral striatum (6). Continuous stimulation of dopaminergic reward pathways causes plastic changes, increasing sensitivity to the addictive substance and associated cues (7). These cues activate the prefrontal cortex (PFC), including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate gyrus, and medial orbitofrontal cortex (8). Neuroimaging studies have shown that the insular cortex is also activated during craving for cocaine and nicotine (9), and the literature suggests that craving often precedes relapse (10).

From a neurobiological perspective, numerous studies have attempted to clarify the mechanisms underlying gambling disorder, but consensus has not yet been reached. The dopamine transporter availability theory suggests that individuals with gambling disorder have reduced dopamine transporter availability in the striatum. Additionally, a potential inverse relationship has been noted between striatal dopamine transporter availability and the number of days spent gambling (11).

## Cognitive functions in gambling disorder

Impulsive behavior, defined as the tendency to act quickly without prior consideration, is regarded as a sign of reduced cognitive control

trole te važnim faktorom u razvoju ovisničkih ponašanja (12). Nedavna istraživanja usmjerena na impulzivnost i gubitak kontrole u kockanju otkrila su slabiju aktivnost GABA-A receptora u primarnom motoričkom korteksu (područje M1) kod kockara što ukazuje na smanjenu inhibiciju odgovora, odnosno sposobnost odgađanja neprimjerenih reakcija na podražaje (13). Prethodno se vjerovalo da je inhibicija odgovora povezana isključivo s aktivnošću prefrontalnog korteksa uključujući DLPFC (14) i desni donji frontalni girus (15).

Istraživanja neurobiologije kockanja su obuhvatila i aspekt odgađanja zadovoljstva kao ključnu komponentu impulzivnosti, povezanu s aktivnošću u PFC i limbičkim regijama (16). Sposobnost izbora opcija koje nude odgođene ali veće nagrade ključna je za održavanje apstinencije od ovisnosti i povezana je s povećanom aktivnošću u PFC-u u usporedbi s aktivnošću u limbičkim regijama. Relaps u stare navike nakon odluke o prestanku ovisnosti može indicirati situaciju gdje DLPFC nije adekvatno aktiviran kako bi inhibirao tendenciju povratka ovisničkom ponašanju u odnosu na ostale opcije (17).

Inhibicija odgovora označava sposobnost suzbijanja automatskog motoričkog odgovora na podražaj a ispituje se zadacima kao što su zadatak kreni-stani (*go/no-go)*. Deficiti u inhibiciji odgovora javljaju se u poremećajima povezanima s upotrebom supstancija i poremećajem kockanja (18). Funkcionalna neuroslikovna istraživanja (fMRI) otkrila su da kod pacijenata s poremećajem kockanja tijekom izvođenja zadataka inhibicije odgovora dolazi do izmijenjene aktivnosti u dorzolateralnim i ventrolateralnim prefrontalnim regijama, uključujući DLPFC, dorzomedijalni prefrontalni korteks (DMPFC), dorzalni prednji cingularni korteks (ACC) i ventrolateralni prefrontalni korteks (VLPFC) (19).

Detekcija konflikta, mjerena Stroopovim zadatkom, odnosi se na sposobnost ignoriranja

and an important factor in the development of addictive behaviors (12). Recent research focusing on impulsive behavior and loss of control in gambling has identified reduced GABA-A receptor activity in the primary motor cortex (M1 area) in individuals with gambling disorder, indicating impaired response inhibition, i.e. reduced ability to delay inappropriate reactions to stimuli (13). Response inhibition was previously believed to be associated exclusively with the activity of the prefrontal cortex, including the DLPFC (14) and the right inferior frontal gyrus (15).

Research on the neurobiology of gambling has also encompassed the aspect of delay discounting as a key component of impulsive behavior, linked to activity in the PFC and limbic regions (16). The ability to choose options that offer delayed but larger rewards is crucial for maintaining abstinence from addiction and is associated with increased activity in the PFC compared to activity in the limbic regions. Relapse into old habits after deciding to cease addictive behavior may indicate a situation where the DLPFC is not adequately activated to inhibit the tendency to revert to addictive behavior in favor of alternative options (17).

Response inhibition refers to the ability to suppress an automatic motor response to a stimulus and is assessed using tasks such as the go/no-go task. Deficits in response inhibition are present in substance use disorders and gambling disorder (18). Functional neuroimaging (fMRI) studies have revealed that patients with gambling disorder exhibit altered activity in dorsolateral and ventrolateral prefrontal regions during response inhibition tasks, including the DLPFC, dorsomedial prefrontal cortex (DMPFC), dorsal anterior cingulate cortex (ACC), and ventrolateral prefrontal cortex (VLPFC) (19).

Conflict detection, measured using the Stroop task, refers to the ability to ignore distracting stimuli during information processing. The

ometajućih podražaja tijekom obrade informacija. Uključene regije mozga su DLPFC, ACC, pre-suplementarni motorički areal (pre-SMA) i VLPFC (20). Lošiji rezultati na ovom zadatku ukazuju na poteškoće u kontroli ponašanja kod kockanja (21).

Donošenje odluka koje se ispituje ispitano Iowa zadatkom kockanja (*Iowa gambling task* (IGT)), fokusira se na izbore koji favoriziraju dugoročne dobitke umjesto trenutačnih, ali rizičnih većih dobitaka (22). U fMRI istraživanjima koja su analizirala proces donošenja odluka, primijećena je neuravnotežena aktivnost u ventromedijalnim prefrontalnim područjima uključujući medijalni orbitofrontalni korteks (OFC) kao i ventralnije dijelove MPFCi ACC (23,24).

Kognitivna fleksibilnost, sposobnost adaptacije strategija rješavanja problema pri promjeni okolnosti često je narušena kod osoba s poremećajem kockanja, što se mjeri Wisconsin testom sortiranja karata (WCST)(25). U jednom fMRI istraživanju osobe s poremećajem kockanja pokazale su smanjenu aktivaciju desnog VLPFC tijekom promjene strategije (26).

## Epidemiologija poremećaja kockanja

Globalno, 8,7 % odraslih upušta se u rizično kockanje, a 1,41 % zadovoljava kriterije za problematično kockanje (27). U Hrvatskoj svaka treća osoba sudjeluje u igrama na sreću, s procjenom da je između 1,4 % i 2,4 % odraslih ovisno o kockanju (28), a prevalencija raste i među adolescentima (29).

Tek jedan od 25 umjerenih kockara te jedna od 5 osoba s problematičnim kockanjem potraže pomoć za probleme vezane uz njihovo kockanje (30). Kada i započnu s liječenjem, 40-50 % pacijenata odustane u tijeku tretmana (31,32). Faktori koji doprinose odustajanju uključuju financijske probleme poput visokih dugova, komorbiditete depresije, komorbidnih ovisno-

brain regions involved include the DLPFC, ACC, pre-supplementary motor area (pre-SMA), and VLPFC (20). Poorer performance on this task indicates difficulties in behavioral control among individuals with gambling disorder (21).

Decision-making, assessed using the Iowa Gambling Task (IGT), focuses on choices that favor long-term gains over immediate but riskier larger rewards (22). In fMRI studies that analyzed the decision-making process, imbalanced activity was observed in the ventromedial prefrontal regions, including the medial orbitofrontal cortex (OFC), as well as more ventral parts of the MPFC and ACC (23, 24).

Cognitive flexibility, the ability to adapt problem-solving strategies when circumstances change, is often impaired in individuals with gambling disorder, as measured by the Wisconsin Card Sorting Test (WCST) (25). In one fMRI study, individuals with gambling disorder demonstrated reduced activation of the right VLPFC during strategy shifting (26).

## Epidemiology of gambling disorder

Globally, 8.7% of adults engage in risky gambling, while 1.41% meet the criteria for problematic gambling (27). In Croatia, every third person participates in games of chance, with estimates indicating that between 1.4% and 2.4% of adults are affected by gambling disorder (28), while its prevalence is increasing among adolescents as well (29).

Only one in 25 moderate gamblers and one in five individuals struggling with problematic gambling seek help for gambling-related issues (30). Even when treatment is initiated, 40–50% of patients drop out during the course of treatment (31, 32). Factors contributing to treatment dropout include financial problems such as high debts, comorbid depression, comorbid substance and nicotine use disorders,

sti o drogama i nikotinu, poremećaja ličnosti te osobne okolnosti (31,33,34).

## Tehnike neinvazivne stimulacije mozga u liječenju ovisnosti

Iako još uvijek ne postoji zlatni standard liječenja, mnoga istraživanja pokazuju obećavajuće rezultate, posebno kada se farmakoterapija kombinira s psihoterapijom (35).Tehnike NIBS sve su više u fokusu istraživanja kao opcije liječenja za bihevioralne ovisnosti te druge psihijatrijske poremećaje, uključujući depresiju (36,37), opsesivno-kompulzivni poremećaj (38), negativne simptome shizofrenije (39,40), anksioznost (41), posttraumatski stresni poremećaj (42,43) i kompulzivno prejedanje (44).

Transkranijalna magnetska stimulacija (TMS) koristi brzo mijenjajuće magnetsko polje koje inducira električne struje na površinskim slojevima moždane kore. Repetitivna TMS (rTMS) se primjenjuje ponavljanim impulsima usmjerenima na specifična moždana područja koristeći zavojnice u obliku broja osam (45). Visoke frekvencije stimulacije imaju ekscitacijski učinak, dok niske frekvrencije imaju inhibitorni, što omogućuje poboljšanje funkcionalnosti prefrontalnih područja ili smanjenje povećane funkcionalnosti limbičkog sustava (46).

Theta-burst stimulacija (TBS) je varijanta rTMS-a koja proizvodi dugotrajne i snažne učinke na kortikalnu fiziologiju i ponašanje s različitim učincima na sinaptičku transmisiju ovisno o protokolu. Intermitentna TBS (iTBS) uglavnom ima facilitatorne učinke, dok kontinuirana TBS (cTBS) ima prevladavajuće inhibitorni učinak (47). Protokoli se koriste za inhibiciju (1 Hz; cTBS) ili ekscitaciju (više od 5 Hz; iTBS) stimuliranih neuralnih krugova (48).

Duboka TMS (dTMS) je tip rTMS-a koji koristi H-zavojnice za produbljivanje dosega stimulacije do oko 4 cm ispod površine lubanje, ciljajući veća područja mozga (49).

personality disorders, and personal circumstances (31, 33, 34).

## Non-invasive brain stimulation techniques in the treatment of addiction

Although a gold standard for treatment has not yet been established, numerous studies have shown promising results, particularly when pharmacotherapy is combined with psychotherapy (35). Additionally, NIBS techniques are increasingly being investigated as treatment options for behavioral addictions and other psychiatric disorders, including depression (36, 37), obsessive-compulsive disorder (38), negative symptoms of schizophrenia (39, 40), anxiety (41), post-traumatic stress disorder (42, 43), and binge eating disorder (44).

Transcranial magnetic stimulation (TMS) uses rapidly changing magnetic fields to induce electric currents in the superficial layers of the cerebral cortex. Repetitive TMS (rTMS) is applied through repeated pulses targeting specific brain regions using figure-eight-shaped coils (45). High-frequency stimulation has an excitatory effect, while low-frequency stimulation has an inhibitory effect, allowing for either the enhancement of prefrontal cortex functionality or the reduction of hyperactivity in the limbic system (46).

Theta-burst stimulation (TBS) is a variant of rTMS that produces long-lasting and strong effects on cortical physiology and behavior, with different effects on synaptic transmission depending on the protocol. Intermittent TBS (iTBS) generally has facilitatory effects, while continuous TBS (cTBS) predominantly has inhibitory effects (47). Protocols are used for the inhibition (1 Hz; cTBS) or excitation (above 5 Hz; iTBS) of the stimulated neural circuits (48).

Deep TMS (dTMS) is a type of rTMS that uses H-coils to extend the stimulation depth to approximately 4 cm beneath the skull, targeting larger brain areas (49).

Transkranijalna direktna stimulacija strujom (tDCS) je neuromodulacijska tehnika koja primjenjuje slabu istosmjernu struju (1-2 mA) anodom i katodom postavljenima na vlasištu (50). Za razliku od TMS-a, intenzitet tDCS-a nije dovoljno jak da izazove promjenu akcijskih potencijala, ali utječe na ekscitabilnost membrane depolarizacijom ili hiperpolarizacijom (51).

Obje tehnike, TMS i tDCS, pokazale su generalno obećavajuće rezultate u liječenju ovisnosti i bihevioralnih poremećaja ciljajući specifične moždane regije, no rezultati donekle variraju zbog razlika u protokolima stimulacije, karakteristikama uzoraka, mjerama ishoda i dizajnu istraživanja. Učinkovitost stimulacije mozga u liječenju alkoholizma pokazuje mješovite rezultate u smanjenju žudnje i konzumacije alkohola, koristeći rTMS i dTMS zavojnicom H1 te ciljajući DLPFC, mPFC, inzulu i prednji cingulatni korteks (52). tDCS je ocijenjen kao "vjerojatno učinkovit" za smanjenje žudnje kod ovisnika o alkoholu primjenom bihemisferične stimulacije DLPFC-a (53). Studije o upotrebi rTMS-a za stimulaciju lijevog ili bilateralnog DLPFC za liječenje ovisnosti o kanabisu nisu pokazale značajno smanjenje konzumacije, ali je zabilježeno smanjenje žudnje (54,55). Za ovisnost o nikotinu FDA je odobrila TMS s H4 zavojnicom koji cilja bilateralni PFC i inzulu (56). I visokofrekventni rTMS iznad lijevog DLPFC je učinkovit u liječenju ovisnosti o kokainu (57). Istraživanja o ovisnosti o metamfetaminima i opijatima pokazuju značajna poboljšanja u smanjenju žudnje i konzumaciji nakon višestrukih sesija rTMS-a usmjerenih na lijevi DLPFC (58).

Iako su preliminarni rezultati obećavajući, primjena neinvazivnih metoda stimulacije mozga u liječenju poremećaja kockanja još uvijek je u ranoj fazi istraživanja, a rezultati su heterogeni. Potrebna je sustavna analiza dosadašnjih nalaza kako bi se procijenio potencijal ovih intervencijskih tehnika.

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that applies a weak direct current (1–2 mA) through an anode and a cathode placed on the scalp (50). Unlike TMS, the intensity of tDCS is not strong enough to induce change in action potentials, but affects membrane excitability through depolarization or hyperpolarization (51).

Both TMS and tDCS have generally shown promising results in the treatment of addiction and behavioral disorders by targeting specific brain regions. However, the results somewhat vary due to differences in stimulation protocols, sample characteristics, outcome measures, and study designs. The effectiveness of brain stimulation in treating alcohol use disorder has shown mixed results in reducing craving and alcohol consumption, using rTMS and dTMS with the H1 coil, and targeting the DLPFC, mPFC, insula, and anterior cingulate cortex (52). tDCS has been rated as "probably effective" for reducing alcohol craving in addicts when using bihemispheric stimulation of the DLPFC (53). Studies investigating rTMS targeting the left or bilateral DLPFC for cannabis use disorder have not shown significant reductions in consumption, but reductions in craving were observed (54, 55). For nicotine addiction, the FDA has approved rTMS with the H4 coil targeting the bilateral PFC and insula (56). Additionally, high-frequency rTMS over the left DLPFC has been effective in the treatment of cocaine addiction (57). Research on methamphetamine and opioid addiction has yielded significant improvements in reducing craving and consumption following multiple sessions of rTMS targeting the left DLPFC (58).

Although the preliminary results are promising, the application of non-invasive brain stimulation methods in the treatment of gambling disorder is still in its early stages, and the results are heterogeneous. A systematic analysis of current findings is necessary to evaluate the potential of these intervention techniques.

## CILJ

Cilj ovog narativnog pregleda je pružiti uvid u dosadašnja istraživanja koja su ispitivala učinke neinvazivnih metoda stimulacije mozga u liječenju poremećaja kockanja:

1. Prikazati koje su metode neinvazivne stimulacije mozga do sada korištene u liječenju poremećaja kockanja te kako su bile protokolarno primijenjene (lokacija, intenzitet, broj sesija).
2. Analizirati ishode istraživanja vezane uz učinak ovih metoda na simptome kockanja, uključujući žudnju, kontrolu impulsa i stvarno kockarsko ponašanje.
3. Ispitati sekundarne ishode poput promjena u razinama depresivnosti, anksioznosti, impulzivnosti, kvalitete sna i svakodnevnog funkcioniranja.
4. Procijeniti sigurnost i podnošljivost različitih NIBS protokola primijenjenih u ovoj populaciji

## AIM

The aim of this narrative review is to provide an overview of the existing studies examining the effects of non-invasive brain stimulation methods in the treatment of gambling disorder:

1. To present which non-invasive brain stimulation methods have been used to date in the treatment of gambling disorder and how they were applied in terms of protocol (location, intensity, number of sessions).
2. To analyze research outcomes related to the effects of these methods on gambling symptoms, including craving, impulse control, and actual gambling behavior.
3. To examine secondary outcomes such as changes in levels of depression, anxiety, impulsive behavior, sleep quality, and daily functioning.
4. To evaluate the safety and tolerability of different NIBS protocols applied in this population.

## MATERIJALI I METODE

Ovaj rad predstavlja narativni pregled originalnih znanstvenih istraživanja koja su ispitivala učinke neinvazivnih metoda stimulacije mozga, uključujući rTMS, dTMS, TBS i tDCS, u kontekstu poremećaja kockanja. U obzir su uzeta istraživanja provedena na pacijentima s dijagnozom poremećaja kockanja, kao i na zdravim dobrovoljcima prije i nakon provođenja zadataka vezanih uz kockanje.

### Izvori podataka i strategija pretraživanja

Sustavno je pretražena baza podataka PubMed (MEDLINE) i prikupljeni su radovi objavljeni zaključno s 19. 10. 2024. Korišten je sljedeći algoritam:[(“Gambling”[Mesh] OR gambling) AND (“Transcranial MagneticStimulation”[Mesh] OR “transcranialmagneticstimulation”)]. Referentne liste uključenih radova dodatno su pregleda-

## MATERIALS AND METHODS

This paper presents a narrative review of original scientific studies that examined the effects of non-invasive brain stimulation methods, including rTMS, dTMS, TBS, and tDCS, in the context of gambling disorder. Studies conducted on patients diagnosed with gambling disorder, as well as on healthy volunteers before and after performing gambling-related tasks, were considered.

### Data sources and research strategy

The PubMed (MEDLINE) database was systematically searched, and studies published up to October 19, 2024, were collected. The following search algorithm was used: [(“Gambling”[Mesh] OR gambling) AND (“Transcranial Magnetic Stimulation”[Mesh] OR “transcranialmagneticstimulation”)]. The reference lists of the in-

ne radi identifikacije potencijalno propuštenih publikacija, no dodatne studije nisu uključene.

## Uključni i isključni kreteriji

U pregled su uključena istraživanja koja su ispunjavala sljedeće uvjete: a) pisana su na engleskom jeziku, b) objavljena su u recenziranim znanstvenim časopisima, c) uključivala su ljudske ispitanike s dijagnozom poremećaja kockanja ili zdrave dobrovoljce koji su bili izloženi zadatcima vezanima uz kockanje, d) primjenjivala su neinvazivne metode stimulacije mozga te e) bila su originalna istraživanja, uključujući randomizirana i nerandomizirana kontrolirana ispitivanja, prospektivne i retrospektivne studije, serije slučajeva i prikaze slučajeva. Obuhvaćena su istraživanja na svim uzorcima, neovisno o spolu, dobi javljanja i trajanju poremećaja kockanja.

Istraživanja su isključena ako su: a) bila pisana na jeziku koji nije engleski, b) nisu bila originalna znanstvena istraživanja (npr. prikazi iz konferencijskih sažetaka, komentari ili poglavlja u knjigama), d) nisu provedena na odrasloj populaciji, e) nisu bila dostupna u cijelosti ili f) nisu procjenjivala ponašanja vezana uz donošenje odluka ili žudnju u kontekstu kockanja kod zdravih ispitanika.

## Odabir i selekcija

Nakon uklanjanja duplikata provedeno je inicijalno pregledavanje naslova i sažetaka. U drugom koraku su u cijelosti pročitani radovi koji su potencijalno zadovoljavali kriterije. Konačno je u narativni pregled uključeno 13 istraživanja koja su ispunjavala sve zadane uvjete.

# REZULTATI

Pretraživanjem baze podataka identificirano je ukupno 66 radova. Nakon uklanjanja duplikata svi su radovi prošli selekciju u dvije faze: najprije na razini naslova i sažetka, a zatim čitanjem cjelovitih tekstova. Dio radova isključen je prema

cluded studies were additionally reviewed to identify any potentially missed publications, however, no additional studies were included.

## Inclusion and exclusion criteria

The studies that met the following criteria were included in the review: a) written in English, b) published in peer-reviewed scientific journals, c) included human participants diagnosed with gambling disorder or healthy volunteers exposed to gambling-related tasks, d) applied non-invasive brain stimulation methods, and e) represented original research, including randomized and non-randomized controlled trials, prospective and retrospective studies, case series, and case reports. Studies on all samples were included, regardless of sex, age of onset, and duration of gambling disorder.

Studies were excluded if they: a) were written in a language other than English, b) were not original scientific studies (e.g., conference abstracts, commentaries, or book chapters), c) were not conducted on adult populations, d) were not available in full text, or e) did not assess decision-making or craving-related behaviors in the context of gambling in healthy participants.

## Selection process

After removing duplicates, an initial screening of titles and abstracts was conducted. In the second step, the full texts of the studies potentially meeting the criteria were reviewed. Ultimately, 13 studies that met all the inclusion criteria were included in this narrative review.

# RESULTS

A total of 66 studies were identified through the database search. After removing duplicates, all the studies underwent a two-phase selection process: first at the title and abstract level, followed by full-text screening. Some studies were excluded according to the predefined inclusion

prethodno definiranim kriterijima uključivanja i isključivanja. U konačnici je u pregled uključeno 13 istraživanja. Rezultati su prikazani u tablici 1 prikazani prema vrsti primijenjene neinvazivne metode stimulacije mozga i tipu studije.

and exclusion criteria. Ultimately, 13 studies were included in this review. The results are presented in Table 1, according to the type of non-invasive brain stimulation method applied and the type of study.

**TABLICA 1.** Pregled istraživanja koja su ispitivala učinke neinvazivnih metoda stimulacije mozga u kontekstu poremećaja kockanja
**TABLE 1.** Overview of studies investigating the effects of non-invasive brain stimulation methods in the context of gambling disorder

| | Autori i godina / Authors and year | Zemlja / Country | Ispitanici Rod/spol / Participants Sex/Age | Ciljevi i dizajn istraživanja / Study aims and design | DG (MKB ili DSM kriteriji) / DG (ICD or DSM criteria) | Skale / Scales | Vrsta tretmana / Type of treatment | Rezultati / Results |
|---|---|---|---|---|---|---|---|---|
| 1. | Zack et al., 2016 (59) | Kanada / Canada | 9 muškaraca / 9 males | Dvostruko slijepo istraživanje s ciljem ispitivanja učinka HF-rTMS i cTBS na žudnju, impulzivnost i kognitivnu kontrolu. Svaki sudionik primio je HF-rTMS, cTBSi sham stimulaciju, redoslijed nasumično dodijeljen. Nakon provedene stimulacije provedeni su zadatci (Stoop test, Delay discounting task i igra na slot aparatu te su provedena psihometrijska mjerenja. / Double-blind study aimed at examining the effects of HF-rTMS and cTBS on craving, impulsive behavior, and cognitive control. Each participant received HF-rTMS, cTBS, and sham stimulation in a randomly assigned order. Following stimulation, tasks were administered (Stroop test, Delay Discounting Task, slot machine task), along with psychometric assessments. | Dijagnoza patološkog kockanja postavljena putem SCID-IV / Diagnosis of pathological gambling established using SCID-IV | SouthOaksGambling Screen (SOGS), Beckov inventar depresije (BDI), Eysenck skala impulzivnosti (EIS), VAS skala žudnje, POMS, ARCI / South Oaks Gambling Screen (SOGS), Beck Depression Inventory (BDI), Eysenck Impulsivity Scale (EIS), VAS Craving Scale, POMS, ARCI | • Visokofrekventna rTMS (10 Hz) zavojnicom u obliku broja 8 na mPFC s jednokratnom seansom podijeljenom u tri serije, s petominutnim pauzama između serija. Tijekom svake serije primijenjeno 10 pulseva s 10-minutnom pauzom između njih, ukupno 450 pulseva, pri 80% motornog praga. / High-frequency rTMS (10 Hz) using a figure-eight coil over the mPFC in a single session divided into three series, with five-minute breaks between series. Each series included 10 pulses with 10-minute intervals, totaling 450 pulses at 80% of the motor threshold.<br>• Za cTBS stimulaciju, svaki TBS impuls sastojao se od 3 pulsa na 50 Hz, pri čemu je svaka serija ponovljena svakih 200 ms (5 Hz). Izvedena su tri cTBS razdoblja s intervalima od 5 minuta između svakog razdoblja, što ukupno iznosi 900 pulsova tijekom sesije cTBS. / For cTBS stimulation, each TBS burst consisted of 3 pulses at 50 Hz, with each burst repeated every 200 ms (5 Hz). Three cTBS periods were administered with five-minute intervals, totaling 900 pulses per cTBS session.<br>• Za kontrolu je korištena pasivna zavojnica. / Sham coil was used for control. | Statistički značajno smanjenje žudnje za kockanjem / Statistically significant reduction in gambling craving. |
| 2. | Gay et al., 2017 (60) | Francuska / France | 22 (14 M, 8 Ž) / 22 (14 M, 8 F) | Dvostruko slijepo cross-over istraživanje s wash-out razdobljem s ciljem ispitivanja učinka jedne HF-rTMS sesije na žudnju izazvanu podražajima vezanim uz kockanje i ponašanje povezano s kockanjem. Svaki je sudionik primio jednu stvarnu i jednu sham sesiju HF-rTMS između kojih je bio wash-out period od 7 dana.Evaluacije su provedene prije i tjedan dana nakon svake sesije, skale su primijenjene prije i nakon gledanja videa o kockanju. / Double-blind cross-over study with a wash-out period, aimed at investigating the effects of a single session of HF-rTMS on cue-induced gambling craving and gambling-related behavior. Each participant received one active and one sham HF-rTMS session, with a 7-day wash-out period between sessions. Evaluations were conducted before and one week after each session, and scales were administered before and after watching a gambling-related video. | Poremećaj kockanja dijagnosticiran prema DSM-IV kriterijima / Gambling disorder diagnosed according to DSM-IV criteria | SOGS, Yale-Brownova ljestvica opsesivno kompulzivnih simptoma (PG-YBOCS), VAS / SOGS, Yale-Brown Obsessive Compulsive Scale for Pathological Gambling (PG-YBOCS), VAS | Jednokratna stimulacija rTMS od 10 Hz primijenjena na lijevi DLPFC; 110% motoričkog praga, ukupno 3.008 pulsova, u intervalima od 10 sekundi i ukupnim trajanjem intervencije od 20 minuta. Kontrolna grupa tretirana je pasivnom zavojnicom. / Single-session 10 Hz rTMS applied over the left DLPFC at 110% of the motor threshold, totaling 3,008 pulses delivered in 10-second intervals, with a total intervention duration of 20 minutes. The control group received sham coil treatment. | Značajno smanjenje žudnje, ali bez statistički značajnog učinka na ukupnu želju za kockanjem i kontrolu nad kockanjem. / Significant reduction in craving, but no statistically significant effect on overall gambling urge or gambling control. |
| 3. | Sauvaget et al., 2018 (61) | Francuska / France | 30 (27 M, 3 Ž) / 30 (27 M, 3 F) | Dvostruko slijepo cross-over istraživanje s wash-out razdobljem s ciljem ispitivanja učinka jedne sesije LF rTMS-a na žudnju izazvanu podražajima povezanim s kockanjem. Svaki ispitanik primio je jednu sesiju aktivne i jednu sesiju sham rTMS u nasumičnom redoslijedu s tjedan dana razmaka.Ishodi su mjereni pri uključivanju i neposredno nakon izlaganja podražajima koji provociraju žudnju za kockanjem. / Double-blind cross-over study with a washout period, aimed at investigating the effects of a single session of low-frequency rTMS on cue-induced gambling craving. Each participant received one session of active and one session of sham rTMS in a randomized order, with a one-week interval between sessions. Outcomes were measured at baseline and immediately after exposure to gambling craving-inducing cues. | Poremećaj kockanja dijagnosticiran prema DSM-IV kriterijima / Gambling disorder diagnosed according to DSM-IV criteria | VAS,ljestvica žudnje za kockom (GamblingCravingScale; GACS), Ljestvice za kognicije povezane s kockanjem (Gambling-RelatedCognitionsScale; GRCS),Mini međunarodni neuropsihijatrijski intervju (M.I.N.I.). / VAS, Gambling Craving Scale (GACS), Gambling-Related Cognitions Scale (GRCS), Mini International Neuropsychiatric Interview (M.I.N.I.) | rTMS 1 Hz; jednokratna stimulacijom desnog DLPFC, na 120% motoričkog praga; primijenjeno 360 pulseva tijekom šest minuta. Kontrolna stimulacija pasivnom zavojnicom. / 1 Hz rTMS; single-session stimulation over the right DLPFC at 120% of the motor threshold; 360 pulses delivered over six minutes. The control condition used sham coil stimulation. | Nema statističkih značajnih razlika između rTMS intervencije i tretmana pasivnom zavojnicom na niti jednom od mjerenih ishoda. / No statistically significant differences between the rTMS intervention and sham treatment on any of the measured outcomes. |

**TABLICA 1.** *Nastavak*
**TABLE 1.** *Continued*

| | Autori i godina / Authors and year | Zemlja / Country | Ispitanici Rod/spol / Participants Sex/Age | Ciljevi i dizajn istraživanja / Study aims and design | DG (MKB ili DSM kriteriji) / DG (ICD or DSM criteria) | Skale / Scales | Vrsta tretmana / Type of treatment | Rezultati / Results |
|---|---|---|---|---|---|---|---|---|
| 4. | Soyata et al., 2018 (62) | Turska / Turkey | 20 muškaraca / 20 males | Trostruko slijepo, randomizirano, placebom kontrolirano istraživanje s ciljem ispitivanja učinka tDCS na donošenje odluka i kognitivnu fleksibilnost kod osoba s poremećajem kockanja. Provedene su 3 sesije aktivnog ili shamtDCS-a nad bilateralnim DLPFC-om, evaluacija IGT-om i WCST-om prije i nakon stimulacije.<br>/ Triple-blind, randomized, placebo-controlled study aimed at investigating the effects of tDCS on decision-making and cognitive flexibility in individuals with gambling disorder. Participants received three sessions of active or sham tDCS over the bilateral DLPFC, with evaluation using the IGT and WCST before and after stimulation. | Poremećaj kockanja dijagnosticiran prema DSM-5 kriterijima.<br>/ Gambling disorder diagnosed according to DSM-5 criteria | SOGS,Kanadski indeks težine problematičnog kockanja (PGSI), BDI, Barratova skala impulzivnosti (BIS-11)<br>/ SOGS, Canadian Problem Gambling Severity Index (PGSI), Beck Depression Inventory (BDI), Barratt Impulsiveness Scale (BIS-11) | tDCS2mA (anodna desno / katodna lijevo na DLPFC), svakodnevo tri stimulacije u trajanju od 20 minuta ili pasivna stimulacija.<br>/ tDCS at 2 mA (anode right / cathode left over DLPFC), three daily stimulation sessions of 20 minutes each or sham stimulation. | Poboljšano donošenje odluka i bolja kognitivna fleksibilnost u skupini koja ja primala aktivnu stimulaciju.<br>/ Improved decision-making and better cognitive flexibility in the active stimulation group. |
| 5. | Martinotti et al., 2019 (63) | Italija / Italy | 34 (30M, 4Ž) / 34 (30M, 4F) | Dvostruko slijepo, randomizirano, placebom kontrolirano istraživanje s aktivnom i shamtDCS skupinom; pet uzastopnih sesija stimulacije.<br>/ Double-blind, randomized, placebo-controlled study with active and sham tDCS groups; five consecutive stimulation sessions. | Osobe s poremećajem ovisnosti, uključujući 4 osobe s poremećajem kockanja.<br>/ Individuals with substance use disorders, including 4 participants with gambling disorder. | VAS, HAM-D, HAM-A, BIS-11, Young skala ocjene manije (YMRS)<br>/ VAS, HAM-D, HAM-A, BIS-11, Young Mania Rating Scale (YMRS) | tDCS: 1.5 mA, (anoda desno/katoda lijevo na DLPFC), 20 min, 5 dana zaredom; aktivna vs sham skupina<br>/ tDCS at 1.5 mA (anode right / cathode left over DLPFC), 20 minutes per session, five consecutive days; active vs. sham group. | Značajno smanjenje žudnje (VAS) u aktivnoj skupini; smanjenje depresivnosti, anksioznosti i impulzivnosti u obje skupine; bez nuspojava.<br>/ Significant reduction in craving (VAS) in the active group; reductions in depression, anxiety, and impulsive behavior in both groups; no adverse effects reported. |
| 6. | Lohse et al., 2023 (64) | Danska / Denmark | 24 osobe (12M, 12 Ž) / 24 individuals (12M, 12 F) | Eksperimentalno istraživanje s ciljem ispitivanja postoji li uzročna povezanost između aktivnosti u preSMA i impulzivnog donošenja odluka tijekom zadatka sekvencijalno kockanja. Svaki je sudionik sudjelovao u dvije sesije s tjedan dana razmaka nakon stimulacije, ispitanici su izvodili zadatak sekvencijalnog kockanja tijekom fMRI snimanja.<br>/ Experimental study aimed at investigating whether there is a causal relationship between pre-SMA activity and impulsive decision-making during a sequential gambling task. Each participant took part in two sessions one week apart; following stimulation, participants performed the sequential gambling task during fMRI scanning. | Zdravi dobrovoljci, bez dijagnosticiranih psihičkih i neuroloških bolesti<br>/ Healthy volunteers with no diagnosed psychiatric or neurological disorders | BIS-11 | rTMS zavojnica (100% praga podražljivosti) i pasivnirTMS (30% praga podražljivosti) iznad desnog pre-SMA područja u dvije odvojene sesije s razmakom od tjedan dana.<br>/ rTMS coil (100% of motor threshold) and sham rTMS (30% of motor threshold) applied over the right pre-SMA in two separate sessions one week apart. | Na fMRI vidljiva promjena u aktivnosti pre-SMA te modulacija impulzivnog odlučivanja (sudionici s prethodno niskom osobinskom impulzivnošću su, nakon primjene rTMS, pokazali veću sklonost prema rizičnim odlukama, dok su sudionici s prethodno visokom osobinskom impulzivnošću pokazali manju sklonost rizičnim izborima)<br>/ fMRI showed changes in pre-SMA activity and modulation of impulsive decision-making (participants with previously low trait impulsivity exhibited greater risk-taking after rTMS, while participants with high trait impulsivity showed reduced risk-taking) |
| 7. | Rosenberg et al., 2013 (65) | Izrael / Israel | 5 muškaraca / 5 males | Pilot studija; ispitivanje učinka dTMS-a na simptome patološkog kockanja<br>/ Pilot study investigating the effects of dTMS on symptoms of pathological gambling. | Dijagnoza patološkog kockanja postavljena po kriterijima DSM-IV-TR<br>/ Diagnosis of pathological gambling established according to DSM-IV-TR criteria | HAM-D, HAM-A,Y-BOCS, SOGS, DannoniAinhold skala kockanja (DAGS), VAS skala žudnje, CGI-I, Mjerenja su izvršena prije prve i 24 sata nakon zadnje aplikacije.<br>/ HAM-D, HAM-A, Y-BOCS, SOGS, Dannon Ainhold gambling scale (DAGS), VAS craving scale, CGI-I, measurements taken before the first and 24 hours after the last application. | dTMS H1 zavojnicom primijenjena na lijevi prefrontalni korteks, 15 dana, s jednom sesijom dnevno, svaka sesija je trajala 10 minuta s frekvencijom od 1 Hz i intenzitetom od 110% motoričkog praga.<br>/ dTMS using an H1 coil applied over the left prefrontal cortex for 15 days, with one session per day; each session lasted 10 minutes with a frequency of 1 Hz at 110% of the motor threshold. | Rezultati na skalama upućuju na poboljšanje, no ono nije bilo popraćeno promjenama u svakodnevnom funkcioniranju.<br>/ Scale results indicated improvement, but this was not accompanied by changes in daily functioning. |
| 8. | Cardullo et al., 2019 (66) | Italija / Italy | 7 muškaraca / 7 males | Serija slučajeva koja ispituje učinak višekratnih HF-rTMS sesija na simptome kockanja, žudnju za kokainom i afektivne simptome. Mjerenja su obavljena na početku, odmah nakon prvog tjedna liječenja te 30 i 60 dana nakon stimulacije.<br>/ Case series investigating the effects of multiple HF-rTMS sessions on gambling symptoms, cocaine craving, and affective symptoms. Measurements were taken at baseline, immediately after the first week of treatment, and at 30 and 60 days post-stimulation. | Poremećaj uporabe kokaina i poremećaj kockanja dijagnosticiran prema DSM-5 kriterijima.<br>/ Cocaine use disorder and gambling disorder diagnosed according to DSM-5 criteria. | Obrasci upotrebe kokaina procjenjivanisamoizvještavanjem i testovima urina.Skala za procjenu simptoma kockanja (G-SAS), Upitnik za žudnju za kokainom (CCQ), BDI-II, skala za samoprocjenu anksioznosti (SAS) i Indeks kvalitete spavanja Pittsburgh (PSQI).<br>/ Cocaine use patterns assessed via self-report and urine tests; Gambling Symptom Assessment Scale (G-SAS), Cocaine Craving Questionnaire (CCQ), Beck Depression Inventory-II (BDI-II), Self-Rating Anxiety Scale (SAS), Pittsburgh Sleep Quality Index (PSQI). | Dva puta dnevno stimulacijalijevog DLPFC tijekom prvih pet uzastopnih dana, nakon toga stimulacije jedan dan u tjednu dva puta dnevno tijekom osam tjedana. Stimulacija je izvršena rTMS frekvencijom 15 Hz, intenziteta 100% motornog praga, 60 impulsa po seriji stimulacije sa intervalom između serija 15 sekundi. Trajanje sesije13 minuta.<br>/ Stimulation of the left DLPFC twice daily during the first five consecutive days, followed by twice-daily sessions once a week for eight weeks. rTMS was administered at 15 Hz, at 100% of the motor threshold, with 60 pulses per stimulation train and 15-second intervals between trains. Each session lasted 13 minutes. | Značajno i održano smanjenje žudnje i simptoma kockanja; poboljšanja sna i afektivnih simptoma.<br>/ Significant and sustained reduction in craving and gambling symptoms; improvements in sleep quality and affective symptoms. |

**TABLICA 1.** *Nastavak*
**TABLE 1.** *Continued*

| | Autori i godina / Authors and year | Zemlja / Country | Ispitanici Rod/spol / Participants Sex/Age | Ciljevi i dizajn istraživanja / Study aims and design | DG (MKB ili DSM kriteriji) / DG (ICD or DSM criteria) | Skale / Scales | Vrsta tretmana / Type of treatment | Rezultati / Results |
|---|---|---|---|---|---|---|---|---|
| 9. | Pettorruso et al., 2019 (67) | Italija / Italy | Jedan muški pacijent / 1 male patient | Prikaz slučaja koji ima za cilj prikazati kliničke i dopaminergičke učinke visokofrekventne rTMS stimulacije lijevog DLPFC-a te procijeniti promjene u dostupnosti dopaminskih transportera (DAT) u caudatusu i putamenu, obostrano-pomoću SPECT snimanja prije i nakon intervencije / Case report aimed at demonstrating the clinical and dopaminergic effects of high-frequency rTMS over the left DLPFC and assessing changes in dopamine transporter (DAT) availability in the caudate and putamen bilaterally, using SPECT imaging before and after the intervention. | Dijagnosticiran poremećaj kockanja prema DSM-5 kriterijima. / Gambling disorder diagnosed according to DSM-5 criteria. | G-SAS, PG-YBOCS, BDI, Indeks ozbiljnosti nesanice (ISI), YMRS / G-SAS, PG-YBOCS, BDI, Insomnia Severity Indeks (ISI), YMRS | 20 sesija stimulacije lijevog DLPFC rTMS tijekom 5 dana u tjednu, Frekvencija 15 Hz i intenzitet 100% motoričkog praga). Potom faza održavanja - dvije aplikacije tjedno tijekom dvanaest tjedana. / 20 sessions of rTMS over the left DLPFC, administered 5 days per week at 15 Hz and 100% of the motor threshold, followed by a maintenance phase with two sessions per week over twelve weeks. | Prekid kockanja i smanjenje žudnje održano tijekom 6 mjeseci; smanjena DAT dostupnost; bez nuspojava. / Gambling cessation and craving reduction maintained over six months; reduced DAT availability; no adverse effects reported |
| 10. | Pettorruso et al., 2019 (68) | Italija / Italy | 8 pacijenata (7M, 1Ž) / 8 patients (7M, 1F) | Otvorena, tromjesečna studija izvedivosti (feasibility), bez kontrolne skupine. Cilj je bio evaluacija učinka višekratnog HF-rTMS-a na simptome poremećaja kockanja i recidiv tijekom 3 mjeseca praćenja. Evaluacije na početku (T0), nakon 2 tjedna (T1), te nakon 4, 8 i 12 tjedana (T2–T4). / Open-label, three-month feasibility study without a control group, aimed at evaluating the effects of multiple HF-rTMS sessions on gambling disorder symptoms and relapse during a three-month follow-up period. Evaluations were conducted at baseline (T0), after 2 weeks (T1), and at 4, 8, and 12 weeks (T2–T4). | Dijagnosticiran poremećaj kockanja prema DSM-5 kriterijima / Gambling disorder diagnosed according to DSM-5 criteria. | G-SAS, PG-YBOCS, BDI, SAS | 20 sesija stimulacije lijevog DLPFC , 15 Hz, intenzitet 100% motoričkog praga. U fazi tretmana stimulacija dva puta dnevno , pet dana u tjednu kroz 2 tjedna. U tromjesečnoj fazi održavanja 2 sesije tjedno (isti dan) kroz 12 tjedana. / 20 sessions of HF-rTMS over the left DLPFC at 15 Hz, 100% of the motor threshold. During the treatment phase, stimulation was applied twice daily, five days per week for two weeks. During the three-month maintenance phase, two sessions were administered on the same day weekly for 12 weeks. | Značajno i održano smanjenje simptoma kockanja i dana provedenih u kockanju; djelomično poboljšanje depresivnih simptoma; održano i tijekom 12 tjedana faze održavanja / Significant and sustained reduction in gambling symptoms and days spent gambling; partial improvement in depressive symptoms; maintained throughout the 12-week maintenance phase. |
| 11. | Salerno et al., 2022 (69) | Italija / Italy | 6 (5M, 1Ž) / 6 (5M, 1F) | Otvorena *proof-of-concept* studija, bez kontrolne skupine s ciljem ispitivanja sigurnosti i preliminarnog učinka cTBS-a na pre-SMA u smanjenju simptoma kod poremećaja kockanja. Evaluacije u tri točke: prije (T0), 10. dan (T1), 30 dana nakon (T2). / Open-label proof-of-concept study without a control group, aimed at assessing the safety and preliminary effects of cTBS over the pre-SMA in reducing symptoms in gambling disorder. Evaluations were conducted at three time points: before treatment (T0), on day 10 (T1), and 30 days post-treatment (T2). | Poremećaj kockanja dijagnosticiran prema kriterijima DSM-5 / Gambling disorder diagnosed according to DSM-5 criteria. | PG-YBOCS, CGI, Upitnik žudnje za kockanjem (GamblingUrgesQuestionnaireGUQ), BIS-11, HAM-A, HAM-D, Sheehan skala invalidnosti (SDS), FTND. / PG-YBOCS, CGI, Gambling Urges Questionnaire (GUQ), BIS-11, HAM-A, HAM-D, Sheehan Disability Scale (SDS), FTND. | 10 sesija cTBS-a na bilateralni pre-SMA. Stimulacija uključuje 2 serije po 600 pulseva (ukupno 1200), 80 % motoričkog praga, neuronavigacija uz korištenje individualnog MRI-a. / 10 sessions of cTBS over the bilateral pre-SMA. Stimulation consisted of 2 trains of 600 pulses each (total of 1,200 pulses) at 80% of the motor threshold, with neuronavigation using individual MRI scans. | Statistički značajne razlike u rezultatima PG-YBOCS u različitim vremenskim točkama tijekom intervencije, značajno smanjenje rezultata na CGI skali, ostale skale bez značajnih promjena / Statistically significant differences in PG-YBOCS scores across different time points during the intervention, significant reduction in CGI scores, with no significant changes on other scales. |
| 12. | Salatino et al., 2022 (70) | Italija / Italy | 1 muškarac / 1 male | Prikaz slučaja s ciljem ispitivanja učinka niskodoznetDCS stimulacije na impulzivnost, donošenje odluka i kognitivno funkcioniranje. IGT primijenjen tijekom posljednje 3 minute trajanja stimulacije. Skale primijenjene u četiri vremenske točke: T0 (7 dana prije), T1 (prije prve sesije), T2 (dan nakon zadnje sesije), T3 (2 tjedna nakon kraja tretmana). / Case report aimed at investigating the effects of low-dose tDCS stimulation on impulsive behavior, decision-making, and cognitive functioning. The IGT was administered during the last 3 minutes of stimulation. Scales were administered at four time points: T0 (7 days before treatment), T1 (before the first session), T2 (the day after the last session), and T3 (2 weeks post-treatment). | Poremećaj kockanja dijagnosticiran prema kriterijima DSM-5 / Gambling disorder diagnosed according to DSM-5 criteria. | HAM-D, BIS-11, SOGS, Canadian Problem Gambling Indeks (CPGI) / HAM-D, BIS-11, SOGS, Canadian Problem Gambling Index (CPGI) | 6 sesija tDCS 1 mA desna anoda / lijeva katoda na lijevi DLPFC jednom dnevno u trajanju od 20 minuta, svaki drugi dan, tijekom dva tjedna / 6 sessions of tDCS at 1 mA with right anode / left cathode over the left DLPFC, administered once daily for 20 minutes, every other day over two weeks. | Smanjeni SOGS i CPGI i impulzivnost; poboljšana kognitivna funkcija i Go/No-go performanse; pogoršanje anksioznosti / Reduced SOGS and CPGI scores and impulsive behavior; improved cognitive function and Go/No-go task performance; increased anxiety. |
| 13. | Dantas et al., 2023 (71) | Nizozemska / The Netherlands | 30 sudionika (18Ž, 12M) / 30 participants (18F, 12M) | Eksperimentalni, randomizirani unutar-ispitanika dizajn studije, u kojem su svi sudionici bili izloženi trima uvjetima stimulacije (cTBS nad rDLPFC, cTBS nad VMPFC i sham stimulacija). Cilj je bio testirati hipoteze da supresija rDLPFC-a povećava sklonost riziku zbog smanjene izvršne kontrole, a supresija VMPFC-a smanjuje sklonost riziku.Prije i poslije svake stimulacije sudionici su rješavali MaastrichtGamblingTask (MGT). / Experimental, randomized within-subject design in which all participants were exposed to three stimulation conditions (cTBS over the right DLPFC, cTBS over the VMPFC, and sham stimulation). The aim was to test the hypotheses that suppression of the right DLPFC increases risk-taking due to reduced executive control, while suppression of the VMPFC decreases risk-taking. Before and after each stimulation session, participants completed the Maastricht Gambling Task (MGT). | Zdravi dobrovoljci, bez dijagnosticiranih psihičkih i neuroloških bolesti / Healthy volunteers with no diagnosed psychiatric or neurological disorders | Nisu korištene skale; promatralo se ponašanju u MGT, zadatku donošenja odluka pod rizikom. / No scales used; behavior was observed during the MGT, a risk-based decision-making task. | cTBS koja se sastojala od 3 impulsa pri 50 Hz unutar svakog bursta,u ukupnom trajanju od 40 sekundi, pri 80 % motoričkog praga. Stimulacija je provedena nad desnim DLPFC-om (lokacija F4) i VMPFC-om dvostrukom konusnom zavojnicom za dublju penetraciju kod VMPFC-a. Tri sesije po sudioniku: cTBS nad desnim DLPFC, VMPFC i sham stimulacija. / cTBS consisting of 3 pulses at 50 Hz within each burst, with a total duration of 40 seconds at 80% of the motor threshold. Stimulation was applied over the right DLPFC (F4 location) and the VMPFC using a double-cone coil for deeper penetration at the VMPFC. Each participant received three sessions: cTBS over the right DLPFC, cTBS over the VMPFC, and sham stimulation. | Obje regije (rDLPFC i VMPFC) sudjeluju u donošenju odluka pod rizikom. Povećana sklonost riziku nakon inhibicije obje regije / Both regions (right DLPFC and VMPFC) are involved in risk-based decision-making. Increased risk-taking was observed after inhibition of both regions. |

## rTMS

### Randomizirana i zaslijepljena istraživanja

Zack i sur. proveli su dvostruko slijepo istraživanje u kojem su ispitani učinci jedne sesije visokofrekventne rTMS (10 Hz) na medijalni prefrontalni korteks te cTBS na desni DLPFC kod devet muškaraca s dijagnosticiranim problematičnim kockanjem. Uspoređujući aktivnu i *sham* stimulaciju, rTMS je rezultirao značajnim smanjenjem žudnje za kockanjem, dok cTBS nije pokazao učinak na impulsivne odluke ni na kognitivnu kontrolu (59).

Gay i sur. proveli su randomiziranu dvostruko slijepu *cross-over* studiju na 22 ispitanika s dijagnosticiranim poremećajem kockanja. Jedna sesija HF-rTMS (10 Hz) primijenjena na lijevi DLPFC dovela je do smanjenja žudnje izazvane podražajima vezanima uz kockanje, iako nije utjecala na ponašanje kockanja ili samokontrolu, a izostanak naknadnog praćenja onemogućio je procjenu trajnosti učinka (60).

Sauvaget i sur. ispitali su učinak jedne sesije niskofrekventne rTMS (1 Hz) nad desnim DLPFC u dvostruko slijepom dizajnu s 30 sudionika. Intervencija nije rezultirala statistički značajnim smanjenjem žudnje za kockanjem ni na samoprocjenskim ljestvicama ni na fiziološkim mjerama u usporedbi sa sham stimulacijom (61).

### Nerandomizirana i/ili nezaslijepljena istraživanja

Cardullo i sur. proveli su seriju slučajeva na sedam muškaraca s komorbidnim poremećajem kockanja i uporabom kokaina. Višekratna HF-rTMS stimulacija lijevog DLPFC-a rezultirala je trajnim poboljšanjima simptoma kockanja, žudnje za kokainom i negativnog afekta, održanim tijekom 60-dnevnog praćenja (66).

Pettorruso i sur. opisali su slučaj pacijenta s poremećajem kockanja kod kojeg je primjena 20 sesija rTMS-a nad lijevim DLPFC-om dovela do

## rTMS

### Randomized and blinded studies

Zack et al. conducted a double-blind study investigating the effects of a single session of high-frequency rTMS (10 Hz) over the medial prefrontal cortex and cTBS over the right DLPFC in nine men diagnosed with problematic gambling. Comparing active and sham stimulations, rTMS resulted in a significant reduction in gambling craving, while cTBS showed no effect on impulsive decisions or cognitive control (59).

Gay et al. conducted a randomized double-blind cross-over study on 22 participants diagnosed with gambling disorder. A single session of HF-rTMS (10 Hz) applied over the left DLPFC led to a reduction in cue-induced gambling craving, although it did not affect gambling behavior or self-control, and the absence of follow-up prevented an assessment of the durability of the effect (60).

Sauvaget et al. examined the effects of a single session of low-frequency rTMS (1 Hz) over the right DLPFC in a double-blind design with 30 participants. The intervention did not result in a statistically significant reduction in gambling craving, neither on self-report scales nor on physiological measures compared to sham stimulation (61).

### Non-randomized and/or unblinded studies

Cardullo et al. conducted a case series on seven men with comorbid gambling disorder and cocaine use. Multiple sessions of HF-rTMS over the left DLPFC resulted in sustained improvements in gambling symptoms, cocaine craving, and negative affect, which were maintained over a 60-day follow-up period (66).

Pettorruso et al. described the case of a patient with gambling disorder in whom 20 sessions of rTMS over the left DLPFC led to clinical improvement and a reduction in dopamine trans-

kliničkog poboljšanja i smanjenja dostupnosti dopaminskog transportera u strijatumu (prema SPECT snimanju) uz održanu apstinenciju tijekom šest mjeseci (67).

U daljnjoj studiji istih autora na osam pacijenata višekratni rTMS tretman praćen tromjesečnom fazom održavanja rezultirao je značajnim i održanim smanjenjem simptoma poremećaja kockanja (G-SAS) i učestalog kockanja, uz dobru podnošljivost terapije (68).

Lohse i sur. testirali su učinke rTMS-a na impulsivno donošenje odluka kod zdravih ispitanika. Rezultati su pokazali da rTMS nad pre-SMA regijom modificira povezanost između osobine impulzivnosti i impulzivnog ponašanja u realnom vremenu, sugerirajući mogućnost ciljane modulacije donošenja odluka (64).

## dTMS

Istraživanje Rosenberga i sur. bila je nerandomizirana probna studija u kojoj je sudjelovalo 5 muških pacijenata s dijagnozom patološkog kockanja liječenih dTMS-om pomoću H1 zavojnice usmjerene na lijevi prefrontalni korteks tijekom 15 dana. Ishodi su procijenjeni pomoću Hamiltonove ljestvice za depresiju i anksioznost (HAM-D, HAM-A), Yale-Brownove opsesivno-kompulzivne ljestvice (Y-BOCS) i South Oaks Gambling Screen (SOGS). Unatoč početnom poboljšanju rezultata na ljestvicama, anamneza je pokazala izostanak promjena u ponašanju (65).

## TBS

Istraživanje Dantas i sur. uključilo je 30 zdravih odraslih osoba (18 žena, 12 muškaraca). Ispitanici su bili podvrgnuti cTBS stimulaciji desnog DLPFC-a, VMPFC-a i sham stimulaciji u unutar-ispitanika dizajnu. Primijenjen je *Maastricht Gambling Task* (MGT) kojim su mjereni ponašajni indikatori rizika uključujući standardnu devijaciju odabira, prosječnu odabranu

porter availability in the striatum (as measured by SPECT imaging), with maintained abstinence over a period of six months (67).

In a subsequent study conducted by the same authors, eight patients underwent multiple rTMS treatments followed by a three-month maintenance phase, which resulted in significant and sustained reductions in gambling disorder symptoms (G-SAS) and gambling frequency, with good treatment tolerability (68).

Lohse et al. tested the effects of rTMS on impulsive decision-making in healthy participants. The results showed that rTMS over the pre-SMA region modified the association between trait impulsivity and real-time impulsive behavior, suggesting a potential for targeted modulation of decision-making (64).

## dTMS

A study by Rosenberg et al. was a non-randomized pilot study involving five male patients diagnosed with pathological gambling, who were treated with dTMS using an H1 coil targeting the left prefrontal cortex over 15 days. The outcomes were assessed using the Hamilton Depression and Anxiety Rating Scales (HAM-D, HAM-A), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and the South Oaks Gambling Screen (SOGS). Despite initial improvement on scale scores, clinical interviews indicated no behavioral changes (65).

## TBS

A study by Dantas et al. included 30 healthy adults (18 women, 12 men). The participants underwent cTBS stimulation over the right DLPFC, VMPFC, and sham stimulation in a within-subject design. The Maastricht Gambling Task (MGT) was used to measure behavioral risk indicators, including standard deviation of choices, average selected value, and reaction time. Following active cTBS stimulation

vrijednost i vrijeme reakcije. Nakon aktivne cTBS stimulacije obje regije, DLPFC i VMPFC, zabilježeno je povećanje rizičnog ponašanja, što ukazuje na funkcionalnu uključenost ovih regija u donošenje odluka kod kockanja (71).

Salerno i sur. proveli su *proof-of-concept* istraživanje u kojem je sudjelovalo 6 pacijenata (5 muškaraca, 1 žena) s poremećajem kockanja. Primijenjeno je 10 sesija cTBS-a nad bilateralnom pre-SMA. Ishodi su procijenjeni pomoću PG-YBOCS, kliničke globalne ljestvice dojma (CGI), ljestvice impulzivnosti (BIS-11), ljestvica za depresiju i anksioznost (HAM-D, HAM-A), GUQ, SDS i FTND. Zabilježeno je statistički značajno smanjenje simptoma kockanja (PG-YBOCS) i poboljšanje CGI dok promjene na ostalim ljestvicama nisu bile značajne (69).

## tDCS

### Randomizirana i zaslijepljena istraživanja

Soyata i sur. proveli su trostruko slijepo, randomizirano, placebom kontrolirano istraživanje 20 muških ispitanika s poremećajem kockanja prema DSM-5. Sudionici su primili tri sesije anodne tDCS stimulacije desno/katodne lijevo (2 mA, 20 minuta) nad bilateralnim DLPFC-om. Ishodi su procijenjeni *Iowa Gambling Taskom* (IGT) i Wisconsin testom sortiranja karata (WCST). Nakon aktivne tDCS stimulacije sudionici su pokazali bolje donošenje odluka i veću kognitivnu fleksibilnost (62).

Martinotti i sur. su u istraživanju na 34 sudionika s poremećajem ovisnosti, od kojih je četvero imalo poremećaj kockanja, procjenjivali utjecaj tDCS na žudnju, depresivne i anksiozne simptome te impulzivnost pomoću VAS, HAM-D, HAM-A i BIS-11. Aktivna stimulacija rezultirala je značajnim smanjenjem žudnje, dok su i aktivna i sham skupina pokazale unutargrupno smanjenje depresije, anksioznosti i impulzivnosti (63).

of both regions, the DLPFC and VMPFC, an increase in risky behavior was observed, indicating a functional involvement of these regions in decision-making while gambling (71).

Salerno et al. conducted a proof-of-concept study involving six patients (five men, one woman) with gambling disorder. Ten sessions of cTBS were applied over the bilateral pre-SMA. The outcomes were assessed using the PG-YBOCS, Clinical Global Impression (CGI) scale, the Barratt Impulsiveness Scale (BIS-11), the Hamilton Depression and Anxiety Rating Scales (HAM-D, HAM-A), the Gambling Urge Questionnaire (GUQ), the Sheehan Disability Scale (SDS), and the Fagerström Test for Nicotine Dependence (FTND). A statistically significant reduction in gambling symptoms (PG-YBOCS) and improvement in CGI were observed, while changes on other scales were not significant (69).

## tDCS

### Randomized and blinded studies

Soyata et al. conducted a triple-blind, randomized, placebo-controlled study involving 20 male participants diagnosed with gambling disorder according to DSM-5. The participants received three sessions of anodal right/cathodal left tDCS (2 mA, 20 minutes) over the bilateral DLPFC. The outcomes were assessed using the Iowa Gambling Task (IGT) and the Wisconsin Card Sorting Test (WCST). Following active tDCS stimulation, the participants showed improved decision-making and greater cognitive flexibility (62).

In a study involving 34 participants with addiction disorders, of which four suffered from gambling disorder, Martinotti et al. evaluated the impact of tDCS on craving, depressive and anxiety symptoms, and impulsive behavior using VAS, HAM-D, HAM-A, and BIS-11. Active stimulation resulted in a significant reduction in craving, while both the active and sham

Od istraživanja koja nisu randomizirana Salatino i sur. opisali su slučaj 45-godišnjeg pacijenta s poremećajem kockanja koji je primio 6 sesija tDCS-a (anodna desno/katodna lijevo) svaki drugi dan tijekom dva tjedna. Evaluacija je uključivala *South Oaks Gambling Screen* (SOGS), CPGI, BIS-11, MoCA, SF-36, HAM-A te kognitivne zadatke poput *Iowa GamblingTaska*, *Go/No-Go*, koji su bili primijenjeni tijekom posljednje tri minute svake sesije stimulacije. Uočeno je smanjenje impulzivnosti i poboljšanje kognitivnih funkcija uz blago povećanje anksioznosti (70).

Sagledano u cjelini, većina uključenih istraživanja koristila je upitnike za procjenu učinaka neinvazivne stimulacije mozga na žudnju za kockanjem i druge simptome poremećaja. Najčešće korištena mjera bila je vizualno-analogna ljestvica za procjenu trenutne žudnje (59-61). Osim nje, primjenjivane su i specifične ljestvice poput G-SAS (66,68) PG-YBOCS (60,61,68,69), GACS (61) te SOGS (60,65,70). U nekim su istraživanjima korišteni dodatni upitnici za ispitivanje sekundarnih ishoda uključujući Beckov inventar depresije (BDI-II) (66), HAM-D, HAM-A (65,69,70), BIS-11 (69,70) i Pittsburgh indeks kvalitete spavanja (PSQI)(66). Kognitivne promjene su značajno rjeđe ispitivane. Samo su dvije studije koje su uključivale pacijente s poremećajem kockanja koristile bihevioralne zadatke, i to IGT i WCST (62,70), za procjenu donošenja odluka i kognitivne fleksibilnosti. Osim toga, jedno istraživanje na zdravim ispitanicima koristilo je MGT za kvantifikaciju rizičnih izbora (71).

Od ukupno 13 uključenih istraživanja, sedam ih je koristilo TMS protokole (59-61,65-68), tri su koristila tDCS (62,63,70), a tri su koristila cTBS kao zasebni oblik stimulacije (59,69,71). Među TMS istraživanjima najčešće su primjenjivani visokofrekventni protokoli (10 ili 15 Hz) usmjereni na lijevi DLPFC ili medijalni prefrontalni korteks (59,60,66-68). U većini slučajeva korištene su zavojnice u obliku broja

groups showed within-group reductions in depression, anxiety, and impulsive behavior (63).

In a non randomized study, Salatino et al. described the case of a 45-year-old male patient with gambling disorder who received six sessions of tDCS (anodal right/cathodal left) every other day for two weeks. Evaluation included the South Oaks Gambling Screen (SOGS), CPGI, BIS-11, MoCA, SF-36, HAM-A, as well as cognitive tasks such as the Iowa Gambling Task, and Go/No-go, administered during the last three minutes of each stimulation session. A reduction in impulsivity and improvement in cognitive functions were observed, with a slight increase in anxiety (70).

Overall, most included studies utilized questionnaires to assess the effects of non-invasive brain stimulation on gambling craving and other symptoms of gambling disorder. The most commonly used measure was the visual analog scale (VAS) for assessing current craving (59, 60, 61). In addition, specific scales such as the Gambling Symptom Assessment Scale (G-SAS) (66, 68) PG-YBOCS (60, 61, 68, 69), GACS (61) and SOGS (60, 65, 70) were employed. Some studies utilized additional questionnaires to examine secondary outcomes, including the Beck Depression Inventory-II (BDI-II) (66), HAM-D, HAM-A (65, 69, 70), BIS-11 (69, 70) and the Pittsburgh Sleep Quality Index (PSQI) (66). Cognitive changes were assessed much less frequently. Only two studies involving patients with gambling disorder used behavioral tasks, namely the IGT and WCST (62, 70), to evaluate decision-making and cognitive flexibility. Additionally, one study on healthy participants utilized the Maastricht Gambling Task (MGT) to quantify risk-taking choices (71).

Out of the 13 included studies, seven utilized TMS protocols (59-61, 65-68), three used tDCS (62, 63, 70), and three used cTBS as a distinct form of stimulation (59, 69, 71). Among the TMS studies, high-frequency protocols (10 or 15 Hz) targeting the left DLPFC or medial pre-

osam, dok suRosenberg i sur. (65) koristili H1 zavojnicu u sklopu duboke TMS. U tDCS istraživanjima sva su se istraživanja usmjerila na bilateralnu stimulaciju DLPFC-a, u konfiguraciji anoda desno/katoda lijevo (62,63,70) s intenzitetima stimulacije između 1 i 2 mA. Broj sesija varirao je od jedne stimulacije do protokola od 6 sesija tijekom dva tjedna.

Dizajn istraživanja bio je raznolik: šest radova bilo je randomiziranih i/ili zaslijepljenih (59-63,71), dok su sedam studija činile nerandomizirane, otvorene studije ili prikazi slučajeva (64-70). Broj i učestalost sesija značajno su se razlikovali te su neka istraživanja koristila jednokratnu stimulaciju (61,63), dok su druga uključivala intenzivne protokole (npr. dva puta/dan tijekom više dana) s kasnijom fazom održavanja (67,68).

Većina istraživanja uključivala je osobe s dijagnozom poremećaja kockanja, većinom muškarce. Dantas i sur. (71) i Lohse i sur. (64) uključili su zdrave dobrovoljce, dok su samo Cardullo i sur. (66) uključili ispitanike s komorbiditetom (poremećaj upotrebe kokaina). Lijekovi su u većini istraživanja bili izostavljeni ili stabilni tijekom definiranog razdoblja, iako kriteriji stabilnosti nisu bili dosljedno specificirani.

Praćenje učinka (*follow-up*) provedeno je u nekoliko radova – primjerice, Pettorruso i sur. (67,68) izvještavaju o poboljšanju koje se održalo tijekom 3 do 6 mjeseci, dok su Salerno i sur. (69) pratili učinke u više točaka tijekom dvotjedne intervencije. Rosenberg i sur. (65) su osim upitnika koristili i heteroanamnezu članova obitelji za procjenu stvarnih promjena u ponašanju.

## RASPRAVA

Unatoč obećavajućim rezultatima u primjeni neinvazivne stimulacije mozga (NIBS) za liječenje poremećaja povezanih s ovisničkim ponašanjima, istraživanja o primjeni NIBS-a za

frontal cortex were most commonly applied (59, 60, 66-68). Figure-eight coils were predominantly used, while Rosenberg et al. (65) used H1 coil for dTMS. In the tDCS studies, all research targeted bilateral DLPFC stimulation using a right anode/left cathode configuration (62, 63, 70) with stimulation intensities ranging between 1 and 2 mA. The number of sessions varied from a single stimulation session to six-session protocols over two weeks.

Study designs were heterogeneous: six studies were randomized and/or blinded (59-63, 71), while seven consisted of non-randomized, open-label studies or case reports (64-70). The number and frequency of sessions varied significantly, with some studies using single-session stimulation (61, 63), while others implemented intensive protocols (e.g., twice daily over multiple days) followed by maintenance phases (67, 68).

Most studies included individuals diagnosed with gambling disorder, predominantly men. Dantas et al. (71) and Lohse et al. (64) included healthy volunteers, while Cardullo et al. (66) conducted the only study that included participants with comorbidity (cocaine use disorder). Medications were either absent or stable during a defined period in most studies, although stability criteria were not consistently specified.

Follow-up assessments were conducted in several studies – for example, Pettorruso et al. (67, 68) reported improvements sustained over 3 to 6 months, while Salerno et al. (69) monitored effects at multiple time points during a two-week intervention. Rosenberg et al. (65) utilized family member interviews in addition to questionnaires to assess actual behavioral changes.

## DISCUSSION

Despite promising results regarding the use of non-invasive brain stimulation (NIBS) in treating addiction-related disorders, research on the

poremećaj uzrokovan kockanjem su rjeđa nego što je to za poremećaje vezane uz druge ovisnosti. Rezultati prikazanih istraživanja upućuju na sve veći znanstveni interes za potencijalnu ulogu neinvazivne stimulacije mozga u liječenju poremećaja kockanja. Iako su metodološki pristupi, ciljne regije i protokoli stimulacije bili raznoliki, većina radova izvještava o pozitivnim učincima na žudnju, simptome poremećaja kockanja i, u manjoj mjeri, na kognitivne funkcije.

Od 13 istraživanja, šest je bilo randomiziranih i kontroliranih pasivnom zavojnicom (placebom), dok su ostale studije bile nerandomizirane, prikazi slučajeva i serije slučajeva. Većina pregledanih studija bila je presječna, a samo tri studije su pratile ispitanike tijekom duljih razdoblja od 60 dana (66), 12 tjedana (68) i šest mjeseci (67).

U većini istraživanja ciljana regija bila je lijevi DLPFC, što je u skladu s literaturom o istraživanjima korištenja NIBS u liječenju poremećaja zloporabe supstancija (72). Iznimke su studije koje su ciljale mPFC(59),VMPFC (71) Ipre-SMA (64,69).

DLPFC ima ključnu ulogu u regulaciji kognitivnih funkcija uključujući izvršne funkcije, inhibiciju i pažnju kao i radno pamćenje, kognitivnu fleksibilnost te planiranje i žudnju (73). Kober i sur. su usporedbom žudnje između poremećaja upotrebe kokaina i poremećaja kockanja ustanovili kako se nakon okidačkog podražaja kod pacijenata s ovim poremećajima žudnja javlja u sličnoj mjeri. No uz DLPFC pokazali su da je povećana aktivnost u dmPFC i dorzalnom prednjem cingularnom korteksu (dACC) prisutna u oba tipa ovisnosti kada se izazove žudnja (74). Goudriaan i sur. su također ustanovili veću subjektivnu žudnju kod kockara u usporedbi s ovisnicima o nikotinu (75), što potvrđuje da je žudnja svakako bitan aspekt poremećaja kockanja.

Primijenjeni protokoli uključivali su visokofrekventni rTMS (59,60,66-68) zavojnicom u obliku broja 8, niskofrekventni rTMS (61), dTMS s

application of NIBS in gambling disorder remains less prevalent compared to other addiction disorders. The findings from the reviewed studies indicate growing scientific interest in the potential role of NIBS in the treatment of gambling disorder. Although methodological approaches, target regions, and stimulation protocols varied across studies, most studies reported positive effects on craving, gambling disorder symptoms, and, to a lesser extent, cognitive functions.

Out of the 13 studies included, six were randomized and sham-controlled (placebo), while the others were non-randomized studies, case reports, and case series. Most of the reviewed studies were cross-sectional, with only three studies monitoring participants over longer periods of 60 days (66), 12 weeks (68) and six months (67), respectively.

In most studies, the left DLPFC was the primary target region, aligning with the existing literature on studies using NIBS in the treatment of substance use disorders (72). Exceptions included studies targeting the mPFC (59), VMPFC (71) and pre-SMA (64, 69).

The DLPFC plays a key role in regulating cognitive functions, including executive functions, inhibition and attention, as well as working memory, cognitive flexibility, planning, and craving (73). Kober et al. found that craving induced by cues in patients with cocaine use disorder and gambling disorder occurred at similar levels. Additionally, they demonstrated that alongside the DLPFC, increased activity in the dmPFC and dorsal anterior cingulate cortex (dACC) was present in both types of addiction during craving induction (74). Goudriaan et al. reported higher subjective craving in individuals with gambling disorder compared to nicotine-dependent individuals (75), confirming that craving is certainly a crucial aspect of gambling disorder.

The applied protocols included high-frequency rTMS (59, 60, 66-68) with figure-eight coil,

H1 zavojnicom (65), cTBS (59,69,71) i tDCS s anodom desno i katodom lijevo (62,63,70). Većina istraživanja izvještava o smanjenju žudnje za kockanjem (59-,61,66,67). Međutim, dva istraživanja nisu pokazala učinke NIBS-a na žudnju za kockanjem. Jedno se koristilo dTMS H1 zavojnicom (65), dok kod druge nije bilo razlike između stvarne i pasivne stimulacije (61). Smanjenje žudnje je skladu s time da je ovisnost o kockanju u DSM-5 svrstana među ovisnosti gdje je žudnja ključna komponenta ovisnosti. Stoga se modeli liječenja razvijeni za poremećaje povezane s psihoaktivnim tvarima često primjenjuju na bihevioralne ovisnosti, iako za sada još uvijek nije u potpunosti jasno u kojoj mjeri se ovi oblici ovisnosti podudaraju (76).

Samo nekoliko istraživanja usredotočilo se na djelovanje NIBS na smanjenje ponašanja povezanog s kockanjem ili poboljšanjem kliničke slike. Istraživanje Gay i sur. nije pokazalo smanjenje na PG-YBOCS (60), istraživanje Sauvaget i sur. nije pokazalo statistički značajno poboljšanje ispitivanih kognitivnih distorzija povezanih s kockanjem (61), a Rosenberg i sur. (65) zabilježili su diskrepanciju između poboljšanja na ljestvicama i stvarnog ponašanja. S druge strane, serije slučajeva pokazale su pozitivan klinički učinak: Cardullo i sur. (66) izvijestili su o poboljšanju kliničke slike koje se održalo tijekom 60-dnevnog praćenja, a pacijenti Pettorrussa i njegovog tima nisu imali relaps kockanja tijekom 12-tjednog praćenja (67) i pokazali su smanjenje dana provedenih u kockanju (68). I kod Salerna i sur. došlo je do smanjenja jačine simptoma poremećaja kockanja te poboljšanja kliničke slike (69). Kada se pogleda broj apliciranih sesija stimulacije, studije Salernovog i Pettorussovog tima koje su pokazale ova poboljšanja na kliničkoj slici imala su više sesija stimulacije no s obzirom na mali broj ispitanika i nekontroliran dizajn, uzročno-posljedična povezanost ostaje nejasna.

U literaturi je opaženo da je kod bihevioralnih ovisnosti i poremećaja povezanih s upotrebom supstancija prisutna povećana razina impul-

low-frequency rTMS (61), dTMS with H1coil (65), cTBS (59, 69, 71) and tDCS with a right anode/left cathode configuration (62, 63, 70). Most studies reported reductions in gambling craving (59, 61, 60, 66, 67). However, there were two studies that found no effect of NIBS on gambling craving: one was using dTMS with the H1 coil (65), while another showed no difference between active and sham stimulation (61). The reduction in craving aligns with the DSM-5 classification of gambling disorder within addictions, where craving is a key component. Consequently, the treatment models developed for psychoactive substance use disorders are often applied to behavioral addictions, although the extent to which these addictions overlap remains unclear (76).

Only a few studies focused on the effects of NIBS on reducing gambling behavior or improving clinical symptoms. Gay et al. found no reduction on the PG-YBOCS (60), Sauvaget et al. reported no significant improvements in gambling-related cognitive distortions examined (61), and Rosenberg et al. (65) observed discrepancies between improvements on scales and actual behavioral changes. In contrast, case series demonstrated positive clinical effects: Cardullo et al. (66) reported symptom improvements maintained over a 60-day follow-up, while Pettorruso et al. observed no gambling relapses during the 12-week follow-up (67) and recorded reductions in gambling days (68). Salerno et al. also reported reductions in the severity of gambling disorder symptoms, as well as clinical improvements (69). In terms of stimulaiton sessions applied, the studies by Pettorruso's and Salerno's teams showing these clinical improvements involved more stimulation sessions, yet due to small sample sizes and uncontrolled designs, causality remains unclear.

The literature highlights increased impulsivity levels in behavioral addictions and substance use disorders (77). Individuals with internet

zivnosti (77) te da osobe ovisne o igrama na internetu i ovisnici o nikotinu imaju smanjenu funkcionalnu povezanost u mirovanju u desnoj inzuli i lijevom donjem frontalnom girusu s DLPFC-om u usporedbi sa zdravim kontrolama, ukazujući na slične neuralne inhibitorne mehanizme koji reguliraju žudnju i impulzivnost (73). Više istraživanja pregledanih u ovom raduje pokazalo je pozitivne učinke NIBS-a na impulzivnost, preuzimanje rizika, donošenje odluka i kognitivnu fleksibilnost (62,70,71).

Iako još nedovoljno istražena, cTBS se pokazala obećavajućom za modulaciju inhibicijskog ponašanja i donošenja odluka, posebice preko pre-SMA regije (69,71) te je pokazala progresivno smanjenje simptoma PG-YBOCS-a i poboljšanje CGI vrijednosti, bez zabilježenih nuspojava, potvrđujući sigurnost metode.

Sve uključene tDCS studije usmjerile su se na DLPFC, većinom konfiguracijom anoda desno/katoda lijevo (62,63,70). Ovaj pristup temelji se na dokazima da takva stimulacija može reducirati žudnju (79). Pokazalo se da tDCS poboljšava donošenje odluka i fleksibilnost bez izraženih nuspojava potvrđujući dobru podnošljivost metode.

Ostali sekundarni ishodi analizirani u pregledanim istraživanjima obuhvaćali su još i promjene u depresivnim i anksioznim simptomima i kvaliteti sna i svakodnevnom funkcioniranju. Iako učinci na ove domene nisu bili primarni fokus većine radova, određeni nalazi ukazuju na potencijalnu širinu terapijskog djelovanja NIBS-a, što je potvrđeno smanjenjem razine depresivnosti i anksioznosti te poboljšanjem kvalitete sna (66,68). Ipak, valja naglasiti da su ove promjene često bile sekundarno analizirane te se rijetko pratilo njihovo trajanje ili klinička relevantnost, što upućuje na potrebu za sustavnijim uključivanjem tih ishoda u budućim istraživanjima.

Nijedno od uključenih istraživanja nije izvijestilo o ozbiljnim nuspojavama, što potvrđuje

gaming disorder and nicotine dependence exhibit reduced resting-state functional connectivity in the right insula and left inferior frontal gyrus with the DLPFC compared to healthy controls, suggesting similar neural inhibitory mechanisms that regulate craving and impulsivity (73). Several studies reviewed here reported positive effects of NIBS on impulsive behavior, risk-taking, decision-making, and cognitive flexibility (62, 70, 71).

Although still under-investigated, cTBS has shown promise in modulating inhibitory behavior and decision-making, particularly via the pre-SMA region (69, 71), while it also demonstrated progressive symptom reductions on the PG-YBOCS and improvements on CGI scores without adverse effects, confirming its safety.

All included tDCS studies targeted the DLPFC, predominantly using a right anode/left cathode configuration (62, 63, 70). This approach is based on evidence suggesting that such stimulation can reduce craving (79). tDCS has been shown to improve decision-making and flexibility without significant adverse effects, thus confirming its good tolerability.

Other secondary outcomes examined in the reviewed studies included changes in depressive and anxiety symptoms, sleep quality, and daily functioning. Although effects on these domains were not the primary focus of most studies, some findings point to the potential therapeutic width of NIBS, which was confirmed by reported reductions in depression and anxiety levels and improved sleep quality (66, 68). However, it should be noted that these changes were often secondary analyses, and their duration or clinical relevance were rarely monitored, indicating a need for a more systematic inclusion of these outcomes in future research.

None of the included studies reported serious adverse events, thus confirming the good

dobar sigurnosni profil neinvazivnih metoda stimulacije mozga kada se provode u skladu s važećim smjernicama za primjenu i doziranje (80). Većina studija izričito navodi da tijekom i nakon tretmana nisu zabilježene štetne reakcije, dok su manje nuspojave poput blage nelagode, umora ili blagog pritiska ispod elektrode rijetke i samolimitirajuće.

Unatoč ohrabrujućim nalazima prisutni su brojni metodološki izazovi. Uključenim studijama zajednički su mali uzorci, često dominantno muškog spola, što je sukladno s time da je kod muškaraca veća prevalencija poremećaja kockanja (81). Zabilježena je znatna heterogenost u protokolima stimulacije, mjerama ishoda, ali i u načinu primjene. Neka istraživanja nisu jasno opisala proces randomizacije, a dio ih je koristio otvoreni dizajn što povećava mogućnost placebo efekta koji može biti zbunjujući čimbenik kod istraživanja koja koriste TMS (82).

Dodatni nedostatci prisutni su i u problemu praćenja nakon tretmana, budući da su istraživanja bila većinom presječna, uz kratka razdoblja praćenja. Nadalje, istraživanja su se razlikovala s obzirom na trenutak isporuke NIBS-a. Neka uključena istraživanja provela su stimulaciju dok su sudionici bili u mirovanju, dok su druga provodila stimulaciju odmah nakon ili tijekom indukcije žudnje. Žudnja je kompleksni fenomen ljudskog ponašanja čija je neuroanatomija još uvijek predmet istraživanja te nije striktno definirana (83) što otežava predviđanje ishoda stimulacije pojedinih dijelova mozga TMS-om.

Trenutni podatci podupiru daljnja istraživanja primjene NIBS-a u liječenju poremećaja kockanja, posebice rTMS-a i tDCS-a usmjerenih na DLPFC. Međutim da bi se potvrdila klinička učinkovitost potrebne su veće, randomizirane i longitudinalne studije s jasno definiranim kriterijima za oporavak i odgovor na liječenje. Važno je i bolje razumjeti neurobiološke me-

safety profile of noninvasive brain stimulation methods when they are conducted according to current guidelines for application and dosing (80). Most studies explicitly stated that no adverse reactions were observed during or after treatment, while minor side effects such as mild discomfort, fatigue, or slight pressure under the electrode were rare and self-limiting.

Despite encouraging findings, numerous methodological challenges remain. The included studies commonly featured small sample sizes, with predominantly male participants, which is consistent with the higher prevalence of gambling disorder among men (81). There was significant heterogeneity in stimulation protocols, outcome measures, and application methods. Some studies did not clearly describe the randomization process, and some used open-label designs, increasing the risk of placebo effects, which can be a confounding factor in studies using TMS (82).

Additional limitations included a lack of follow-up assessments after the treatment, as most studies were cross-sectional and with short monitoring periods. Furthermore, studies differed regarding the timing of NIBS delivery. Some administered stimulation at rest, while others did so immediately after or during craving induction. Craving is a complex phenomenon of human behavior, with neuroanatomical correlates still under investigation and not strictly defined (83), which complicates predictions of the outcomes of stimulating pecific brain regions with TMS.

The current data support further research into the application of NIBS in the treatment of gambling disorder, particularly rTMS and tDCS targeting the DLPFC. However, in order to confirm clinical efficacy, larger, randomized, and longitudinal studies with clearly defined recovery and treatment response criteria are required. Additionally, it is essential to better understand the neurobiological mechanisms and biomarkers

hanizme i biomarkere koji bi mogli predvidjeti odgovor na liječenje čime bi se smanjila heterogenost nalaza i unaprijedila personalizacija terapije. Poseban je izazov činjenica da oporavak od poremećaja kockanja nema jedinstvenu i precizno definiranu kliničku definiciju, što otežava mjerljivost i usporedivost učinkovitosti tretmana.

## ZAKLJUČAK

Ovaj narativni pregled pruža sustavan uvid u postojeća istraživanja o primjeni metoda neinvazivne stimulacije mozga u liječenju poremećaja kockanja. Pregledani radovi ukazuju na to da su rTMS i tDCS nad dorzolateralnim prefrontalnim korteksom najčešće korištene metode te da obje pokazuju potencijal za smanjenje žudnje za kockanjem, osobito kada se primjenjuju u višekratnim sesijama.

Iako su rezultati ohrabrujući, učinci NIBS-a na ponašanje i kliničku sliku ostaju nedovoljno istraženi, a nalazima često nedostaje konzistentnost. Sekundarni ishodi, poput razina depresivnosti, anksioznosti, impulzivnosti i kvalitete sna, pozitivno su se mijenjali u dijelu studija no bez sustavne evaluacije ili dugoročnog praćenja. Uočena je značajna metodološka heterogenost, kako u kriterijima dijagnosticiranja poremećaja kockanja, tako i u protokolima stimulacije, mjernim instrumentima i načinu primjene tretmana. Pritom valja istaknuti da nijedna studija nije zabilježila ozbiljne nuspojave-

Na temelju analize dosadašnjih istraživanja može se zaključiti da su metode NIBS-a obećavajući terapijski pristup, posebno u ciljanju žudnje i regulaciji impulzivnog ponašanja. Međutim, za jasnije određivanje njihove kliničke uloge nužna su dobro dizajnirana, randomizirana istraživanja s većim uzorcima, preciznijim neuroanatomski definiranim ciljevima i dugoročnim praćenjem kliničkih ishoda.

that could predict treatment response, which would reduce heterogeneity in findings and improve treatment personalization. A particular challenge is that recovery from gambling disorder lacks a single, precise clinical definition, thus complicating the measurability and comparability of treatment effectiveness.

## CONCLUSION

This narrative review provides a systematic overview of the existing studies on the application of non-invasive brain stimulation (NIBS) methods in the treatment of gambling disorder. The reviewed studies indicate that rTMS and tDCS targeting the dorsolateral prefrontal cortex are the most commonly used methods, both showing potential in reducing gambling craving, particularly when applied through multiple sessions.

Although the results are encouraging, the effects of NIBS on behavior and clinical outcomes remain insufficiently explored, with findings often lacking consistency. Secondary outcomes, such as levels of depression, anxiety, impulsive behavior, and sleep quality, showed positive changes in some studies, but without systematic evaluation or long-term follow-up. Significant methodological heterogeneity was observed, both in the diagnostic criteria for gambling disorder and in stimulation protocols, measurement instruments, and treatment application methods. Notably, none of the studies reported serious adverse effects.

Based on the analysis of current research, NIBS methods represent a promising therapeutic approach, particularly in targeting craving and regulating impulsive behavior. However, to clearly define their clinical role, well-designed, randomized studies with larger sample sizes, precisely defined neuroanatomical targets, and long-term monitoring of clinical outcomes are necessary.

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# Neurobiologija poremećaja pažnje i hiperaktivnosti

## */ Neurobiology of Attention Deficit Hyperactivity Disorder*

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Poremećaj pažnje i hiperaktivnosti (engl. *Attention deficit hyperactivity disorder,* ADHD) neurorazvojni je poremećaj karakteriziran poremećajem pažnje, prekomjernom motoričkom aktivnosti i impulzivnošću. Dijagnoza se postavlja na temelju kliničkog intervjua, opservacije ponašanja djeteta, heteroanamnestičkih podataka, važećih klasifikacija, odnosno različitim koracima u dijagnostičkom procesu. Ovaj pregledni rad ima za cilj prikazati aktuelno razumijevanje neurobioloških mehanizama koji doprinose mogućem nastanku i održavanju ADHD-a uključujući genetiku, moždane strukture i funkcije, kao i neurotransmitore. Ova tema je posebno interesantna s obzirom na etiopatogenetsku isprepletenost individualnih (biologijskih i psiholoških) i okolišnih čimbenika kod ADHD-a, a što je prikazano radovima u ovom pregledu. U liječenju ADHD-a koristimo psihosocijalne intervencije, kao i druge metode liječenja, a koje uključuju i farmakološko liječenje.

*/ Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by attention deficits, excessive motor activity, and impulsivity. Diagnosis is based on a clinical interview, observation of the child's behavior, heteroanamnestic data, valid classifications, and various steps in the diagnostic process. This review aims to present the current understanding of neurobiological mechanisms that contribute to the possible emergence and maintenance of ADHD, including genetics, brain structure and function, as well as neurotransmitters. This topic is particularly interesting due to the interplay of individual (biological and psychological) and environmental factors in ADHD, which is demonstrated in this review. In the treatment of ADHD, we use psychosocial interventions, as well as other treatment methods, which include pharmacological treatment.*

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**KLJUČNE RIJEČI / *KEY WORDS:***
Poremećaj pažnje i hiperaktivnosti / *Attention Deficit Hyperactivity Disorder*
Neurobiologija / *Neurobiology*

**TO LINK TO THIS ARTICLE:** https://doi.org/10.24869/spsih.2025.172

## UVOD

Poremećaj pažnje i hiperaktivnosti (engl. *Attention Deficit Hyperactivity Disorder,* ADHD) neurorazvojni je poremećaj karakteriziran trijasom simptoma koji uključuju visok stupanj motoričkog nemira, impulzivno ponašanje i poremećaj pažnje (1). Međutim, kriteriji su različiti za ADHD prema jedanaestoj reviziji Međunarodne klasifikacije bolesti i srodnih stanja Svjetske zdravstvene organizacije (MKB-11/ICD-11) (2) u odnosu na ADHD prema petoj reviziji Dijagnostičkog i statističkog priručnika za duševne poremećaje (DSM-5 ) Američke psihijatrijske udruge (3).

Sveukupno, pojavljuju se tri glavne razlike u ove dvije klasifikacije:

1. Broj dijagnostičkih kriterija za simptome nepažnje (IA), hiperaktivnosti (HY) i impulzivnosti (IM) (tj. DSM-5 ima devet IA i devet HY/IM simptoma, dok ICD-11 ima 11 IA i 11 HY/IM simptoma);
2. Jasnoća i standardizacija dijagnostičkih pragova (tj. dijagnostički pragovi za broj simptoma u IA i HY/IM domenama su eksplicitno navedeni u DSM-5, dok u ICD-11 nisu; i
3. Podjela HY i IM simptoma u poddimenzije (tj. razlika u podjeli domena simptoma HY i IM povezana je s razlikama između trenutnog i prethodnih izdanja DSM-a i MKB/ICD-a , a to ima važne istraživačke implikacije) (4).

Prema MKB-11/ICD-11 klasifikaciji (6A05), poremećaj pažnje i hiperaktivnosti karakteriziran je trajnim obrascem (najmanje 6 mjeseci) nepažnje i/ili hiperaktivnosti-impulzivnosti koji ima izravan negativan utjecaj na akademsko, profesionalno ili socijalno funkcioniranje. Da bi se postavila dijagnoza, simptomi nepažnje i/ili hiperaktivnosti-impulzivnosti moraju biti prisutni u više situacija ili okruženja (npr. kod kuće, u školi, na poslu, s prijateljima ili rodbinom), ali vjerojatno će varirati ovisno o strukturi i zahtjevima okruženja. Simptomi variraju ovisno o kronološkoj dobi i težini poremećaja. Simptomi se ne mogu bolje objasniti drugim mentalnim

## INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a triad of symptoms including high levels of motor restlessness, impulsive behavior, and inattention (1). However, the diagnostic criteria for ADHD differ between the 11th revision of the International Classification of Diseases (ICD-11) by the World Health Organization (2) and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (3).

Overall, three main differences exist between these two classifications:

1. The number of diagnostic criteria for symptoms of inattention (IA), hyperactivity (HY), and impulsivity (IM) (i.e., DSM-5 includes nine IA and nine HY/IM symptoms, whereas ICD-11 includes 11 IA and 11 HY/IM symptoms);
2. The clarity and standardization of diagnostic thresholds (i.e., the DSM-5 explicitly defines thresholds for the number of symptoms required in the IA and HY/IM domains, while the ICD-11 does not); and
3. The separation of HY and IM symptoms into subdimensions (i.e., the differences in the subdivision of HY and IM domains are associated with changes between current and previous editions of DSM and ICD, which has important research implications) (4).

According to ICD-11 classification (code 6A05), ADHD is characterized by a persistent pattern (minimum 6 months) of inattention and/or hyperactivity-impulsivity that significantly impairs academic, occupational, or social functioning. For diagnosis, symptoms must be present across multiple settings (e.g., at home, school, work, with friends or relatives), although they may vary depending on the structure and demands of the environment.

(ili duševnim) poremećajem (npr. poremećajem povezanim s anksioznošću ili strahom, neurokognitivnim poremećajem poput delirija). Simptomi nisu posljedica učinaka tvari (npr. kokaina) ili lijekova (npr. bronhodilatatora, lijekova za nadomjestak štitnjače) na središnji živčani sustav, uključujući i simptome odvikavanja, te nisu posljedica bolesti živčanog sustava.

Simptomi nepažnje uključuju:

- Teškoće u održavanju pažnje na zadacima koji ne pružaju visoku razinu stimulacije ili nagrade ili zahtijevaju kontinuirani mentalni napor; nedostatak pažnje prema detaljima; pravljenje pogrešaka u školskim ili radnim zadacima; nedovršavanje zadataka.
- Lako se ometa stranim podražajima ili mislima koje nisu povezane sa zadatkom; često se čini da ne sluša kada mu se izravno govori; često se čini da sanjari ili da su mu misli negdje drugdje.
- Gubi stvari; zaboravan je u svakodnevnim aktivnostima; ima poteškoća s pamćenjem dovršetka nadolazećih dnevnih zadataka ili aktivnosti; teškoće u planiranju, upravljanju i organiziranju školskih aktivnosti, zadataka i drugih aktivnosti.

Napomena: Nepažnja možda neće biti vidljiva kada je pojedinac uključen u aktivnosti koje pružaju intenzivnu stimulaciju i česte nagrade.

Simptomi hiperaktivnosti/impulzivnosti najočitiji su u strukturiranim situacijama koje zahtijevaju samokontrolu ponašanja,a uključuju:

- prekomjernu motoričku aktivnost; napuštanje mjesta kada se očekuje da mirno sjedi; često trči okolo; ima poteškoća sa mirnim sjedenjem bez vrpoljenja (mlađa djeca); osjećaji fizičkog nemira, osjećaj nelagode zbog tišine ili mirnog sjedenja (adolescenti i odrasli). Previše govori, izbrblja kod odgovoranja u školi, komentira na poslu; teško čeka red u razgovoru, igrama ili aktivnostima; prekida ili se miješa u tuđe razgovore ili igre.

Symptoms vary depending on the individual's chronological age and the severity of the disorder. Symptoms must not be better explained by another mental disorder (e.g., anxiety-related disorders, neurocognitive disorders such as delirium), nor be due to the effects of substances (e.g., cocaine) or medications (e.g., bronchodilators, thyroid hormone replacements) on the central nervous system, including withdrawal effects, nor due to neurological diseases.

Symptoms of inattention include:

- Difficulty sustaining attention on tasks that do not provide high stimulation or reward, or that require sustained mental effort;lack of attention to detail; careless mistakes in school or work tasks; unfinished tasks;
- Easily distracted by external stimuli or unrelated thoughts; often appears not to listen when spoken to directly; seems to daydream or to have thoughts elsewhere;
- Frequently loses items; forgetful in daily activities; trouble remembering upcoming tasks; difficulty planning, managing, and organizing schoolwork or other responsibilities.

Note: Inattention may not be apparent when the individual is engaged in activities offering intense stimulation or frequent rewards.

Symptoms of hyperactivity/impulsivity are most evident in structured situations requiring self-control, and include:

- Excessive motor activity; leaving one's seat when expected to remain seated; frequent running; difficulty sitting still (younger children); physical restlessness and discomfort with silence or stillness (adolescents and adults). Excessive talking, blurting out answers in class, making comments at work; difficulty waiting for one's turn in conversations or games; interrupting or intruding in others' conversations or play.

- Prisutna je sklonost impulzivnom djelovanju kao odgovor na neposredne podražaje bez promišljanja ili razmatranja rizika i posljedica (npr. sudjelovanje u ponašanjima s potencijalom za tjelesne ozljede; impulzivne odluke; nepromišljena vožnja) (2).

Prema DSM-5 klasifikaciji, u jednoj su skupini (klasteru) sindrom prekomjerne aktivnosti i impulzivnosti, a dob početka simptoma je podignuta na 12 godina života. Traži se da bude zadovoljeno barem šest od devet kriterija u vezi s nepažnjom i/ili barem šest od devet kriterija u vezi s hiperaktivošću/ impulzivnošću. Iznimka je u osoba starijih od 17 godina kada je dovoljno barem pet simptoma iz područja nepažnje i / ili barem pet simptoma iz područja hiperaktivnosti/impulzivnosti (1). Longitudinalne studije sugeriraju mogućnost najmanje četiri razvojna pravca ADHD-a koje uključuju rani početak (predškolski ADHD 3-5 godina), početak u srednjem djetinjstvu (6-14 godina) s postojanim tijekom, početak u srednjem djetinjstvu s adolescentnim pomakom i početak u adolescenciji ili odrasloj dobi (16 godina i stariji) (5,6). ADHD rijetko utječe na samo jednu životnu domenu. On utječe na mnoge aspekte života pojedinca uključujući fizičko zdravlje te školsko, društveno i radno funkcioniranje (7). Simptomi su povezani sa funkcionalnim oštećenjem i povećanim rizikom od depresije, zlouporabe sredstava ovisnosti i antisocijalnim ponašanjem (8). Pojedinci s ADHD-om imaju poteškoće u nekoliko domena uključujući pažnju i kognitivne funkcije: rješavanje problema, planiranje, orijentacija, upozoravanje, kognitivna fleksibilnost, održavanje pažnje i radna memorija (9,10).

Ovaj poremećaj pogađa djecu i odrasle diljem svijeta,a početak simptoma ima u ranoj dječjoj dobi načelno prije 5. godine života (11). Prema svjetskim podacima procjenjuje se da je prevalencija ADHD-a kod djece između 2,6 i 4,5 % (12) dok je kod odraslih oko 2,9 % (13).

ADHD se češće javlja u dječaka u odnosu na djevojčice (14).

- Tendency toward impulsive actions in response to immediate stimuli without reflection or consideration of risks and consequences (e.g., engaging in potentially dangerous behaviors; impulsive decisions; reckless driving) (2).

According to DSM-5, hyperactivity and impulsivity are grouped together, and the age of onset was raised to 12 years. At least six out of nine criteria related to inattention and/or at least six out of nine criteria related to hyperactivity/impulsivity must be met. An exception applies to individuals over the age of 17, for whom at least five symptoms in the domain of inattention and/or at least five symptoms in the domain of hyperactivity/impulsivity are sufficient (1). Longitudinal studies suggest at least four developmental trajectories of ADHD: early onset (preschool ADHD, ages 3–5), onset in middle childhood (ages 6–14) with a persistent course, onset in middle childhood with adolescent remission, and onset in adolescence or adulthood (age 16 and older) (5,6). ADHD rarely affects only one domain of life. It impacts many aspects, including physical health, academic performance, social interactions, and work functioning (7). Symptoms are associated with functional impairment and increased risk of depression, substance abuse, and antisocial behavior (8). Individuals with ADHD show deficits in various domains, including attention and cognitive functions: problem-solving, planning, orientation, alertness, cognitive flexibility, sustained attention, and working memory (9,10).

This disorder affects children and adults worldwide, with symptom onset typically before the age of five (11). Global estimates suggest a prevalence of 2.6–4.5% in children (12) and about 2.9% in adults (13).

ADHD is more prevalent in boys than in girls (14).

Dijagnoza ADHD-a postavlja se na temelju kliničkog intervjua, opservacije ponašanja djeteta ili osobe,heteroanamnestičkih podataka i važećih klasifikacija DSM-5 i MKB-11, a koristi se dijagnostički proces koji se inače koristi u dječjoj psihijatriji (15). Postavljanje dijagnoze ADHD-a ponekad je izazovno zbog značajne heterogenosti poremećaja u smislu kliničkih i patofizioloških aspekata (16). Bitno je voditi računa o diferencijalnoj dijagnozi koja pomaže kliničarima da razlikuju ADHD od drugih potencijalnih medicinskih stanja koja uzrokuju slične simptome, osiguravajući time provedbu odgovarajućih i učinkovitih strategija liječenja. Visoke stope psihijatrijskih komorbiditeta uočenih u bolesnika s ADHD-om i značajan udio preklapanja simptoma i uzroka s drugim mentalnim poremećajima važni su čimbenici koje treba razmotriti. Više od 60 % osoba s dijagnozom ADHD-a ima barem jedan komorbiditetni psihijatrijski poremećaj uključujući depresiju, anksioznost i poremećaj ponašanja. Međutim, sukladno njemačkim autorima, treba voditi brigu o vodećoj dijagnozi, odnosno ne preporučuje se davanje više od tri dijagnoze (17). Najčešći komorbiditeti u djece uključuju eksternalizirajuće (opozicijsko i prkosno ponašanje) poremećaje i poremećaje učenja (18,19,20). Anksioznost i depresija česti su komorbiditeti među adolescentima s ADHD-om. Istraživanja pokazuju da više od jedne trećine adolescenata s ADHD-om ima komorbidne anksiozne poremećaje(21). Nacionalno istraživanje o zdravlju djece u Sjedinjenim Državama iz 2007. godine pokazalo je da su djeca i adolescenti s ADHD-om imali veću vjerojatnost da će imati depresiju od onih bez ADHD-a (14%:1%) (22). Lee i sur. proveli su meta-analizu longitudinalnih studija koje su prospektivno pratile djecu sa i bez ADHD-a u adolescenciji ili odrasloj dobi. Djeca s ADHD-om imala su značajno veću vjerojatnost da će razviti poremećaje zlouporabe/ovisnosti o nikotinu, alkoholu, marihuani, kokainu i drugim drogama (23).

Nedavna istraživanja su pokazala da drugi neurorazvojni poremećaji poput autizma,

Diagnosis is based on clinical interviews, behavioral observation, hetero-anamnestic information, and the use of current classification systems (DSM-5 and ICD-11), following standard diagnostic procedures in child psychiatry (15). Diagnosing ADHD can be challenging due to the disorder's considerable heterogeneity in clinical and pathophysiological presentation (16). Differential diagnosis is essential to distinguish ADHD from other medical conditions that may produce similar symptoms and to implement appropriate treatment strategies. High rates of psychiatric comorbidity and symptom overlap with other mental disorders must be considered. Over 60% of individuals with ADHD have at least one comorbid psychiatric disorder, including depression, anxiety, and conduct disorders. However, according to German authors, attention should be paid to the primary diagnosis, and it is not recommended to assign more than three diagnoses (17). In children, the most common comorbidities include externalizing disorders (oppositional defiant disorder) and learning disabilities (18,19,20). Anxiety and depression are common among adolescents with ADHD, with research indicating that more than one-third have comorbid anxiety disorders (21). A 2007 U.S. National Survey of Children's Health found that children and adolescents with ADHD were more likely to be diagnosed with depression than those without (14% vs. 1%) (22). A meta-analysis by Lee et al. tracked children with and without ADHD into adolescence or adulthood. Children with ADHD had significantly higher odds of developing substance abuse or dependency on nicotine, alcohol, cannabis, cocaine, and other drugs (23).

Recent research suggests that other neurodevelopmental disorders such as autism, schizophrenia, and epilepsy share genetic variants with ADHD, indicating potential comorbidities (24). Individuals with ADHD also have higher

shizofrenije i epilepsije dijele genske varijante s ADHD-om, a što bi također upućivalo na moguće komorbiditete (24). Bolesnici s ADHD-om također imaju veću stopu pretilosti, poremećaja spavanja, astme, autoimunih i upalnih bolesti te drugih somatskih i metaboličkih problema (25,26,27). Aktualno razumijevanje neurobioloških mehanizama koji doprinose mogućem nastanku i održavanju ADHD-a, uključujući genetiku, moždane strukture i funkcije, i neurotransmitore čini nam se posebno interesantnom temom s obzirom na isprepletenost individualno-bioloških, individualno-psiholoških i okolišnih čimbenika kod ADHD-a.

U svrhu ovog preglednog rada pretražene su baze podataka *WOS*, *Medline*, *Scopus*, *PubMed* i *Google Scholar* pristupom koji koristi kombinacije ključnih riječi poremećaj pažnje i aktivnosti */attention deficit hyperactivity disorder* i neurobiologija */neurobiology*. Kriterij odabira referenci bili su pregledni radovi, meta-analiza i originalni istraživački radovi na engleskom ili hrvatskom jeziku u području neurobiologije ADHD-a.

## ETIOPATOGENEZA ADHD-a

### Općeniti aspekti

Etiopatogeneza poremećaja pažnje i hiperaktivnosti nije do kraja poznata, odnosno pretpostavlja se da je multifaktorijalna te se čini da u njoj ravnomjerno sudjeluju individualni (neuro/biološki i psihološki) i okolišni čimbenici. Od individualno-bioloških čimbenika treba spomenuti genetske čimbenike, epigenetske čimbenike, prenatalni čimbenici (alkohol, duhan) i perinatalne čimbenike (prematuritet, hipoksija tijekom poroda). U ovom modelu također su važni i individualno-psihološki čimbenici koji uključuju razvoj ličnosti, privrženost i adaptaciju (vulnerabilnost vs. otpornost) i drugi čimbenici. O ovim aspektima se u ovom radu neće detaljnije pisati, vidi o tome drugu dostupnu literaturu (1).

rates of obesity, sleep disorders, asthma, autoimmune and inflammatory diseases, and other somatic and metabolic conditions (25,26,27). The current understanding of the neurobiological mechanisms contributing to the possible development and maintenance of ADHD — including genetics, brain structures and functions, and neurotransmitters — appears to us to be a particularly interesting topic, given the interplay of individual-biological, individual-psychological, and environmental factors in ADHD.

For the purposes of this review, the databases WOS, Medline, Scopus, PubMed, and Google Scholar were searched using a keyword combination approach with terms such as attention deficit hyperactivity disorder and neurobiology. The selection criteria for references included review articles, meta-analyses, and original research papers in English or Croatian in the field of ADHD neurobiology.

## ETIOPATHOGENESIS OF ADHD

### General Aspects

The etiopathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) is not yet fully understood. It is assumed to be multifactorial, involving both individual (neurobiological and psychological) and environmental factors in relatively equal measure. Among the individual-biological factors, it is important to mention genetic and epigenetic factors, prenatal influences (such as alcohol and tobacco exposure), and perinatal factors (such as prematurity and hypoxia during birth). This model also emphasizes the importance of individual-psychological factors, which include personality development, attachment, and adaptation (vulnerability vs. resilience), among others. These psychological aspects will not be discussed in detail in this paper—see other available literature on the topic (1).

Od okolišnih čimbenika mogu biti prisutni stresori, trauma, životni događaji, obiteljski čimbenici, škola, socijalni i ekološki uvjeti. Ako bi ADHD u dječjoj psihijatriji usporedili s drugim poremećajima kod djece i adolescenata, kod ovih poremećaja bi mogli zaista ustvrditi o ravnomjernoj isprepletenosti individualnih (neuro/bioloških i psiholoških) i okolišnih čimbenika, uz prevagu prema biološkim čimbenicima (28).

## Individualno- biologijsko-genetski čimbenici

Genetski čimbenici uključeni su u etiopatogenezu ADHD-a, ali mehanizam djelovanja nije u potpunosti razjašnjen. ADHD ima moguću složenu poligensku pozadinu u kojoj više genetskih varijanti doprinosi etiologiji poremećaja kod većine pacijenata. Iako je veliki dio etiopatogeneze ADHD-a uzrokovan genima, mnogi okolišni čimbenici i potencijalne interakcije gena i okoliša također su povezane s povećanim rizikom za razvoj poremećaja (29,30). Studije blizanaca i obitelji poduprle su snažan genetski doprinos poremećaju s nasljednošću u rasponu od 60 do 90 % (31).

Za identifikaciju rizičnih gena ADHD-a provedena su višestruka molekularna genetička istraživanja. Zbog visoke prevalencije ADHD-a u populaciji, potraga za genetskim čimbenicima uglavnom je usmjerena na uobičajene genetske varijante (32,33).

Studija asocijacije na razini cijelog genoma (engl. genome-wide association study, GWAS) pomaže znanstvenicima identificirati gene povezane s određenom bolešću. GWAS studija ukazala je na postojanje gena koji igraju ulogu u nastanku ADHD-a, a koji bi se mogli povezati s mehanizmima neuronske plastičnosti (migracija neurona, adhezija stanica i proliferacija neurona) (34) ili s nedostacima u sintezi neurotransmitora (NT), uglavnom dopamina, ali također i serotonina i noradrenalina (35,36).

Environmental factors may include stressors, trauma, life events, family-related issues, school influences, and broader social and ecological conditions. Compared to other psychiatric disorders in childhood and adolescence, ADHD appears to involve a relatively balanced interplay of individual (neurobiological and psychological) and environmental contributors, with a predominance of biological factors (28).

## Individual-Biological-Genetic Factors

Genetic factors are involved in the etiopathogenesis of ADHD, although the exact mechanisms remain unclear. ADHD may have a complex polygenic background, in which multiple genetic variants contribute to the disorder's etiology in most patients. Although genes account for a large part of ADHD's etiopathogenesis, numerous environmental factors and potential gene–environment interactions are also associated with increased risk (29,30). Twin and family studies have demonstrated a strong genetic contribution, with heritability estimates ranging from 60% to 90% (31).

To identify ADHD risk genes, numerous molecular genetic studies have been conducted. Given the high prevalence of ADHD, research has largely focused on common genetic variants (32,33).

Genome-wide association studies (GWAS) help researchers identify genes linked to specific disorders. GWAS studies have pointed to the existence of genes that play a role in the development of ADHD and may be linked to mechanisms of neuronal plasticity (such as neuron migration, cell adhesion, and neuronal proliferation) (34), or to deficiencies in neurotransmitter synthesis—primarily dopamine, but also serotonin and norepinephrine (35,36). Meta-analyses of these studies have revealed significant associations with common variants in several candidate genes. These include genes coding for

Meta-analize provedenih studija identificirale su moguće značajne povezanosti uobičajenih genskih varijanti u nekoliko gena kandidata.

To su geni koji kodiraju transportere dopamina i serotonina, SLC6A3/DATI i SLC6A4/5HTT, geni koji kodiraju D4 i D5 dopaminske receptore DRD4 i DRD 5, serotoninski receptor, HTRIB i gen za sinaptosomski-povezani protein 25, SNAP25. U provedenoj meta-analizi identificirani su dodatni geni koji kodiraju dopamin beta-hidroksilazu DBH, adenoreceptor alfa 2A (ADRA2A), tripotofan hidroksilazu 2 (TPH2) i monoamino oksidazu A (MAOA),a povezani su s ADHD-om (37,38,39). Studije skeniranja genoma o potencijalnim alelima za ADHD pokazale su povezanost na kromosomima 5p13, 6q12, 16p13, 17p11 i 11q 22-25 (40,41). U osoba s ADHD-om prijavljena je povećana stopa velikih, rijetkih kromosomskih delecija i duplikacija poznatih kao varijante broja kopija (24).

## Strukturne i funkcionalne promjene mozga kod ADHD-a

Neuroslikovne studije dale su mogući uvid u etiopatogenezu i patofiziologiju ADHD-a prikazujući razlike u strukturnoj i funkcionalnoj arhitekturi mozga između pacijenata s ADHD-om i neurotipičnih pojedinaca, posebno djece (42). Te razlike primarno uključuju promjene u volumenu mozga, kortikalnoj debljini i površini (43). Specifične regije mozga uključene su u moguću patofiziologiju ADHD-a, a istraživanja ukazuju na smanjenje volumena u prefrontalnom korteksu, bazalnim ganglijima, *corpus callosumu* i malom mozgu (44,45). Prefrontalni korteks uključen je u izvršne funkcije poput pažnje, radne memorije i kontrole impulsa. Strukturne slikovne studije izvjestile su o mogućem smanjenom volumenu i kortikalnoj debljini prefrontalnog korteksa u pacijenata s ADHD-om, a osobito u dorzolateralnom i orbitofrontalnom prefrontalnom korteksu (46). Nadalje, bazalni gangliji

dopamine and serotonin transporters (SLC6A3/DAT1 and SLC6A4/5-HTT), dopamine receptors D4 and D5 (DRD4, DRD5), the serotonin receptor HTR1B, and the synaptosomal-associated protein SNAP25. In the conducted meta-analysis, additional genes were identified that encode dopamine beta-hydroxylase (DBH), the alpha-2A adrenergic receptor (ADRA2A), tryptophan hydroxylase 2 (TPH2), and monoamine oxidase A (MAOA), all of which have been linked to ADHD (37,38,39). Genome scanning studies have identified potential ADHD-related alleles on chromosomes 5p13, 6q12, 16p13, 17p11, and 11q22–25 (40,41). Individuals with ADHD have also shown increased rates of rare large chromosomal deletions and duplications—known as copy number variants (CNVs) (24).

## Structural and Functional Brain Changes in ADHD

Neuroimaging studies have offered valuable insight into the etiopathogenesis and pathophysiology of ADHD by highlighting structural and functional differences in the brains of individuals with ADHD compared to neurotypical controls, particularly in children (42). These differences primarily involve alterations in brain volume, cortical thickness, and surface area (43). Specific brain regions implicated in ADHD pathophysiology include the prefrontal cortex, basal ganglia, corpus callosum, and cerebellum, all of which have been found to exhibit reduced volume in individuals with ADHD (44,45). The prefrontal cortex is responsible for executive functions such as attention, working memory, and impulse control. Structural imaging studies have reported reduced volume and cortical thickness in this region, particularly in the dorsolateral and orbitofrontal areas (46). Furthermore, the basal ganglia play a key role in motor control, learning, and executive functions. In patients with ADHD, possible volumetric reductions in the basal ganglia have been observed (44,45). Structural imaging studies have shown potential reductions

igraju ključnu ulogu u motoričkoj kontroli, učenju i izvršnim funkcijama. Kod pacijenata s ADHD-om uočena su moguća volumetrijska smanjenja bazalnih ganglija (44,45). Strukturalne slikovne studije pokazale su moguće smanjenje volumena i promijenjenu morfologiju korpusa kalozuma kod osoba s ADHD-om što može ukazivati na poremećaj u komunikaciji među moždanim hemisferama s obzirom da *corpus callosum* povezuje desnu i lijevu moždanu hemisferu (44,47). Mali mozak uključen je u koordinaciju motorike, održavanje ravnoteže i kognitivne funkcije koje uključuju pažnju i radnu memoriju. Strukturalne slikovne studije izvjestile su o mogućem smanjenom volumenu malog mozga u osoba s ADHD-om (46,47). Longitudinalne studije pružile su dokaze o mogućem odgođenom kortikalnom sazrijevanju kod osoba s ADHD-om, posebno u prefrontalnom korteksu (48). Velika meta-analiza ADHD radne skupine ENIGMA (*Enchancing Neuroimaging Genetics through Meta-Analysis*) izvjestila je da djeca s ADHD-om mogu imati manji volumen u različitim subkortikalnim regijama mozga (npr. *nucleus accumbens*, amigdala, kaudatus, hipokampus, putamen) i ukupni intrakranijski volumen (49) kao i smanjenu kortikalnu površinu (uglavnom u frontalnim, cingularnim i temporalnim regijama) i debljinu (u fuziformnom i temporalnom girusu)(50). Analizom morfometrijskih slika cijeloga mozga prijavljena je moguća povezanost ADHD-a sa smanjenim volumenom u frontalnim režnjevima i striatumu kod djece i kod odraslih (51). Studija *The Adolescent Brain and Cognitive Development* (ABCD) također sugerira moguće smanjenje strukturne mjere mozga u djece s ADHD-om (52). Potrebne su daljnje multimodalne studije kako bi se istražila povezanost između strukturnih i funkcionalnih promjena kod ADHD-a. Razvojne studije mogu dalje pomoći u rasvijetljavanju mehanizama koji bi objasnili evoluciju kliničke prezentacije ADHD-a tijekom životnog vijeka (53).

in volume and altered morphology of the corpus callosum in individuals with ADHD, which may suggest impaired interhemispheric communication, given that the corpus callosum connects the right and left cerebral hemispheres (44,47). The cerebellum is involved in motor coordination, balance maintenance, and cognitive functions such as attention and working memory. Structural imaging studies have reported a possible reduction in cerebellar volume in individuals with ADHD (46,47). Longitudinal studies have provided evidence of possible delayed cortical maturation in individuals with ADHD, particularly in the prefrontal cortex (48). The large ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) consortium meta-analysis reported smaller volumes in various subcortical regions (e.g., nucleus accumbens, amygdala, caudate nucleus, hippocampus, and putamen), as well as reduced total intracranial volume in children with ADHD (49). Reductions in cortical surface area (mainly in frontal, cingulate, and temporal regions) and cortical thickness (in fusiform and temporal gyri) have also been observed (50). Whole-brain morphometric imaging analysis has reported a possible association between ADHD and reduced volume in the frontal lobes and striatum in both children and adults (51). The Adolescent Brain and Cognitive Development (ABCD) study has also indicated reduced structural brain metrics in children with ADHD (52). Multimodal studies are needed to better understand the relationship between structural and functional brain alterations in ADHD. Developmental research may further clarify mechanisms underlying the evolution of ADHD's clinical presentation across the lifespan (53).

## Dysfunction of Neurotransmitter Systems

The prefrontal cortex, *caudate nucleus*, and cerebellum are considered the primary brain regions responsible for the development of ADHD, as they are involved in regulating consciousness,

## Disfunkcija neurotransmiterskih sustava

Prefrontalni korteks, *nucleus caudatus* i mali mozak moguća su glavna područja mozga odgovorna za razvoj ADHD-a s obzirom da su uključeni u kontrolu svjesnosti, osjećaja, impulsa i ponašanja (54,55). Funkcija puteva unutar ovih regija regulirana je neurotransmitorima kao što su dopamin (DA),noradenalin (NE), serotonin (5-HT), glutamat i gama-aminomaslačna kiselina (GABA) (54). Razvoj ADHD-a može se objasniti nedostatkom katekolamina kao što su DA i NE (54) ili disregulacijom ovih neurotransmitora koji su neophodni za normalnu funkciju mozga, uključujući izvršne funkcije i funkcije pažnje (16). Istraživanja ADHD-a tradicionalno su usmjerena na katekolaminergičnu neurotransmisiju (56). Dopamin i noradrenalin glavni su katekolamini u mozgu i imaju predominantno modulatorno djelovanje na druge neurotransmitore.

Postoje dvije obitelji dopaminskih receptora, D1 (uključujući D1 i D5) i D2 (uključujući D2,D3,D4) koji su različito raspoređeni u mozgu (57,58). Dopamin djeluje kroz visoko topografski organizirane projekcije kao što je nigrostrijatalni put koji je dobro poznat po svojoj ulozi u regulaciji kretanja. Nadalje, mezokortikalni i mezolimbički dopaminergični putevi uključeni su u izvršne funkcije (59). ADHD se čini da je povezan s difunkcijom u sva tri puta (60,61). Također se istraživala uloga frontostrijatalnih puteva u ADHD-u (62), a oni doprinose motoričkoj, kognitivnoj i afektivnoj regulaciji (63). Nadalje, ADHD se čini da je povezan s noradrenergičkom disfunkcijom (64). Tehnike nuklearne medicine PET i SPECT omogućile su istraživanje disfunkcije katekolaminergičkih puteva kod ADHD-a (65). Nedostatak dopamina igra ključnu ulogu u medijaciji regulacije kortikalnog sustava pamćenja, raspoloženja, anticipacije događaja, motivacije, inhibicije ponašanja, donošenja odluka i rješavanja problema (66-68). Disfunkcija DA receptora (DRD1-5) i DA transpotera (DAT-1)

emotions, impulses, and behavior (54,55). The functioning of neural pathways in these regions is regulated by neurotransmitters such as dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate, and gamma-aminobutyric acid (GABA) (54). The development of ADHD may be explained by a deficiency of catecholamines such as DA and NE (54), or by dysregulation of these neurotransmitters, which are essential for normal brain functioning, including executive function and attentional processes (16). Research on ADHD has traditionally focused on catecholaminergic neurotransmission (56). Dopamine and norepinephrine are the primary catecholamines in the brain and exert predominantly modulatory effects on other neurotransmitters.

There are two families of dopamine receptors: D1 (which includes D1 and D5) and D2 (which includes D2, D3, and D4), and these receptors are differently distributed throughout the brain (57,58). Dopamine acts via highly topographically organized projections such as the nigrostriatal pathway, which plays a well-established role in motor regulation. Additionally, the mesocortical and mesolimbic dopaminergic pathways are involved in executive functions (59). ADHD appears to be associated with dysfunction across all three of these pathways (60,61). Research has also explored the role of the frontostriatal pathways in ADHD (62), which contribute to motor, cognitive, and emotional regulation (63). Furthermore, ADHD is associated with noradrenergic dysfunction (64). Nuclear medicine techniques such as PET and SPECT have enabled the investigation of catecholaminergic pathway dysfunction in ADHD (65). Dopamine deficiency plays a key role in regulating cortical systems responsible for memory, mood, event anticipation, motivation, behavioral inhibition, decision-making, and problem-solving (66-68). Dysfunction of dopamine receptors (DRD1–5) and the dopamine transporter (DAT-1) are believed to be major contributors to altered dopaminergic

se čine da su glavni razlozi za promijenjenu aktivnost u dopaminergičnom sustavu igrajući značajnu ulogu u patogenezi ADHD-a (69). Metilfenidat i spojevi izvedeni iz amfetamina djeluju na DAT-1 receptore inhibirajući njegovu prijenosnu funkciju i time povećavajući razine izvanstaničnog DA (70).

Noradrenalin (NE) je važan neurotransmitor u kontroli ponašanja i igra važnu ulogu u kognitivnim procesima kao što su radna memorija i inhibicijski odgovor a za koje se čini da su poremećeni kod ADHD-a (71). NE je također uključen u regulaciju pažnje (72). Protein prijenosnik NE (NET) uključen je u ponovnu pohranu NE, a abnormalnosti u funkciji NET-a pridonose razvoju ADHD-a smanjenjem razina izvanstaničnog noradrenalina. Lijekovi za liječenje ADHD-a kao što su metilfenidat i amfetamin povećavaju razine noradrenalina i time smanjuju simptome hiperaktivnosti i impulzivnosti (71).

Neravnoteža ekscitatorne funkcije serotonina (5-HT) također može biti povezana s razvojem ADHD-a. (73,74). Disfunkcija serotonina može igrati ulogu u hiperaktivnom i impulzivnom ponašanju povezanim sa ADHD-om (75). Serotonin regulira aktivnost dopamina putem svojih receptora 5-hidroksitriptaminskog receptora 1B (5-HTR1B) ili 5-hidroksitriptaminskog receptora 2A (5-HTR2A). Disfunkcija ovih receptora može narušiti dinamiku serotonin-dopamin što rezultira simptomima ADHD-a (73,74). Nadalje, promjena ravnoteže glutamat/GABA povezana je sa smanjenom sposobnošću fokusiranja na zahtjevne zadatke i rezultira disregulacijom dopamina (76).

## Okolišni čimbenici

Procijenjeni utjecaj okolišnih čimbenika u patogenezi ADHD-a iznosi oko 20 do 30 %. Prenatalni, perinatalni i postnatalni čimbenici igraju važnu ulogu u nastanku ovog poremećaja. Prenatalni čimbenici povezani su s majčinim načinom života tijekom trudnoće, npr. prena-

system activity and play a significant role in the pathogenesis of ADHD (69). Methylphenidate and amphetamine-derived compounds act on DAT-1 receptors by inhibiting their transport function, which leads to elevated levels of extracellular dopamine (DA) (70).

Norepinephrine (NE) is another crucial neurotransmitter in behavioral control and plays an important role in cognitive processes such as working memory and inhibitory control, which are often impaired in ADHD (71). NE is also involved in attentional regulation (72). The norepinephrine transporter protein (NET) is involved in the reuptake of NE, and abnormalities in NET function contribute to the development of ADHD by reducing extracellular norepinephrine levels. Medications such as methylphenidate and amphetamines raise NE levels and consequently reduce hyperactivity and impulsivity symptoms (71).

Imbalance in the excitatory function of serotonin (5-HT) may also be associated with ADHD development (73,74). Serotonergic dysfunction may play a role in the hyperactive and impulsive behaviors linked to ADHD (75). Serotonin regulates dopamine activity through its receptors, specifically the 5-hydroxytryptamine receptor 1B (5-HTR1B) and the 5-hydroxytryptamine receptor 2A (5-HTR2A). Dysfunction of these receptors may disrupt serotonin-dopamine dynamics, resulting in ADHD symptoms (73,74). Furthermore, glutamate/GABA imbalance has been linked to reduced ability to focus on demanding tasks and to dysregulation of dopamine activity (76).

## Environmental Factors

The estimated contribution of environmental factors to the pathogenesis of ADHD ranges between 20% and 30%. Prenatal, perinatal, and postnatal influences play important roles in the development of this disorder. Prenatal factors are associated with maternal lifestyle during

talna izloženost alkoholu uzrokuje strukturne anomalije mozga, osobito malog mozga (77). Pušenje majke tijekom trudnoće dovodi do 2,7 puta većeg rizika za razvoj ADHD-a (78,79). Istraživanja su pokazala da značajan učinak ima i izloženost majke stresnim događajima, zdravstvenim problemima (80), lijekovima (79,81,82) i drugim tvarima kao što su olovo i mangan (83). Uočeno je da je izloženost acetaminofenu tijekom trudnoće povezana s visokom učestalošću ADHD-a u djece (84). Neki od perinatalnih čimbenika uključuju smanjenu porođajnu masu djeteta i komplikacije pri porodu (inducirani porod i hitni carski rez) (51,52). Postnatalni čimbenici uključuju pothranjenost, neravnotežu unosa esencijalnih masnih kiselina (omega 3 i omega 6) iako su potrebni dodatni dokazi kako bi se potvrdile ove tvrdnje (85).

Okolišni čimbenici povezani s razvojem ADHD-a uključuju nadalje lošiji socioekonomski status, nasilje u obitelji, narušen odnos roditelj-dijete, psihičku bolest majke, udomiteljstvo (86).

Nadalje, važno je spomenuti traumu i traumatski stres u djetinjstvu koji su prema sve većem broju istraživanja usko povezani s ADHD-om. Trauma može promijeniti arhitekturu mozga, posebno kod djece, što djelomično može objasniti njihovu vezu s razvojem ADHD-a. Klinička slika ADHD-a i traume također mogu pokazivati slične simptome, što može otežati procjenu (87). Istraživanja su pokazala da bi disregulacija osi HPA (hipotalamus-hipofiza-nadbubrežna žlijezda) mogla biti povezana s ADHD-om, a neke studije ukazuju na korelaciju između razine hormona HPA osi i težine simptoma ADHD-a, posebno nepažnje (88,89).

## LIJEČENJE ADHD-a

Liječenje ADHD-a uključuje načelno psihosocijalne terapije (nefarmakološke) i farmakološke strategije. Osnova liječenja, kao i kod drugih

pregnancy. For example, prenatal exposure to alcohol can lead to structural brain abnormalities, especially in the cerebellum (77). Maternal smoking during pregnancy increases the risk of developing ADHD by 2.7 times (78,79). Research has also shown a significant impact of maternal exposure to stressful life events, health issues (80), medications (79,81,82), and toxins such as lead and manganese (83). Exposure to acetaminophen during pregnancy has been associated with a higher prevalence of ADHD in children (84). Perinatal factors include low birth weight and complications during delivery (e.g., induced labor and emergency cesarean section) (51,52). Postnatal factors may include malnutrition and imbalanced intake of essential fatty acids (omega-3 and omega-6), although further evidence is required to confirm these associations (85).

Environmental risk factors also include low socioeconomic status, domestic violence, disrupted parent-child relationships, maternal mental illness, and foster care placement (86).

Moreover, it is important to emphasize the role of trauma and traumatic stress in childhood, which, according to increasing research, are closely linked to ADHD. Trauma can alter brain architecture, particularly in children, which may partly explain its relationship to ADHD development. The clinical presentations of trauma and ADHD may overlap, which may complicate accurate assessment(87). Studies have also shown that dysregulation of the HPA (hypothalamic–pituitary–adrenal) axis may be associated with ADHD, while some findings point to a correlation between levels of HPA-axis hormones and the severity of ADHD symptoms, particularly inattention (88,89).

## TREATMENT OF ADHD

The treatment of ADHD generally includes both psychosocial (non-pharmacological) and pharmacological strategies. As with other dis-

poremećaja u dječjoj psihijatriji jesu psihosocijalne intervencije (1).

Psihosocijalno liječenje ADHD-a uključuje načelno bihevioralne, kognitivne i psihodinamske terapije, a koriste se i drugi oblici liječenja (npr. *neurofeedback*).

Bihevioralne terapije koriste metode treninga, modifikaciju ponašanja i operantne metode, a u terapiju su uključena djeca, kao i njihovi roditelji (90).

Kognitivne terapije se zasnivaju na samoinstrukcijama, odnosno dijete uči samostalno regulirati vlastite impulse, kako definirati problem, istraživati načine rješavanja problema I kako postupati kod pogrešaka, a s ciljem razvoja samokontrole (91)

Psihodinamske terapije orijentirat će se na povećanje simbolizacijskih i mentalizacijskih mogućnosti djeteta putem sadržavajuće funkcije terapeuta (92).

Kao druge moguće terapije unutar multimodalnoga pristupa mogu biti motorički treninzi, odnosno fizičko vježbanje (aerobik, joga i dr.) (93), senzorički trening, radna terapija, *neurofeedback*, muzikoterapija, metode relaksacije, terapijsko jahanje konja (94).

Prva linija u farmakološkom liječenju su tzv. „stimulansi"- metilfenidat (MPH). Druga linija farmakološkog liječenja uključuje tzv. „nestimulativne" lijekove - atomoksetin. Stimulansi su korišteni kao prva linija farmakološkog liječenja zahvaljujući većoj učinkovitosti u smanjenju simptoma u usporedbi s nestimulirajućim lijekovima u svim dobnim skupinama (djeca, adolescenti i odrasli) (95,96). Nestimulativni lijekovi se primjenjuju kada su stimulansi kontraindicirani ili zbog nedostatnog odgovora na liječenje stimulansima ili u slučaju intolerancije na lijek (96). Također je moguća primjena lijekova iz drugih skupina: npr. antipsihotici, guanfacin, klonidin itd. (1).

U svijetu postoje različite smjernice liječenja ADHD-a (97,98).

orders in child psychiatry, psychosocial interventions form the foundation of treatment (1).

Psychosocial treatment of ADHD primarily involves behavioral, cognitive, and psychodynamic therapies, as well as other approaches (e.g., neurofeedback).

Behavioral therapies apply training methods, behavior modification techniques, and operant conditioning strategies, involving both the child and their parents (90).

Cognitive therapies focus on self-instruction, teaching the child to independently regulate impulses, define problems, explore problem-solving strategies, and manage mistakes, with the goal of developing self-control (91).

Psychodynamic therapies focus on strengthening the child's ability to symbolize and mentalize through the therapist's containing function (92).

Other possible therapies within a multimodal approach include motor training or physical exercise (e.g., aerobics, yoga) (93), sensory integration therapy, occupational therapy, neurofeedback, music therapy, relaxation techniques, and equine-assisted therapy (94).

The first-line pharmacological treatment consists of so-called stimulants, particularly methylphenidate (MPH). The second-line pharmacological treatment includes non-stimulant medications, such as atomoxetine. Stimulants are preferred as first-line agents due to their greater effectiveness in reducing symptoms compared to non-stimulants across all age groups (95,96). Non-stimulants are prescribed when stimulants are contraindicated, when there is insufficient response to stimulants, or when stimulants are not well tolerated (96). Other medication classes may also be considered, including antipsychotics, guanfacine, clonidine, etc. (1).

Various treatment guidelines exist worldwide (97,98).

Terapijske smjernice europskog stručnog društva (ESCAP *European Society for Child and Adolescent Psychiatry*) (97) ne preporučavaju davanje lijekova predškolskoj djeci, dok prema smjernicama Američke akademije za dječju i adolescentnu psihijatriju (*American Academy of Child and Adolescent Psychiatry*) to ne isključuju (98).

Liječenje treba biti individualno prilagođeno svakom pojedinom djetetu, s ravnomjernom procjenom problema, ali i određenih snaga i sposobnosti djeteta (1).

Terapijske smjernice Britanskog društva za psihofarmakologiju (*British Assosiation of Psychofarmacology*) (99) i Nacionalnog instituta za zdravlje i izvrsnost usluge (*National Institute for Health and Care Excellence*) (100) preporučuju tzv. „stimulanse" kao farmakološki tretman prvog izbora za umjerene do teške slučajeve ADHD-a kod pacijenata u dobi od 6 godina i starije. Druga linija liječenja su tzv. „nestimulativni" lijekovi (npr. atomoksetin), nakon čega slijede adrenergični lijekovi (npr. klonidin, guanfacin) ili alternativni nestimulansi kao što su triciklički antidepresivi i bupropion (99-102). Premda niti jedan antipsihotik nije odobren za primjenu kod ADHD-a, relativno se često propisuju kod izostanka učinka psihostimulansa također i za poremećaj ponašanja u komorbiditetu s ADHD-om. Pri tome se najviše propisuje risperidon zbog dobro utvrđenog učinka na agresivno ponašanje (103). Dvostruko slijepo, placebom kontrolirano kliničko ispitivanje Aman i sur. pokazalo je da risperidon može značajno smanjiti simptome ADHD-a, te navode da su kombinacija risperidona i psihostimulansa bolja u kontroli hiperaktivnosti od one kod koje se postiže samo liječenjem stimulansima (104), te se može reći da je ovo inovativno područje, jer se sugerira kombinacija dvije vrsta lijekova.

Pojedine studije su pokazale da risperidon daje jednako dobre ili čak i bolje rezultate u liječenju ADHD-a u usporedbi s onim što se postiže primjenom metilfenidata (105,106). Studija Correia i sur. uključivala je djecu s umjerenim intelek-

The European Society for Child and Adolescent Psychiatry (ESCAP) does not recommend pharmacological treatment for preschool-aged children (97), whereas guidelines from the American Academy of Child and Adolescent Psychiatry do not exclude such use (98).

Treatment should be individually tailored, considering both the child's difficulties and their strengths and capabilities (1).

Guidelines from the British Association for Psychopharmacology (99) and the National Institute for Health and Care Excellence (100) recommend stimulants as the first-line pharmacological treatment for moderate to severe ADHD in patients aged 6 and older. The second-line treatment includes non-stimulant medications (e.g., atomoxetine), followed by adrenergic agents (e.g., clonidine, guanfacine), or alternative non-stimulants such as tricyclic antidepressants and bupropion (99-102). Although no antipsychotic medication is officially approved for the treatment of ADHD, antipsychotics are frequently prescribed in cases where psychostimulants are ineffective, especially in comorbid conduct disorders. The most commonly prescribed antipsychotic is risperidone, due to its well-established effect on aggressive behavior (103). A double-blind, placebo-controlled clinical trial by Aman et al. showed that risperidone significantly reduces ADHD symptoms, and that the combination of risperidone and a stimulant is more effective for managing hyperactivity than stimulant treatment alone (104). This suggests a potentially innovative therapeutic approach by combining two different medication classes.

Some studies indicate that risperidone is as effective, or even more effective, than methylphenidate in treating ADHD symptoms (105,106). For instance, a study by Correia et al. involving children with moderate intellectual disability and ADHD found that risperidone led to greater symptom reduction than methylphenidate. Comorbidity and side effect

tualnim teškoćama i ADHD-om. Rezultati studije su pokazali da je risperidon povezan s većim smanjenjem ukupnog rezultata ADHD-a nego metilfenidat kod djece s umjerenim intelektualnim teškoćama i ADHD-om. Komorbiditet i profil nuspojava mogu biti važni pri odabiru između lijekova, iako je obično razumno isprobati stimulanse prije antipsihotika kod ove djece (106).

Upotreba antipsihotika novije generacije u djece i adolescenata povezana je s mogućim debljanjem i kardiometaboličkim nuspojavama poput dislipidemije, inzulinske rezistencije i povišenog krvnog tlaka kod neke djece (107) i hiperprolaktinemijom (108).

Sigurnost i učinkovitost često korištenih lijekova za liječenje ADHD-a podupiru meta-analize (Cortese i sur. 2018) (62). Metilfenidat se dobiva iz piperidina i strukturno je sličan amfetaminu (109). Liječenje metilfenidatom uzrokuje povećanje dopaminske signalizacije kroz višestruke radnje koje uključuju blokadu ponovne pohrane dopamina, pojačanje trajanja odgovora dopamina i dezinhibiciju dopaminskog D2 receptora (110). Metilfenidat je također inhibitor ponovne pohrane noradrenalina (111). Dakle, farmakološka aktivnost metilfenidata uglavnom je rezultat blokiranja DAT-a i NET-a čime se inhibira ponovna pohrana ovih neurotransmitora u presinaptičke neurone. Regulacija ovog procesa može uključivati modulaciju funkcija kao što su pažnja, zadovoljstvo i motorička aktivnost (95). Stimulansi također poboljšavaju izvršne funkcije koje su često poremećene kod osoba s ADHD-om (112,113,114). Amfetamini i metilfenidat imaju sličan profil nuspojava koje su obično blage i prolazne, a najčešće uključuju smanjeni apetit, suha usta, razdražljivost, poremećaj spavanja, tahikardiju i glavobolju. Povezani su i s višom stopom nuspojava kao što su gubitak na tjelesnoj masi i nesanica (115). Učinkovitost psihostimulansa u smanjenju simptoma ADHD-a prikazana je u brojnim kliničkim studijama u djece i odraslih s ADHD-om (116). Meta-analiza koja je uključila više od 10000 djece i adolescenata u trajanju od tri mjeseca, otkrila je da su i metilfenidat i amfetamin imali umjerene

profiles should be considered when selecting medication, although it is generally advisable to try stimulants before antipsychotics in such population (106).

Use of second-generation antipsychotics in children and adolescents has been associated with potential side effects, including weight gain, cardiometabolic risks (e.g., dyslipidemia, insulin resistance, hypertension) (107), and hyperprolactinemia (108).

The safety and efficacy of commonly used ADHD medications is supported by meta-analyses (62). Methylphenidate is a piperidine derivative and structurally similar to amphetamine (109). It increases dopaminergic signaling via multiple mechanisms, including blocking dopamine reuptake, prolonging dopamine response, and disinhibiting dopamine D2 receptors (110). Methylphenidate is also a norepinephrine reuptake inhibitor (111). Thus, its pharmacological activity is primarily due to blocking DAT and NET, thereby inhibiting the reuptake of these neurotransmitters into presynaptic neurons. Regulation of this process may affect functions such as attention, reward, and motor activity (95). Stimulants also enhance executive functions, which are frequently impaired in individuals with ADHD (112,113,114). Amphetamines and methylphenidate have similar side effect profiles, typically mild and transient, most commonly appetite suppression, dry mouth, irritability, sleep disturbances, tachycardia, and headache. They are also associated with higher rates of weight loss and insomnia (115). The efficacy of psychostimulants in reducing ADHD symptoms has been demonstrated in numerous clinical trials involving both children and adults (116). A meta-analysis involving over 10,000 children and adolescents over a three-month period found that both methylphenidate and amphetamines produced moderate to large improvements in ADHD symptoms (25). Another meta-analysis of 18 studies confirmed the effectiveness of methylphenidate in adults with ADHD (117).

do visoke učinke na simptome ADHD-a (25). Meta-analiza 18 studija pokazala je da je metilfenidat također učinkovit kod odraslih (117).

Atomoksetin je snažan i selektivni inhibitor ponovne pohrane noradrenalina koji djeluje putem bolkade NET-a. Takva presinaptička inhibicija NET-a dovodi do povećanja izvanstanične razine noradrenalina uglavnom u prefrontalnom korteksu, ali ne i u mezolimbičkim i mezokortikalnim putevima do nukleusa akumbensa zbog čega nema potencijal za moguću zloupotrebu ili stvaranje ovisnosti (118). Atomoksetin ima smanjeni afinitet za DAT, ali također potiče povećanje koncentracije dopamina u prefrontalnom korteksu što može biti posljedica nespecifične modulacije ponovne pohrane dopamina putem NET-a (119). Atomoksetin je pokazao učinkovitost u liječenju simptoma ADHD-a u komorbiditetu s anksioznim poremećajem ili tikovima (120,121). Guanfacin je selektivni agonist alfa-2 adrenergičkih receptora i moguće je da poboljšava radnu memoriju stimulacijom postsinaptičkih alfa-2 receptora jačajući funkcionalnu povezanost mreža prefronatalnog korteksa (122) i pokazao je moguću učinkovitost u smanjenju simptoma ADHD-a (123). Meta-analiza 25 ispitivanja atomoksetina u djece s ADHD-om pokazala je umjerenu veličinu učinka međutim veliki dio pacijenata (otprilike 40%) imao je trajne simptome koji su zahtijevali dodatnu kliničku intervenciju (124). Malo se zna o dugoročnim učincima stimulansa na funkcionalnu organizaciju mozga u razvoju, što iziskuje također klinički i znanstveni oprez (125) te daljnja istraživanja. Nedavna dvogodišnja longitudinalna studija (ADDUCE study) pokazala je da je metilfenidat siguran za dugotrajnu upotrebu (do dvije godine) kod djece i adolescenata s ADHD-om (126).

## ZAKLJUČAK

Etiopatogeneza poremećaja pažnje i aktivnosti je kompleksna i još uvijek nije u potpunosti razjašnjena. Istraživanja su ukazala na moguću

Atomoxetine is a potent and selective norepinephrine reuptake inhibitor that acts by blocking NET. This presynaptic inhibition raises extracellular norepinephrine levels, especially in the prefrontal cortex, but not in the mesolimbic and mesocortical pathways leading to the nucleus accumbens, which may explain its lack of abuse or addiction potential (118). Atomoxetine has a low affinity for DAT but also increases dopamine concentrations in the prefrontal cortex, likely via nonspecific modulation of dopamine reuptake through NET (119). Atomoxetine has shown effectiveness in treating ADHD symptoms comorbid with anxiety disorders or tics (120,121). Guanfacine is a selective alpha-2 adrenergic receptor agonist that may enhance working memory by stimulating postsynaptic alpha-2 receptors, strengthening functional connectivity within prefrontal cortex networks (122). It has demonstrated potential efficacy in reducing ADHD symptoms (123). A meta-analysis of 25 atomoxetine trials in children with ADHD found a moderate effect size, but approximately 40% of patients had persistent symptoms requiring further clinical intervention (124). Little is known about the long-term effects of stimulants on the functional organization of the developing brain, which calls for both clinical and scientific caution (125), as well as further research. A recent two-year longitudinal study (the ADDUCE study) demonstrated that methylphenidate is safe for long-term use (up to two years) in children and adolescents with ADHD (126).

## CONCLUSION

The etiopathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) is complex and not yet fully understood. Research has pointed to the potential involvement of genetic factors, brain structures and functions, and several neurotransmitter systems in the development

uključenost gena, moždanih struktura i funkcija, te nekoliko neurotransmitorskih sustava u nastanku i održavanju ovog poremećaja. Razumijevanje ovih mehanizama može biti važno za razvoj i identificiranje specifičnijih i ciljanijih metoda liječenja.

Daljnja istraživanja su potrebna za potpunije razumijevanje interakcije gena i okoline u razvoju ADHD-a kao i za razvoj novih i inovativnih metoda liječenja. Posebna pažnja treba biti posvećena personaliziranoj medicini, koja uzima u obzir individualne i okolišne faktore prilikom odabira optimalnog tretmana.

Napredak u neuroimaging tehnikama i genetičkim istraživanjima će vjerojatno dovesti do daljnjeg napretka u razumijevanju neurobiologije ADHD-a i poboljšanju kvalitete života osoba s ovim poremećajem.

and maintenance of the disorder. Understanding these mechanisms may be crucial for the development and identification of more specific and targeted treatment methods.

Further studies are needed to gain a more comprehensive understanding of gene–environment interactions in ADHD, as well as to develop new and innovative therapeutic approaches. Special attention should be given to personalized medicine, which takes into account individual and environmental factors in selecting the optimal treatment strategy.

Advancements in neuroimaging techniques and genetic research are likely to contribute significantly to further progress in understanding the neurobiology of ADHD and improving the quality of life for individuals affected by this disorder.

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# In memoriam

## */ Obituary*

Silvana Pleština

Mr. sc., dr. med / MD, MSc

Poštovane kolegice i kolege, dragi prijatelji!

Ovime Vas s tugom obavještavamo da je naša draga kolegica mr. sc. Silvana Pleština, dr.med. dana 14. 4. 2024. blago preminula nakon teške bolesti. Sprovod je bio dana 18.4.2024. u Zagrebu. Već je prošla i godišnjica njezine smrti, koju smo skromno obilježili.

Pišem ove retke u ime nas kolega i prijatelja, sa Klinike za dječju i adolescentnu psihijatriju KBC-a Zagreb, te sa Klinike za psihijatriju i psihološku medicinu, HD društva za dječju i adolescentnu psihijatriju i psihoterapiju pri HLZ-u kojega je bila članica. Baš smo se svi lijepo družili i nadopunjavali! Surađivali smo izvrsno. Ako mogu reći, ono što smo mogli dobiti od Silvane, bila je vizija, pojednostavljenje kompliciranih ideja, požrtvovnost u kliničkom radu s maloljetnim pacijentima, te okušavanje u strateškom razmišljanju. Hvala puno na njezinom doprinosu našem zajedničkom timu!

Dr. Silvana Pleština je imala impresivnu karijeru kao liječnica i pripadala zaista visokoeduciranom kadru. Gotovo je trideset godina

Distinguished colleagues, dear friends!

It is with great sadness that we inform you that our dear colleague Silvana Pleština, MD, MSc, passed away on April 14, 2024, after a serious illness. The funeral was held in Zagreb on April 18, 2024. The first anniversary of her death has already passed, which we modestly commemorated.

I am writing this tribute on behalf of our colleagues and friends, employed at the Department of Child and Adolescent Psychiatry within the University Hospital Centre Zagreb, as well as at the Clinical Department of Psychiatry and Psychological Medicine, and the Croatian Society for Child and Adolescent Psychiatry and Psychotherapy at the Croatian Medical Association, which she was a member of. We all had a wonderful time together and complemented each other very well! Our cooperation was excellent. If I may say, what we gained from Silvana was her vision, simplification of complex ideas, selflessness in clinical work with young patients, and experimentation in strategic thinking. We are extremely grateful for her contribution to our team!

Dr. Silvana Pleština had an impressive career as a doctor and was part of a truly highly educated

radila pri KBC-u Zagreb, na početku u Kliničkom zavodu za laboratorijsku dijagnostiku kao znanstveni novak. Temom iz tog područja je i znanstveno magistrirala, a poslije radila kao specijalizant psihijatrije pri Klinici za psihološku medicinu. Uspješno je završila specijalizaciju iz psihijatrije i vrlo se rano nakon specijalizacije usmjerila u rad u području dječje psihijatrije iz kojega je položila subspecijalistički ispit. Također je stekla titulu subspecijalista iz psihoterapije. Istovremeno je sudjelovala u različitim osobnim edukacijama, iz grupne analize, kao i psihoanalitičke individualne psihoterapije, te supervizijama. Cijeli radni vijek, a posebno u zadnjih petnaestak godina konstruktivno i inovativno sudjeluje uz starije učitelje i kolege u konstruiranju dnevnih bolnica za adolescentne pri KBC-u Zagreb, negdje oko godine 2006., što je bio u to vrijeme kvalitativni iskorak, a kasnije sudjeluje i u reorganizaciji dnevnih bolnica kao i u pionirskom timskom pristupu djevojkama s poremećajima jedenja u KBC-u Zagreb, što također započinje prije petnaestak godina u okvirima dnevnih bolnica ili stacionarnog liječenja. Uz klinički rad uočava se i njena znanstvena aktivnost. Aktivno sudjeluje u kreiranju nove Klinike za dječju i adolescentnu psihijatriju pri KBC-u Zagreb, koja je započela s radom 2024. godine kao prva takve vrste u Hrvatskoj.

Ako bismo izdvojili ono što je bila njena nekako najvažnija aktivnost, to je bio klinički rad s pacijentima, i posvećenost i briga usmjerenosti prema takvom radu, ali i istovremeni rad s roditeljima pacijenata. Pacijenti su voljeli dolaziti kod dr. Silvane, rado su se njoj obraćali, jer su osjećali njezinu genuinu zainteresiranost i veliku brigu. To su bili vrlo kompliciranI adolescentni pacijenti kod kojih se nikada ne zna ideš li baš potpuno ispravnim razvojnim putem. Često se tu radilo o dugotrajnim zahtjevnim psihoterapijama, koje su trajale i mjesecima i godinama, a što je iscrpljivalo nas terapeute, kao i dr. Silvanu. Često se tu

team. She worked at the University Hospital Centre Zagreb for almost thirty years, starting out as a research fellow at the Department of Laboratory Diagnostics. After completing her master's degree in the same field, she later worked as a psychiatry resident at the Department of Psychological Medicine. She successfully completed her psychiatry residency and very early on focused on the field of child psychiatry, for which she passed her subspecialty exam. She also acquired the title of subspecialist in psychotherapy. At the same time, she participated in numerous personal educations and trainings, both in group analysis, psychoanalytic individual psychotherapy, and supervisions. Throughout her entire career, and especially during the last fifteen years, together with her older teachers and colleagues she constructively and innovatively participated in the formation of day hospitals for adolescents at the University Hospital Centre Zagreb. These efforts took place around 2006, and at the time represented a qualitative leap forward. She later participated in the reorganization of day hospitals, and in the formation of the pioneering team approach to the treatment of girls with eating disorders at the University Hospital Centre Zagreb, which was also initiated fifteen years ago within the scope of day hospitals or in-patient treatment. In addition to her clinical work, she was also active in scientific research. She actively participated in the creation of the new Department of Child and Adolescent Psychiatry within the University Hospital Centre Zagreb, which started its operation in 2024 as the first of its kind in Croatia.

If we were to single out what was in a way her most important activity, it was clinical work with her patients, along with the dedication and caring orientation to such work, in addition to simultaneously working with the parents of her patients. The patients loved visiting Dr. Silvana, they liked talking to her because they could feel her genuine interest and great care. These were very complicated adolescent patients, with whom one could never know if they were following the correct developmental path. It also often involved long-term demanding psychotherapy sessions that would take months or years, which was exhausting both for us ther-

terapeut i sam osjeća nesigurno, bespomoćno, konfuzno, u nemogućnosti da se nekako izrazi. Često smo u zajedničkim trenucima jednostavno razgovarali, požalili se jedni drugima, slično supervizijskim i intervizijskim aktivnostima, pa je nekada teret rada bio barem malo olakšan. Kakva je bila posvećenost Silvane, govori i podatak, da je negdje prije godinu dana, prije dijagnosticiranja njezine teške bolesti, u ponedjeljak s nejasnim bolovima radila kao terapeut, sa svojim pacijentima, a isti se tjedan u četvrtak saznalo da Silvana ima tešku bolest. Pacijenti su zapitkivali tijekom bolesti kada će se dr. Silvana vratiti, a ona je tijekom svoje bolesti i dalje pitala za neke svoje pacijente, pa smo se opet zajednički nekako međusobno nadopunjavali.

Dr. Silvana Pleština bila je omiljena i među različitim članovima tima, a tu su bili osim liječnika i medicinske sestre, defektolozi, psiholozi, učitelji u bolnici, socijalni radnici, administratori, kao i drugi djelatnici. Nije se libila sudjelovati u našim zajedničkim druženjima i izvan bolnice. Također se istaknula kao važan sugovornik specijalizantima dječje i adolescentne psihijatrije odnosno aktivno je sudjelovala u edukaciji specijalizanata, kao i edukaciji putem vježbi studenata medicine. Dr. Silvana je bila primjer kliničkog liječnika koji u tišini, i konstantno radi na boljitak svojih pacijenata, uz dobru suradnju s kolegama.

Osim kliničkog liječničkog rada bila je vrlo posvećena svojoj obitelji, a posebno svom sinu. Uvijek smo na poslu dijelili svoje male i velike obiteljske brige i međusobno se podupirali.

Što ćemo mi sada, ostaje nam praznina, tuga i nevjerica. Međutim, Silvana je bila i borac, fajter, nije se ona tako lako predavala u stručnom radu ni u svojim zadnjim danima. Zapamtit ćemo Te kao takvu, hvala Ti Silvana!

Neka ti je laka hrvatska zemlja!

U travnju 2025.

Ivan Begovac

apists, and for Dr. Silvana. In such situations, the therapist often feels insecure, helpless, confused and unable to express themselves. In our moments together, we often simply talked, complained to each other, similar to supervisory and intervision activities, which would sometimes make the workload at least a little lighter. Silvana's dedication is evident in the fact that, sometime a year ago and before she was diagnosed with her severe illness, on Monday she was working as a therapist with her patients and experiencing vague pain, while on Thursday of the same week it was discovered that she was severely ill. During her illness, the patients asked about Dr. Silvana's return, and she inquired about some of her patients as well, so we all complemented each other in some ways again.

Dr. Silvana Pleština was beloved among the various members of our team, which alongside doctors and nurses also includes special education teachers, psychologists, teachers at the hospital, social workers, administrators and other employees. She did not hesitate to participate in our social gatherings outside the hospital either. She was also a prominent advisor to child and adolescent psychiatry residents, actively participating in the education of residents, as well as in medical students' training practice. Dr. Silvana was an exemplary clinician who silently, but constantly, worked for the wellbeing of her patients, maintaining good cooperation with her colleagues.

In addition to her clinical medical work, she was very dedicated to her family, particularly to her son. We would always share our little and big family worries at work, providing support to each other.

We wonder what we will do now that we are faced with a void, sadness and disbelief. Nevertheless, Silvana was a strong fighter, who refused to give up easily in her professional work even in her last days. We will remember You this way, Silvana. Thank you!

May you rest in peace!

In April 2025,

Ivan Begovac

# Upute autorima

## O časopisu

*Socijalna psihijatrija* je recenzirani časopis koji je namijenjen objavljivanju radova iz područja socijalne psihijatrije, ali i iz kliničke psihijatrije i psihologije, biologijske psihijatrije, psihoterapije, forenzičke psihijatrije, ratne psihijatrije, alkohologije i drugih ovisnosti, zaštite mentalnog zdravlja osoba s intelektualnim teškoćama i razvojnim poremećajima, epidemiologije, deontologije, organizacije psihijatrijske službe. Praktički nema područja psihijatrije iz kojeg do sada nije objavljen pregledni ili stručni rad.

Svi radovi trebaju biti pisani na hrvatskom i engleskom jeziku.

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Tijekom cijelog redakcijskog postupka, *Socijalna psihijatrija* slijedi sve smjernice Odbora za etiku objavljivanja (*Committee of publication ethics* – COPE), detaljnjije na: https://publicationethics.org/files/Code%20of%20Conduct_2.pdf, kao i preporuke ponašanja, izvještavanja, uređivanja i objavljivanja znanstvenih radova u časopisima medicinske tematike kojeje objavio Međunarodni odbor urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE), detaljnije na: http://www.icmje.org/journals-following-the-icmje-recommendations/.

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# Instructions to authors

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*Socijalna psihijatrija* is a peer-reviewed journal intended for publication of manuscripts from the fields of social psychiatry, clinical psychiatry and psychology, biopsychology, psychotherapy, forensic psychiatry, war psychiatry, alcoholism and other addictions, mental health protection among persons with intellectual and developing disabilities, epidemiology, deontology and psychiatric service organisations.

All manuscripts must be written in the Croatian and English language.

All manuscripts undergo the same review process if they follow the scope of the Journal and fulfil the conditions according to the Author guidelines.

The Editorial board will not take the responsibility for the viewpoint of the Author's manuscript – it remains the exclusive responsibility of an Author.

*Socijalna psihijatrija* publishes the following types of articles: editorials, original scientific papers, professional papers, review's, case reports, reports on drugs and methods of treatment, short announcements, annotations, news, book review's, letters to the editor, and other papers in the field of social psychiatry.

Exceptionally, the Editorial board can accept other kinds of paper (social psychiatry event paper, social psychiatry history-related paper, etc.).

During the whole peer-reviewed process, the *Socijalna psihijatrija* journal follows the Committee of publication ethics (COPE) guidelines (https://publicationethics.org/files/Code%20of%20Conduct_2.pdf) as well as the "Recommendations for the conduct, reporting editing, and publication of scholarly work in medical journals" set by the International Committee of Medical Journal Editors (ICMJE - http://www.icmje.org/journals-following-the-icmje-recommendations/).

Editors at the *Socijalna psihijatrija* journal pay close attention to the integrity and visibility of scholarly publications as stated in Sarajevo Declaration (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209927/).

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There should be a title, name and surname, address, town, state and e-mail indicated for the corresponding author.

The title page should contain: the full and shortened title of the article, full names and full surnames of all authors of the article, and the institution they work for. All the authors should also provide an ORCID ID (please check the following website: https://orcid.org/register). The article should have a summary not exceeding 200 words. The summary should briefly describe the topic and aim, the methods, main results,

*Cilj* je kratak opis što se namjerava istraživati, tj. što je svrha istraživanja.

*Metode* se prikazuju tako da se čitatelju omogući ponavljanje opisanog istraživanja. Metode poznate iz literature ne opisuju se, već se navode izvorni literaturni podatci. Ako se navode lijekovi, rabe se njihova generička imena (u zagradi se može navesti njihovo tvorničko ime).

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and conclusion. The summary should be followed by 3 to 5 key words for easy identification and classification of the content of the article.

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The Aim section briefly describes the goals and intentions of the research, i.e. the point of the research.

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In case the manuscript has six or fewer Authors, all of them should be listed. Should the manuscript have more than six Authors, the first six should be listed and the rest of them marked with the abbreviation *et al.* or i sur. First list the surname and then the initials of the first name(s). Multiple initials for the same person should be written without spaces.

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Primjer:

Kingdon DG, Aschroft K, Bhandari B, Gleeson S, Warikoo N, Symons M et al. Schizophrenia and borderline personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia and childhood trauma. J Nerv Ment Dis 2010; 10(6): 399-403.

### 5. Izdanje knjige

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