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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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. • 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. • 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. / 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. / Gambling disorder diagnosed according to DSM-5 criteria	SOGS,Kanadski indeks težine problematičnog kockanja (PGSI), BDI, Barratova skala impulzivnosti (BIS-11) / 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. / 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. / 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. / 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. / Individuals with substance use disorders, including 4 participants with gambling disorder.	VAS, HAM-D, HAM-A, BIS-11, Young skala ocjene manije (YMRS) / 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 / 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. / 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. / 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 / 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. / 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) / 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 / Pilot study investigating the effects of dTMS on symptoms of pathological gambling.	Dijagnoza patološkog kockanja postavljena po kriterijima DSM-IV-TR / 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. / 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. / 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. / 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. / 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. / 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). / 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. / 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. / 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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