Effect of add-on transcranial alternating current stimulation (t in ma or de ressi e disorder randomi ed controlled trial

ing ing ou[a] an i[a] u ang e[a] ui iu[a] uan eng[a]

a or de ressi e disorder (is a common disease affecting more t an million eo le t is a leading cause of disa ilit orld-ide and a ma or contri utor to t e o erall glo al urden of disease (orld ealt rgani ation erefore t e de elo ment of effecti e accessi le inter entions for is a ig riorit for t e im ro ement of u lic ealt irst-line e idence- ased treatment o - tions for include s c o armacolog and s c ot era eutic a roac es o e er – of atients do not ade uatel res ond to rst-line treatments ic generall in ol e a com ination of antide-ressants and cogniti e- e a ioral t era so t ere is an urgent need for ne treatment o tions

ranscranial alternating current stimulation (t is a neuro-modulation tec ni ue t at a lies electrical currents it c anging intensit to t e scal to regulate cortical e cita ilit and s ontaneous rain acti it t as een used for o er a decade in different elds (for instance cogniti e neuroscience o e er it as onl een a lied in s c iatric clinical researc in recent ears t resent most clinical studies on de ression used t it fre uencies of or and stimulation sites selected in t e frontal lo e ne stud as ro ed t at t it a current of m and a fre uenc of can deli er electrical currents to dee rain tissues t as also found t at t (fre uenc en anced t e le els of endor ins and neurotransmitters (including serotonin in t e rainstem ot alamus and corte β ome of endor ins and neurotransmitters c anges are elie ed to e t e neuro iological mec anisms for im ro ing de ressi e s m toms

stud e amining t 's role in treating re ealed t at t it m and as effecti e in alle iating de ressi e s m - toms in o e er ecause onl rst-e isode drug-nai e a-tients it ere included in t e stud t e generali a ilit of its ndings as limited not er stud e amined t e ef cac of t com ined it s ut it did not limit t e t e and dose of t e an-tide ressants used in t e stud s t e antide ressant ef cac of different s aried it is still un no n et er t e com ination of antide ressants and t could en ance t e ef cac of antide res-sants and ridge t e ga in t e rst fe ee s en antide ressants a e not ta en effect n addition t e antide ressant mec anism of t is com le and currentl unclear

e ression is related to a com le icture of altered rain oscilla-tions e resting-state lo -fre uenc ands (delta eta and al a in electroence alogra (EE es eciall t e al a and ere en anced in atients it de ression in terms of eit er o er or co erence oreo er t e en ancement ersisted e en after an indi-idual c anged from an e e-closed to an e e-o en state – a-tients it e i it ele ated oscillator acti it s eci call in t e al a fre uenc and (– lt oug al a oscillations ser e im ortant functions in t e ealt rain increased al a oscillation in atients it de ression re resents a state of neuronal oacti it leading to disru ted affecti e rocessing esearc ers found t at t e left refrontal corte as in i ited inde ed increased al a fre uenc o er during t e rocessing of ositi e emotions in indi iduals it de ression ince t e ele ated am litude of left frontal al a oscillations is t eori ed to corres ond to a reduction in a roac ing ositi e e eriences e ot esi ed t at a stimulation ma roduce a selecti e decrease in left frontal al a os-cillations to ards images rated as ositi e

erefore e conducted a dou le- lind stud to e aluate t e feasi ilit safet and ef cac of t as a treatment for t e s m toms of de ression o understand o t affects rain acti it e measured al a o er c anges as our secondar outcome using ig - densit EE

2.1. Study Design and participants

e - ee dou le- lind randomi ed s am-controlled trial as erformed at ei ing nding os ital a ital edical ni ersit from anuar to ecem er e trial recei ed institutional re ie oard a ro al as erformed in accordance it et ical rinci les originating in t e eclaration of elsin i and as re-orted in accordance it guidelines e stud as registered on t e ictr org cn e site efore enrollment (i tt s c ictr org cn inde tml ere as no c ange in t e rotocol during t e stud ll atients ro ided ritten informed consent rior to enrollment e trial as com leted on reac ing redetermined target enrollment num ers fter t e - ee trial all atients entered t e de ression co ort and ere follo ed u for ee s

2.2. Sample size calculation

re iousl t ere is onl one randomi ed controlled trial in esti-gating t e effecti eness of t as an add-on to antide ressants in treating de ression o e er e found t at t e effect si e deri ed from t is stud as e tremel large e sam le si e calculated ased on t is effect si e as ic ould e too small to erif t e effect statisticall erefore e used a conser ati e estimate of ic as considered t e criteria for large effects to calculate our sam le si e instead as a lied to calculate t e sam le si e e set effect si e = α (t o-sided = o er = and β = and found after calculation t at eac grou ould re uire artici ants it a dro out rate erefore t e e erimental and control grou s ould need artici ants eac ma ing a total sam le si e of

2.3. Inclusion/exclusion criteria

artici ants ere recruited t roug sician referrals and osters e inclusion criteria ere (eing – ears old (eing diag-nosed it a s c iatrist using t e tructured linical nter-ie for iagnostic and tatistical anual of ental isorders ift Edition (- (a ing a total score of or more on t e -item amilton ating cale for e ression (- and a - tem (e ression score of or more (a ing not recei ed an antide ressant medications for t e current de ressi e e isode (eing a le to understand and sign t e informed consent ome of t e e clusion criteria ere (a ing a current or istor of sei ures e ile s - droce alus central ner ous s stem tumors or acute rain in ur and infection (a ing a signi cant ris of suicide indicated a score of or on t e - tem or it a istor of suicidal e a ior (a ing een e osed to electrocon ulsi e t era (E modi ed electrocon ulsi e t era (E transcranial magnetic stimulation (transcranial direct current stimulation (t t or ot er neurostimulation treatments in one mont efore enrollment (eing regnant or reastfeeding (atients it an se ere organic diseases or ere in an unsta le condition ecause of an organic disease e trial rotocol ic contains additional inclusion and all e clusion criteria is a aila le in u lement

2.4. Randomization, concealment, and blinding

com uter-generated randomi ation sc edule using randoml ermuted loc s randoml assigned eligi le atients to t e acti e and s am t grou s in a ratio irst a random num er ta le con-taining randomi ation se uences as generated it t e ste in t e soft are a statistician not in ol ed in conducting t is trial econd a nurse (also not in ol ed in conducting t is trial ut

grou assignment results generated from t e random num er ta le in identical se uentiall num ered o a ue sealed en elo es ird eac atient recei ed a sealed en elo e at enrollment inall on t e a-tient's rst da of enrollment or t e da t e atient recei ed t e rst stimulation session t e en elo e it grou assignment information ould e o ened a researc er

n t e ole randomi ation rocess and t roug out t e trial t e acti e or s am grou s as ell as t e acti e or s am stimulation de ices ere re resented it t e letters or (onl t e de ice o erators got t e information on t e letter assigned to a atient so t at all in-di iduals in ol ed in t e trial ere linded to t e t e of stimulation (acti e or s am t e ga e or recei ed lso t ere as no difference et een t e acti e and s am stimulation de ices in terms of a earance and t e a t e in uence t e atient's senses so t e atient and t e o erator could not distinguis ic instrument as t e acti e stimu-lation de ice ased on t e a earance of t e de ice or t e su ecti e feelings of t e atients fter statistical anal ses in t is stud ere com leted un linding as erformed

2.5. Procedures

artici ants ere as ed to sit comforta l in reclining c airs ile recei ing (ational edical roducts dministration a ro ed t (e alin ec nolog nc administered trained nurses in accordance it standardi ed instructions × cm electrode as laced on t e fore ead at and in t e international lacement s stem o × cm electrodes ere laced on eac side of t e mastoid e t stimulation a eforms include ram -u and ram -do n eriods of and s res ecti el e a eforms ere s uare a es it an a erage am litude of m and ere distri uted e uall from t e frontal region to t e mastoid areas (am litudes ere re orted as ero-to- ea

ll artici ants recei ed sessions of stimulation at and m ile t e s am t ad no acti e stimulation rom onda to rida one -min session as administered at a ed time eac da uring t e - ee trial all artici ants ere also as ed to ta e – mg of escitalo ram eac da

is stud in ol ed t e com ined use of escitalo ram t roug out t e - ee eriod ll medications ere ta en orall after rea fast (once dail e medication used in t is stud as -mg escitalo ram ta -lets ose titration as erformed t e researc ers ased on side ef-fects and or clinical course e initial dose of escitalo ram as mg da ic could e increased to mg da after ee s ased on t e atient's condition e dose could e furt er increased to mg da if necessar Eac increase in dose s ould e s aced a out ee s a art and not less t an da s a art

2.6. EEG

esting-state EE data ere collected at aseline and t e ee - follo -u using a -c annel EE s stem (rain roducts erman e electrodes ere ositioned according to t e standard international s stem e sam ling fre uenc as and electrode im edance as e t elo Ω artici ants ad t eir e es o en for min t en ad t eir e es closed for min uring t e e es-o en condi-tion artici ants ere instructed to ate on a cross- air artici ants also com leted a face- ord troo tas t e results of ic are not resented ere

e EE tool o in atla as used to re rocess t e EE data e ste s of EE data re rocessing ere (c annel selection (remo ed c annel (and ass lter (– (seg-mentation of e oc s into -s segments (ad c annels re ection (resam ling to (re-reference to ilateral mastoid (nde-endent om onent nal sis (and - ased manual artifact remo al fter re rocessing t e o er s ectral densit (of EE as estimated it t e fast ourier transform met od and t e of t e al a fre uenc and (– as calculated to com are t e c anges in EE annels of t e left frontal lo e ere selected and a eraged to re resent t e al a o er in t e left frontal lo e

2.7. Outcome measures

e rimar ef cac end oint as t e c ange in - scores from aseline to ee (it treatment sessions com leted econdar ef cac end oints included linical lo al m ression of m ro ement (- at ee s and t e c anges from aseline to ee (it treatment sessions com leted in t e scores on t e - re ecting de ression (tems an iet (tems insomnia (tems and somatic s m toms (tems enerali ed n iet isorder- (- -item uic n entor of e ressi e m tomatolog elf- e ort (- itts urg lee ualit nde (lin-ical lo al m ressions- e erit of llness cale (- t e ro-ortions of res onders (de ned it a reduction of or more from aseline in t e - total score at eac isits and e ile tiform acti ities re ealed EE recordings

afet and tolera ilit ere e aluated it ad erse e ents (Es ital signs clinical la orator e aluations and electrocardiogram a-rameters erious Es ere de ned as an unto ard medical occurrence t at resulted in deat as life t reatening (at t e time of t e e ent re uired in atient os itali ation resulted in ersistent or signi cant disa ilit

2.8. Statistical analysis

e main anal ses ere com leted on an intent-to-treat asis meaning all randomi ed atients ere included issing data for - scores ere im uted using t e last o ser ation carried for-ard escri ti e data at aseline ere re orted it mean (standard de iation or median and inter uartile range (for continuous ar-ia les and count (ercentage for categorical aria les

e rimar end oint as assessed it an inde endent-sam le *t*-test ased on data it t e last o ser ation carried for ard (im utation e erformed t ree sensiti it anal ses for t e rimar outcome to assess t e ro ustness of t e results n ensiti it nal sis multi le im utation for monotone missing data e tted a regression model from o ser ed data and otential redictors (i e age se aseline score rst e isode to generate im uted alues e used multi le im utations (to im ute alues for eac missing o ser ation and com ined estimates using E in ensiti it nal sis a er- rotocol anal sis as also erformed to e amine et er t e reductions in t e scores on t e - and t e res onse rates differed et een t e t o grou s ensiti it nal sis e aluated t e effect of t e inter ention on t e - scores it linear mi ed modeling (ased on all a aila le data it out im utation it t e treatment grou isit and t eir interaction (grou × isit as ed effects and t e artici ant as a random effect

secondar outcome t e res onse rate as com ared using t e c i-s uare test e reductions in t e scores of eac factor of t e - and t e scores of and - ere com ared using t e ilco on ran -sum test n inde endent-sam le *t*-test as used to com are t e differences et een t e reductions in t e scores on t e - - and in t e acti e and s am t grou s e correlation et een t e mean reduction in EE and t e mean reduction in t e - total score from aseline to ee as e aluated it earman correlation anal sis

ll data ere anal ed using for indo s ersion (nstitute ar and (oundation for tatistical om uting ienna ustria ll alues ere t o-sided and t e differences ere considered statisticall signi cant en t e alue as <

3.1. Participants

total of atients it ere assessed for eligi ilit and atients met t e inclusion criteria and ere randoml allocated to t e acti e t grou (n = or s am t grou (n = fter randomi ation se en artici ants in t e s am t grou ere lost at ee and t o artici ants in t e acti e t grou did not com lete t e stud (ig e artici ants' demogra ic and clinical c arac-teristics are summari ed in a le ore t an alf of t e artici ants ere female (mean alues for ot er demogra ics included ± ears for age ± g m for and (– mont s for t e duration of t e recent e isode f all artici ants ere rst e isode and ad a famil istor of mental disorders f t e atients started at a dose of mg da of escitalo ram and increased to mg da after da s it t o atients in eac grou increasing to mg da after ee s n addition one atient in t e acti e t grou did not ta e escitalo ram and one atient in t e s am t grou maintained a dose of mg da

3.2. Primary outcomes

n t e intention-to-treat anal sis signi cant differences ere found in t e mean reduction of t e - scores at ee (t = P = ere ere also statisticall signi cant differences in t e reduction of t e - scores et een t e t o grou s at ot ee s and (ee t = P < ee t = P = (ig e ra and reduction mean scores of all outcomes at all time oints are s o n in u lementar aterials a le

3.3. Secondary outcomes

igni cantl more artici ants in t e acti e t grou (n = res onded (de ned it a reduction of or more from

asic information

aria les	cti e t	am t
e		
ale	(	(
emale	(	(
Educational le el		
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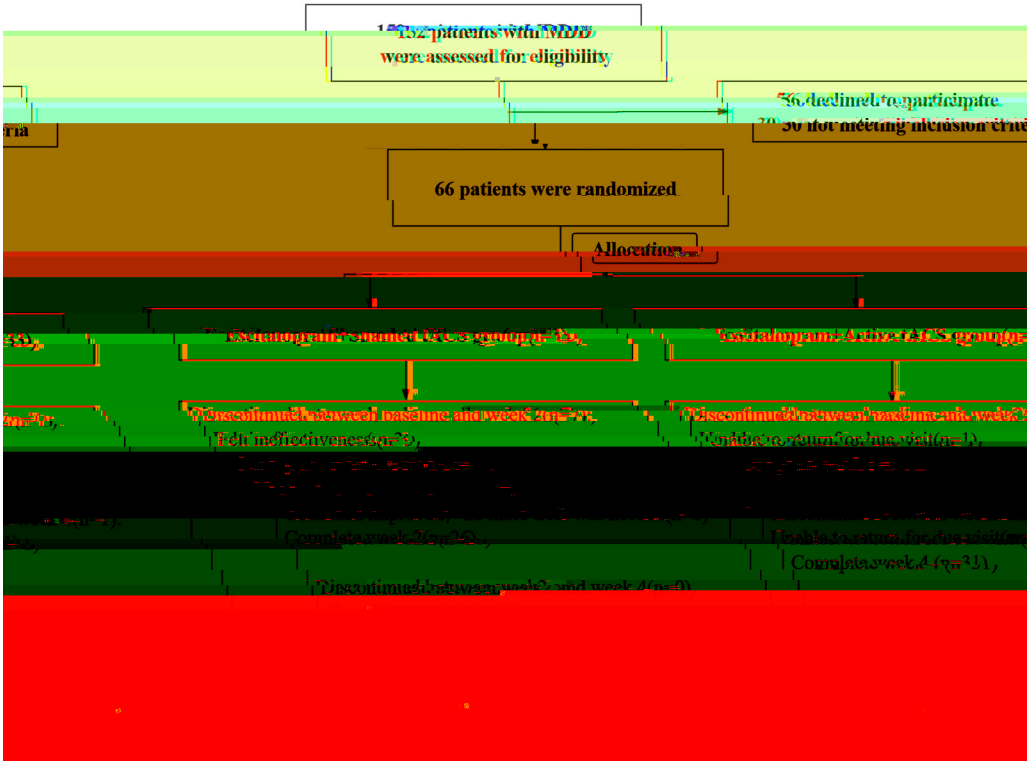
otal course of (mont s	(–	(–
uration of current e isode (mont s	(–	(–
otal score of - at aseline	(–	(–
re uenc of e isode	(–	(–

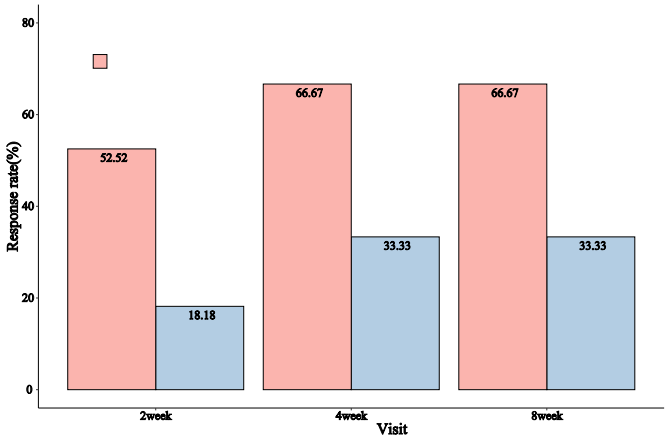
ote n (or mean (standard de iation or median (inter uartile range



lo art

e ean eductions of t e -item amilton ating cale for e ression (- cores from aseline to ee s and in t e cti e t and am t rou s
ote - (t e - item amilton ating cale for e ression range – ig er scores indicate more se ere de ressi e s m toms e error ars indicate Es e missing data of t e - scores for atient in ee and atients in ee ere im uted using t e last o ser ation carried for ard a re resents <

aseline in t e - total score at ee com ared it t ose in t e s am t grou (n = χ = P = is difference as also o ser ed at ee (acti e t n = s am t n = χ = P = and ee (acti e t n = s am t n = χ = P = (ig om ared it t ose in t e s am t grou t e reductions in t e scores on t e de ression and insomnia su scales of t e - in t e acti e t grou at ee ere signi cantl larger (< t ee t e reductions in t e scores on t e de ression insomnia and somatic su scales of t e - in t e acti e t grou ere signi cantl larger (u lementar materials a le t ee t e - score reduction in t e acti e t grou as signif- icantl ig er (= – P = (u lementar materials a le e differences et een t e reductions in t e - - and scores in t e acti e and s amed t grou s ere not statisticall signi cant (P > (u lementar aterials a le



e es onse ates at ifferent isits in t e cti e t and am t rou s
ote es onse as de ned as a reduction in t e -item amilton ating cale for e ression (- range – ig er scores indicating more se ere de ressi e s m toms issing data of t e - scores for atient in ee and in ee ere im uted using t e last o ser ation carried for ard
a re resents <

3.4. Sensitivity analysis

e results of t e multi le im utation ere consistent it t ose of t e rimar anal sis e results s o ed t at t e estimated mean - reduction in t e acti e t grou as larger t an in t e s am t grou (t = P = at ee e er- rotocol anal sis also su orted t is result (u lementar aterials a le n addition a mi ed-effects model anal sis it t e treatment grou isit and t eir interaction (grou × isit as ed effects and t e artici ant as a random effect re ealed a signi cant treatment grou - - time interaction (= P = e im ro ement o er isits in t e stud (aseline ee and ee as signi cantl greater in t e acti e t grou e least-s uares mean reduction in t e - score from aseline to ee as (se in t e acti e t grou and (se in t e s am t grou (et een-grou dif- ference se to = (u lementar materials a le

3.5. Blinding integrity

o test t e uality of t e linding in our stud e aid return isits to all atients n t e acti e stimulation grou atients t oug t t e recei ed acti e stimulation t oug t t e recei ed s am stimulation and ere lost to follo -u in t e s am stimulation grou t oug t t e recei ed acti e stimulation t oug t t e recei ed s am stimu- lation and ere lost to follo -u n ot t e acti e and s am stim- ulation grou s most atients (and res ecti el elie ed t e recei ed acti e t lso t ere as no statistical difference e- t een t e t o grou s in t e num er of atients o elie ed t e recei ed acti e or s am stimulations (=

3.6. Mechanism exploration

o erif et er t as effecti e in c anging al a oscillations e assessed t e c anges in resting-state al a o er at t e ee - follo -u in t e sam le aseline al a o er as not different et een t e t o grou s e com ared t e c anges in al a o er

et een t e treatment grou s ut found no signi cant difference (u lementar materials ig en e conducted an in-de t e lorator anal sis n t e acti e t grou e found a correlation et een t e mean reduction of in e e-closed state EE and t e mean reduction in t e - total score from aseline to ee (r = P = lso in t e acti e t grou t e mean reduction of from aseline to ee in e e-closed state EE as signi cantl larger in t e res onders t an in t e non-res onders (= = n t e ot er and in t e s am t grou no consistent results ere found (ig similar anal sis of t e e e-o en state did not re eal an signi cant effect of t e stimulation on c anging al a o er a en toget er our results indicate t at t as effecti e in targeting al a oscillations in t e left frontal regions and t is c ange ad a relations i it clinical s m toms

3.7. Safety

o serious ad erse e ents ere o ser ed in t is trial e re orted general side effects in t e acti e t grou (com ared it t e s am t grou included eadac e (com ared it

it antide ressants t e a erage reduction rate of t e scores reac ed le ander et al randomi ed atients it into t ree stud grou s of - t - t and s am stimulation and administered one -min interention session eac da for consecuti e da s along it antide ressants e res onse rate of t e - t grou at ee as signi cantl ig er t an t e - and s am stimulation grou s suggesting t at - t ad a etter antide ressant ef cac e most relia le e idence in is for t it m n of t in drug-na e atients it s o ed a res onse rate of and a remission rate of after ee s of t treatment ic ere signi cantl ig er t an t e res onse and remission rates after s am stimulation (and o e er t is stud onl included rst-e isode drug-na e atients and t e more signi cant treatment effect ma e ecause of t at not er studied t com ined it antide ressants in atients and found a romising clinical ef cac it a reduction of in t e scores in t e acti e grou and in t e s am grou at t e end of ee lt oug t is stud ad limitations and t e use of antide ressants as not limited t as an add-on to antide ressants ma e a good o tion for atients o need a fast effect long it ot er neuromodulations r also en ances t e clinical res onse to antide ressants and signi cantl accelerates t e alle iation of de ressi e s m toms in atients it stud of - ee r com ined it citalo ram found t at t e res onse rates in t e acti e grou ersus t e s am grou ere ersus at ee and ersus at ee stud of - ee r in com ination it aro etine found a res onse rate of and a remission rate of in t e acti e grou ic ere signi cantl ig er t an t ose in t e s am grou (and at ee alt oug t ere as no signi cant difference at ee tudies of t as an add-on treatment to antide ressants also demonstrated t e s nergistic effect of com ination t era ne stud found t at artic- i ants recei ing ee s of t com ined it sertraline ad a res onse rate of and a remission rate of signi cantl ig er t an t ose in t e sertraline-onl grou (and n anot er stud atients it ere di ided into t ree grou s -min -min and s am t com ined it sertraline fter ten da s of t stimulation t e -min -min and s am grou s s o ed res onse rates of and and remission rates of and res ecti el e im ro ement in de ressi e s m toms as more su stantial in t e acti e stimulation grou s and t e im ro ement in t e -min grou as signi cantl larger t an in t e -min grou n summar t is e ected to e an effecti e add-on antide ressant treatment com ara le to r and t o - e er considering t at r and t a e een e aluated in large-scale multi-center trials ereas t as onl een studied in small-scale trials it s ould e noted t at t ere is a ris of false- ositi e ndings and our ndings need to e con rmed larger trials in t e future e - scores did not re eal an signi cant treatment ad antage in t e acti e t stimulation grou o er t e s am stimulation grou ome studies a e found t at atients scored t emsel es ig er on self-re ort measures t an t e clinicians rated t em E lanations for t is enomenon include t e differences in t e focus of t e clinician and atient o erestimation of s m tom se erit t e atients ig le els of an iet need for a ro al (es eciall social desira ilit and ig le els of self-transcendence (es eciall self-forgetfulness urt ermore after com aring eac factor in t e - e found t at t e factors de ressed mood insomnia and somati ation s o ed more ronounced im ro ements ereas t ese s m toms ere lig ter eig ted in t e - t is difference ma e art of t e reasons t e c anges in t e total score ere not signi cant re ious studies e amining t e concordance et een self-re ort and clinician-rated measures ere inconsistent and t is is t e main reason most clinical trials ould use ot self-re ort and clinician-rated measures as outcome instruments it t e latter ser ing as t e measurement tool for t e rimar outcome e as also used to assess t e se erit of t e atient's de ressi e s m toms and t e degree of im ro ement e - scores at ee suggested t at t e t grou ad more im ro ement t an t e s am grou e results of t e - re ealed t e ositi e im act of t on t e o erall clinical im ression of atients it lt oug t e is an instrument rel ing on t e su ecti e udgment of t e e aluators it ro ides im ortant information on t e effecti eness of treatment es eciall for t e e aluation of ractical clinical signi cance e safet of using ig currents is a concern n t is stud (of t e artici ants com leted t e - ee stud e dro out rate as lo er t an t e estimation of suggesting t at t e t used in t is stud as safe and ell tolerated ll atients ere follo ed u for ad erse e ents and most side effects in t is stud ere mild (some atients e erienced di iness eadac e and da time slee iness ore im ortantl t ere as a difference et een t e ad erse e ents in t e t o grou s re ious studies did not re ort side effects of da time slee iness o e er e o ser ed rolonged da time slee iness t at as clearl related to t e treatment it slee iness eing t e most ronounced at t e end of t (alt oug it s ould e noted t at t is nding still needs to e alidated in future studies erefore it ma e necessar to notif atients o dri e e icles n addition no manic or omanic s m toms sei ures neurologic complications o tical illusions deat s or ot er serious ad erse e ents ere o ser ed in our stud erall t e safet of t in com ination it antide ressants for t e treatment of as con rmed suggesting t at future clinical trials it t are feasi le e siological target of t e current stud as left frontal al a oscillations EE al a acti it is more ronounced it e es closed and al a o er as mmetr as een found to e more relia le it e es closed t an it e es o en e alteration of al a o er in our stud also occurred onl in t e e e-closed state is alteration as t oug t to re ect reduced neuronal acti it in t e left frontal lo e one of se eral e regions ere a normalities a e een found in rain imaging studies of de ression ne article as e amined EE c anges after recei ing t in atients it it found t at - t resulted in a signi cant reduction in al a oscillations in t e left frontal region it e es closed ereas no c anges ere found it - t n addition - t s o ed etter antide ressant effects not er stud found t at t it indi iduali ed al a frequenc (could reduce resting-state left frontal al a o er in atients it urt ermore t e reduction of left frontal al a oscillation t as s eci c for stimuli it ositi e alence ur stud also found a decrease in left frontal al a fre uenc in atients o res onded to t e t treatment ut not in atients it no res onse e ot esi e t at t e antide ressant effect of t ma e related to t e decrease in left frontal al a o er e e act mec anism of t as not een determined studies a e s o n t at t induces cortical oscillations entrainment and s i e-timing de endent lasticit tudies a e consistentl demonstrated t e locali ed o er en ancement after t and a e found t at immediate t after-effects led to an increase in resting-state al a o er e transient al a o er en ancement after a single t treatment ma e due to a stimulus dose t at is not suf cientl ersistent to induce long-term lasticit e increase in transient al a o er ma re ect neural induction of time-s nc roni ed cortical oscillations e ogenous stimuli ut e idence for long-term effects remains limited e found a decrease in al a o er after sessions of t ic is o osite to t e immediate effect suggesting t at re eated a lication of t ma lead to oscillator resetting ic in turn leads to a decrease in al a o er t roug a omeostatic mec anism roducing an antide ressant effect erefore t e results of t is stud once again suggested t at t e intrinsic regulation of al a oscillations ma e an im ortant mec anism for t e antide ressant effect of t is stud as some limitations irst e onl o ser ed t e ef cac in t e acute ase and e onl included a - ee follo -u ic is rat er s ort com ared to current est- ractice s in erefore

t e maintenance effect still needs to e furt er in estigated econd e used onl t it m and a ed stimulation osition e antide ressant ef cac of different fre uencies currents and electrode com inations is un no n ird e onl com ared t e c anges in left frontal al a o er and it is unclear et er t e EE at ot er locations and fre uencies c anged lso all atients used antide ressants ic ma a e affected t e EE e gro ing recognition of t e resence of a normal oscillator d namics in t e at olog of as generated strong interest in t e direct modulation of endogenous oscillations uture studies on arious forms of neuromodulation and EE alterations in unmedicated atients are needed inall t e dro out rates ere ig er in t e s am grou ic mig t e related to t e lac of antide ressant effect in t at grou uture studies s ould ma e efforts to reduce t e dro out rate in t e s am grou n summar alt oug our trial ro ided reliminar e idence for t e antide ressant effects of t larger long-term trials are needed to deri e more relia le conclusions

ur results suggest t at t e additional antide ressant effect of t as signi cant and lasted for at least ee s and com ining t it antide ressants is a feasi le and effecti e a roac for t e treatment of e antide ressant mec anism of t ma e t e reduction of t e al a o er in t e left frontal lo e uture researc directions ma include e loring more a ro riate treatment arameters of t

is stud as funded - a or ro ects raining lan for ig e el u lic ealt ec - nical alents onstruction ro ect isci line ac ones– – and a ital ealt esearc e elo ment ecial ro ect - -

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e aut ors declare no com eting interests

e ould li e to t an t e doctors and nurses for t eir generous su ort during t e conduct of t e stud and all t e atients and t eir families for artici ating in t is trial e also t an e alin ec nolog nc ouston for ro iding t e transcranial alternating current stimulation de ices free of c arge eit er of t e mentioned funders or com an as in ol ed in t e conce tion and erformance of t e stud

u lementar data to t is article can e found online at tt s doi org rs

us ri edi isnie s i ieren erg te art arden et al cute and longer-term outcomes in de ressed out atients re uiring one or se eral treatment ste s a re ort m s c iatr – ntal oros oreis aie erne aulus om arati el ea after-effects of transcranial alternating current stimulation t on cortical e cita ilit in umans rain timul – ars all elgadóttir ölle orn oosting slo oscillations during slee otentiates memor ature – ang ang ang ue eng un et al Effect of transcranial alternating current stimulation for t e treatment of c ronic insomnia a randomi ed dou le- lind arallel-grou lace o-controlled clinical trial s c ot er s c osom – El aman eic t errmann ulert ranscranial alternating current stimulation t from asic mec anisms to ards rst a lications in s c iatr Eur rc s c iatr lin eurosci – le ander laga an ugo E ellin usten erger u ino et al ou le- lind randomi ed ilot clinical trial targeting al a oscillations it transcranial alternating current stimulation t for t e treatment of ma or de ressi e disorder ransl s c iatr aller enner runoni ad erg alm amma transcranial alternating current stimulation im ro es mood and cognition in atients it ma or de ression s c iatr es – ang ang ue eng in u et al ranscranial alternating current stimulation for treating de ression a randomi ed controlled trial rain – an ang ang ang ao uang et al E idence of a large current of transcranial alternating current stimulation directl to dee rain regions ol s c iatr – e ede al gin o ale s i c o a isoe ro oto et al e ices for nonin asi e transcranial electrostimulation of t e rain endor inergic s stem a lication for im ro ement of uman s c o- siological status rtif rgans – ite E ic ards e alin and related forms of su cortical electrical stimulation n t mic stimulation rocedures in neuromodulation Else ier – egadoren 'donnell anius ou land aca e- asmonteil e role of β-endor in in t e at o siolog of ma or de ression euro e tides – a erg rannan e ell il a a urin c innis et al egional meta olic effects of uo etine in ma or de ression serial c anges and relations i to clinical res onse iol s c iatr – iong uo an eigang et al Ef cac and safet of transcranial alternating current stimulation com ined it antide ressants in de ressi e e isodes ournal of a ital edical ni ersit – i riani uru a a alanti aimani t inson ga a et al om arati e ef cac and acce ta ilit of antide ressant drugs for t e acute treatment of adults it ma or de ressi e disorder a s stematic re ie and net or meta-anal sis ancet – ingel urts ingel urts ltered structure of d namic electroence alogram oscillator attern in ma or de ression iol s c iatr – mart iru adi a erg ultimodal a roac es to de ne net or oscillations in de ression iol s c iatr – l ric rns EE iomar ers in ma or de ressi e disorder discriminati e o er and rediction of treatment res onse nt e s c iatr – ort off o do resting state c anges in de ression translate into s c o at ological s m toms rom ' atiotem oral corres ondence' to ' atiotem oral s c o at olog ' urr in s c iatr – e son iagara an EE fre uenc ands in s c iatric disorders a re ie of resting state studies ront um eurosci euc ter oo unter ai or at esting-state uantitati e electroence alogra re eals increased neuro siologic connecti it in de ression o ne e ensen a a eri a ing functional arc itecture oscillator al a acti it gating in i ition ront um eurosci limesc α- and oscillations attention and controlled access to stored information rends ognit ci – armon- ones E a le n t e role of as mmetric frontal cortical acti it in a roac and it dra al moti ation an u dated re ie of t e e idence s c o siolog a idson nterior cere ral as mmetr and t e nature of emotion rain ognit – orld edical ssociation eclaration of elsin i Et ical rinci les for medical researc in ol ing uman su ects ull orld ealt rgan – outron o er ltman c ul a aud E tending t e statement to randomi ed trials of non armacologic treatment e lanation and ela oration nn ntern ed – elorme a eig EE an o en source tool o for anal sis of single-trial EE d namics including inde endent com onent anal sis eurosci et ods – eng ao illi s iu ai un et al alidit and relia ilit of t e inese amilton de ression rating scale r s c iatr –

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il ening ur ec ec antsreiter E ad erg alm ranscranial alternating current stimulation for t e treatment of ma or de ression during regnanc s c iatr es –
erlim an den E nde as ala is ig -fre uenc re etiti e transcranial magnetic stimulation accelerates and en ances t e clinical res onse to antide ressants in ma or de ression a meta-anal sis of randomi ed dou le- lind and s am-controlled trials lin s c iatr ❨ e –
umi atta igonatti osa regni osa et al ranscranial