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Fea ed A icle

The effec of 7-week cogni i e aining in pa ien wi h a c la cogni i e impai men , no demen ia (he Cog-VACCINE dy): A andomized con olled ial

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Abstract

Introduction: E idence fo he efficacy of cogni i e aining in pa ien wi h bco ical a c la cogni i e impai men no demen ia i ill lacking.

Methods: A andomized, ac i e con olled de ign ing m l idomain, adap i e, comp e ized cogni i e aining fo 30 min e , 5 day /week fo 7 week . A e men incl ded global cogni i e f nc ion and exec i e f nc ion (p ima y o come) and b ain f nc ional connec i i y and c al change (econda y o come).

Results: Six y pa ien we e andomized ac o h ee medical cen e in Beijing. A he end of he in e en ion, he cogni i e aining g o p howed ignifican imp o emen in Mon eal Cogni i e A e men ela i e o he ac i e con ol g o p ($P = .013$) and ignifican ly inc ea ed f nc ional connec i i y be ween he lef do ola e al p ef on al co ex and medial p ef on al co ex, which wa ignifican ly co ela ed wi h Mon eal Cogni i e A e men change ($P = .017$).

Discussion: Comp e ized cogni i e aining ignifican ly imp o ed global cogni i e f nc ion, which wa ppo ed by he imp o ed b ain pla ici y. Inco po a ion of bioma ke ho ld be implemen ed in cogni i e aining ial .

K :

Va c la cogni i e impai men no demen ia; Comp e ized cogni i e aining; Randomized con olled ial; B ain pla ici y

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1. Introduction

Va c la cogni i e impai men (VCI) i one of he mo common ca e of acq i ed cogni i e impai men , econd only o Alzheime ' di ea e (AD) [1]. Va c la cogni i e impai men no demen ia (VCIND) efe o cogni i e defici a ocia ed wi h nde lying a c la ca e ha a e in fficien o confi m a diagno i of demen ia. Acco ding o he China Cogni ion and Aging S dy, VCIND acco n fo 42.0% of ca e of mild cogni i e impai men (MCI) in China, ende ing i he mo common b ype of MCI he ein [2]. A 5-yea follow- p of pa ien wi h VCIND e ealed ha 50.0% of he pa ien de eloped demen ia, incl ding AD [3].

Al ho gh VCIND i po en ially a key age a which ea ly in e en ion may delay o p e en demen ia, an app o ed me hod of in e en ion ha ye o be de eloped. Recen ad ance in cogni i e aining, howe e , may info m a egie o ea VCIND. In a heal hy elde ly pop la ion, he Ad anced Cogni i e T aining fo Independen and Vi al Elde ly ial led o imp o emen in a ge ed domain and daily f nc ion, which wa main ained ac o long- e m follow- p [4]. In addi ion, comp e ized cogni i e aining ha demon a ed po en ial a an effec i e in e en ion fo pa ien wi h MCI o ea ly AD [5]. De pi e he p omi e of ch finding , fa fewe e o ce ha e been alloca ed o nonpha macological app oache o ea ing demen ia, incl ding cogni i e aining, han o he de elopmen of pha macological di ea e-modifying he apie [6]. E idence fo he efficacy of cogni i e aining in pa ien wi h VCIND i con eq en ly lacking. Con ide ing he ignifican he e ogenei y of VCIND, e ea ch m add e he dea h of da a on he efficacy of in e en ion ial wi h e pec o VCIND b ype .

The p e en dy foc ed on he mo common b ype of he di o de , VCIND ca ed by bco ical i chemic mall e el di ea e (bco ical VCIND), a i ela i ely homogeno fea e ende i a i able a ge condi ion fo in e en ion ial . We cond c ed a andomized, ac i e con olled ial o de e mine he efficacy of a 7-week m l idomain, adap i e, comp e ized cogni i e aining egimen in pa ien wi h bco ical VCIND (he Cog-VACCINE dy). A exec i e dy f nc ion i he p ima y impai men a ocia ed wi h bco ical VCIND [7], we ed he T ail Making Te (TMT) in andem wi h a e e ing global cogni i e f nc ion ia he Mon eal Cogni i e A e men (MoCA) a an addi ional p ima y o come o confi m whe he cogni i e aining co ld a en a e exec i e dy f nc ion in pa ien wi h bco ical VCIND. Ob e ed alle ia ion of cogni i e dy f nc ion wo ld likely be acco n ed fo by change o b ain pla ici y [8], incl ding inc ea ed g ay ma e ol me, imp o ed whi e ma e in eg i y, and change in ne onal f nc ional connec i i y. To a e e he e econda y o come and el cida e he mechani m nde lying a po ible effec of cogni i e aining, we pe fo med c al magne ic e onance imaging (MRI) and f nc ional magne ic e onance imaging (fMRI).

2. Methods

2.1. S ⁄ ⁄ ⁄

The p e en andomized, ac i e con olled clinical ial wa cond c ed in acco dance wi h bo h he CONSORT a emen and he CONSORT a emen fo nonpha maco- logical in e en ion . Pa icipan wi h bco ical VCIND we e ec i ed f om h ee cen e : X anw Ho pi al; Beijing F iend hip Ho pi al; and F Xing Ho pi al, Capi al Medical Uni e i y. All pa icipan p o ided w i en info med con en . E hical app o al wa ob ained f om he E hic Commi ee of X anw Ho pi al, Capi al Medical Uni e i y (2015010). The ial wa egi e ed nde ClinicalT ial .go (NCT02640716) and i p o ocol ha been p bli hed p e io ly [9].

2.2. P/ ⁄ ⁄

The diagno i of VCIND wa ba ed on e idence of bo h cogni i e impai men wi ho demen ia and mall e el i chemic di ea e. All pa ien we e diagno ed by a con en panel incl ding h ee enio ne ologi and me he following incl ion c i e ia: (1) li e a e in Han Chine e wi h a con i en ca egi e (>4 day /week); (2) complain and/o info man epo of cogni i e impai men in ol ing memo y and/o o he cogni i e domain wi h a d a ion of a lea 3 mon h ; (3) acco ding o he Diagno ic and S a i ical Man al of Men al Di o de , Fo h Edi ion, he pa ien we e nei he no mal no demen ed a indica ed by a clinical demen ia a ing of ≥0.5 on a lea one domain, a global co e of ≤0.5, and a Mini–Men al S a e Examina ion co e of ≥20 (p ima y chool) o ≥24 (j nio chool o abo e); and (4) no mal o ligh ly impai ed daily li ing ac i i ie a defined by a o al co e of ≤1.5 fo he h ee f nc ional clinical demen ia a ing domain (home and hobbie , comm ni y affai , and pe onal ca e). We excl ded pa icipan who exhibi ed any condi ion ha wo ld p ecl de comple ion of ne op ychological e ing o di o de o he han bco ical VCIND ha wo ld affec cogni ion.

The MRI-ba ed incl ion c i e ia de ail we e a follow : (1) m l iple (≥3) p a en o ial bco ical mall infa c (3–20 mm in diame e) wi h/wi ho whi e ma e le ion of any deg ee o mode a e- o- e e e whi e ma e le ion (co e of ≥2 acco ding o he Fazeka a ing cale [10]) wi h/wi ho mall infa c ; (2) ab ence of co ical o wa e hed infa c , hemo hage , hyd ocephal , o whi e ma e le ion wi h pecific ca e (e.g., m l iple cle o i); and (3) no hippocampal o en o hinal co ex a ophy (co e of ze o acco ding o he medial empo al lobe a ophy cale of Schel en [11]).

Excl ion c i e ia incl ded he following: (1) e e e apha ia o o he fac o ha migh p ecl de comple ion of

ne op ychological a : e : men : o MRI; (2) clinically : ignifican ga oin e inal, enal, hepa ic, e pi a o y, o o he : y emic di ea e ; and (3) o he di o de : o : e of medica ion ha migh affec cogni i e f nc ion .

2.3. B

The pa icipan : we e andomly a : igned o aining o ac i e con ol g o p. The pe : onnel in ol ed in cond c ing he : dy and da a analy i we e ma ked o he pa ien andomiza ion. S dy pa icipan : , hei ca egi e , and all a : e : o : we e blinded o ea men a : ignmen h o gho he : dy.

2.4. P

Pa ien : in he in e en ion g o p ecei ed a comp e ized, m l idomain, adap i e aining p og am fo 7 week . The aining domain incl ded p oce : ing : peed, a en ion, pe cep ion, long- e m memo y, wo king memo y, calc la ion, exec i e con ol, ea oning, and p oblem : ol ing. The igo wi h which each domain wa ained diffe ed acco ding o each a k and info med he g o ping of he a k . Pa icipan : we e eq i ed o comple e 30 min of aining pe day (fi e 2-min a k comple ed h ice), 5 day a week. Wi hin each a k, high acc acy (>80%) wa eq i ed o pg ade o he nex diffic l y le el.

The ac i e con ol g o p ecei ed fi e p oce : ing : peed and a en ion a k , who e d a ion o aled o 30 min each aining day. Howe e , he e a k we e : e o a fixed, p ima y diffic l y le el ac o : he : dy.

The aining of all pa icipan : wa comple ed a home and : pe i ed by an independen ne ologi o e he In e ne (www.66nao.com) o g a an ee he f lfillmen of he aining.

The in e en ion began di ec ly af e andomiza ion. All he o come we e a : e : ed a he ba eline, end of in e en ion, and 6 mon h af e andomiza ion o mea e long- e m e ilience of he effec . Fo he de ail of he in e en ion , : ee Me hod in S pplemen a y Ma e ial .

2.5. O

The p ima y o come mea e we e global cogni i e f nc ion, mea ed by MoCA, and exec i e f nc ion, mea ed by TMT B-A; bo h we e cen ally a : e : ed.

Ba ed on p e io : : die , we hypo he ized ha cogni i e aining co ld enhance f nc ional and : c al connec i i y and/o local mo phome y. The : econda y o come of he p e en : dy he efo e incl ded : c al and f nc ional indice : he g ay-ma e ol me of he hippocamp : , a key b ain : c e linked wi h memo y impai men [12]; and whi e-ma e (WM) in eg i y, which

Fi he ' Z an fo ma ion co ela ion coefficien we e hen ex ac ed fo each pai in each ime poin and ed a inp fo he co ponding linea mixed effec model .

2.7. S / _ / / /

All da a we e analyzed acco ding o in en - o- ea p inciple . The effec of cogni i e aining on ne op ychological co e and MRI da a we e examined ing linea mixed effec model ne ed wi hin indi id al . Time wa a igned a he epea ed a iable. G o p, ime, and g o p-by- ime we e incl ded a fixed effec . We analyzed he change in he ne op ychological co e and MRI da a f om he ba eline o he end of in e en ion and f om ba eline o 6-mon h follow- p. A a i ically ignifican diffe ence (wo ailed, $P < .05$) fo any of he wo p ima y o come a he end of he in e en ion wo ld be con ide ed a p elimina y e idence of efficacy. Co ela ion analy e be ween ignifican b ain f nc ional change and ne op ychological co e we e hen pe fo med o explo e a po en ial ne al mechani m fo cogni i e f nc ional change .

3. Results

3.1. P/ _ _ / ' / / _ _

Pa icipan we e en olled f om Decembe 22, 2015 h o gh No embe 7, 2016. The la follow- p mea emen we e ob ained in May 8, 2017. The flow of pa icipan h o gh he dy i hown in Fig. 1. A o al of 212 indi id al f om he ne ology and ge ia ic clinic we e incl ded and a e ed fo eligibili y. Of he e, 152 we e excl ded and he p e en dy he efo e en olled a o al of 60 pa ien . They we e andomly a igned o he cogni i e aining o ac i e con ol g o p . A o al of 54 pa icipan (27 in each g o p) fini hed he ial wi h good compliance. A o al of 44 pa icipan (23 in he aining g o p and 21 in he ac i e con ol g o p) comple ed he 6-mon h follow- p. Of he 16 pa icipan (26.7%) who wi hd ew f om he dy, fi e epo ed heal h i e , fo epo ed ime con ain , fi e we e di a i fied, and wo epo ed pe onal i e . Ba eline cha ac e i ic and ne op ychological a e men da a a e hown in Table 1. We fo nd no g o p diffe ence in age, ex, o d a ion of ed ca ion. Excep fo immedia e ecall, he ne op ychological e ing co e we e ma ched be ween he wo g o p . All pa icipan comple ed mo e han 90% of he aining eq i emen . The e wa no ignifican g o p diffe ence in bo h aining day. ($P = .167$) and aining ime pe day ($P = .134$) (Table 1).

3.2. P / /

The change f om he ba eline o he end of he 7-week in e en ion and f om he ba eline o he end of he 6-mon h follow- p fo he p ima y o come a e hown in

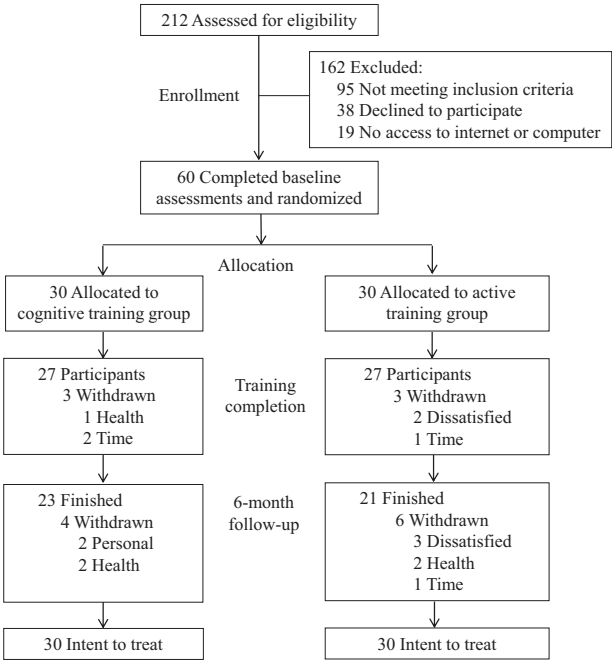

Fig. 1. The flowcha fo he Cog-VACCINE dy.

Fig. 2 and Table 2. The e wa a ignifican g o p × ime in e ac ion in MoCA a he end of he in e en ion pe iod. Af e 7 week , MoCA had ignifican ly imp o ed in he cogni i e aining g o p (f om 21.87 o 25.22) ela i e o

Table 1
Ba eline cha ac e i ic and aining adhe ence of he wo g o p

Va iable	T aining g o p (n = 30)	Ac i e con ol g o p (n = 30)
Age, y	63.9 (7.9)	64.9 (6.6)
Female	12 (40.0%)	8 (26.7%)
Ed ca ion, y	10.8 (3.5)	10.0 (2.8)
MoCA	21.9 (3.8)	21.2 (3.8)
ADL	21.7 (3.1)	21.5 (2.8)
Digi pan fo wa d	7.4 (1.6)	7.2 (1.1)
Digi pan backwa d	4.3 (1.5)	4.2 (1.1)
BNT	22.2 (3.7)	23.4 (3.6)
WHO-UCLA AVLT		
Immedia e ecall	22.9 (5.8)	19.2 (6.7)
Delayed ecall	7.3 (2.7)	6.3 (3.3)
Recogni ion	10.9 (2.7)	9.9 (2.9)
TMT B-A	74.0 (56.6)	77.0 (65.3)
Hachin ki Ł chemic Scale	3.5 (3.0)	2.3 (2.7)
NPI*	3.9 (3.9)	2.7 (4.4)
GDS	8.9 (6.7)	7.4 (5.7)
T aining day. (day.)	34.0 (1.0)	33.6 (1.1)
T aining ime/day (min e)	29.2 (1.9)	28.3 (2.1)

Abb e ia ion : MoCA, Mon eal Cogni i e A e men ; ADL, ac i i ie of daily li ing; BNT, Bo on Naming Te ; WHO-UCLA AVLT, WHO-UCLA A di o y Ve bal Lea ning Te ; TMT B-A, T ail Making Te B-A; NPI, Ne op ychia ic In en o y; GSD, Ge ia ic Dep e ion Scale.

*Tho gh he da a a e no no mally di ib ed, he mean and anda d de ia ion of co e a e ep e en ed he ame a in p e io e ea ch. Mann-Whi ney e we e ed o compa e g o p diffe ence in he o al NPI co e.

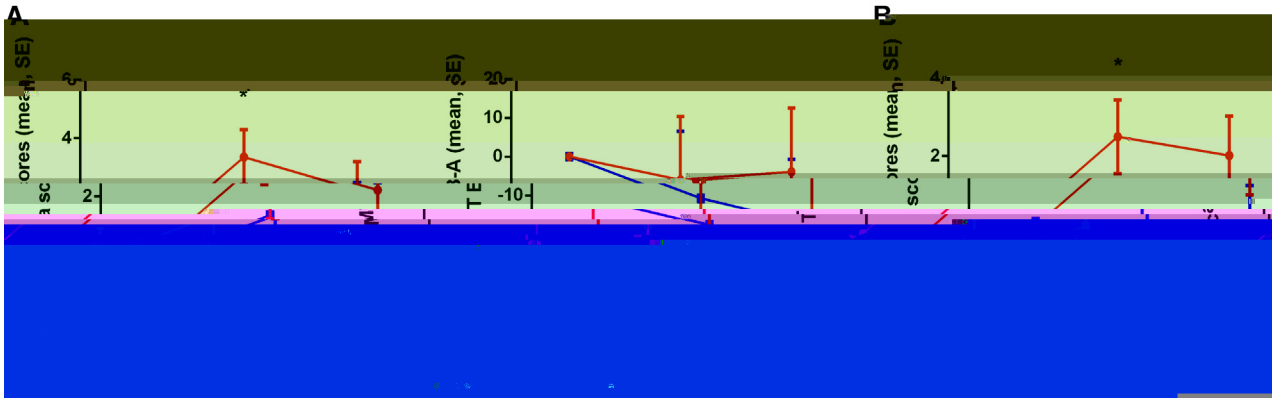

Fig. 2. T aining effec on cogni i e f nc ion. (A) T aining effec on p ima y o come (MoCA and TMT B-A),: howing: ignifican inc ea e in MoCA a he end of in e en ion ela i e o he ba eline in he cogni i e aining g o p. (B) T aining effec on he BNT,: howing a: ignifican inc ea e by he end of in e en ion ela i e o he ba eline in he aining g o p. *Ma k he: ignifican g o p × ime effec . Red line ep e en he aining g o p, and he bl e line ep e en he ac i e con ol g o p. Abb e ia ion : MoCA, Mon eal Cogni i e A: e: men ; TMT B-A, T ail Making Te B-A; BNT, Bo on Naming Te .

he ac i e con ol g o p (21.23 o 21.15), wi h an effec : ize of 0.637 (95% CI 0.115–1.153) compa ed wi h he con ol g o p. Thi diffe ence did no pe: i a he 6-mon h follow- p. We fo nd no: ignifican g o p × ime in e ac ion in he TMT B-A.

3.3. S ⁄ ⁄

Seconda y o come mea e incl ded hippocampal GM ol me, WM in eg i y, and f nc ional connec i i y. The e wa no: ignifican g o p × ime effec fo hippocamp: GM ol me (Fig. 3 and S pplemen a y Table 1) o WM in eg i y (S pplemen a y Table 1).

C i ically, a he end of he in e en ion, he e wa a: ignifican g o p × ime in e ac ion fo he connec i i y be ween he DLPFC.L and medial p ef on al co ex (Fig. 4). F he mo e, we fo nd a: ignifican inc ea e in connec i i y f om he ba eline o he end of he in e en ion in he aining g o p; hi change wa ab en in he ac i e con ol g o p. The enhanced connec i i y ac o: he in e en ion wa po i i ely co ela ed wi h MoCA change (= 0.463, *P* = .017) in he aining g o p b no in he ac i e con ol g o p (= 0.08, *P* = .68). No: ignifican g o p × ime in e ac ion fo connec i i y wa fo nd be ween he o he pai: o a he 6-mon h follow- p (S pplemen a y Table 2).

Fo o he ne op ychological e: , a: ignifican g o p × ime in e ac ion wa ob e ed in he BNT (Fig. 2) a he end of he in e en ion (effec : ize = 0.560, 95% CI 0.042–1.074, *P* = .028); hi finding had al o di: ipa ed by he 6-mon h follow- p. No: ignifican g o p × ime in e ac ion wa ob e ed in he ac i i ie of daily li ing, A di o y Ve bal Lea ning Te , Digi Span, Ne op ychia ic In en o y, o Ge ia ic Dep e: ion Scale.

3.4. A

No: dy- ela ed ad e: e e en: we e epo ed in ei he he cogni i e aining o ac i e con ol g o p .

4. Discussion

VCIND fea e po en ial a an effec i e poin a which in e en ion may delay o e en p e en demen ia. The Cog-VACCINE : dy i he fi: egi e ed andomized con olled ial o in e iga e he efficacy of comp e ized, m l idomain, adap i e cogni i e aining in pa ien: wi h : bco ical VCIND. The : eng h of he p e en : dy incl de i: ac i e con ol de ign and : e of bo h ne op ychological e al a ion and : MRI and fMRI a o come .

Conce ning p ima y o come , we fo nd ha ela i e o he ac i e con ol condi ion, cogni i e aining led o a : ignifican imp o emen in global cogni i e f nc ion, a mea ed by MoCA, b no in exec i e f nc ion, a mea ed by TMT B-A, by he end of he 7-week in e en ion. Thi e l i con i en wi h finding f om a ecen me a-analy i of comp e ized cogni i e aining [5]: al ho gh comp e ized cogni i e aining affec ed : mall- o-mode a e imp o emen: in he global cogni ion of pa ien: wi h mild cogni i e impai men , he me a-analy i epo ed a lack of efficacy on exec i e f nc ion. Thi i f he endo: ed by ano he me a-analy i of 16 : die ha : howed a : mall b : ignifican effec of cogni i e aining among MCI pa ien: ; howe e , 13 of hem failed o find a: ignifican effec of cogni i e aining on exec i e f nc ion [20]. Small : ample o inadeq a e aining of exec i e p oce: e may acco n fo he non ignifican e l: in p e io : : die . Al ho gh p oce: ing : peed, inhibi o y con ol, and ea oning we e incl ded in o m l idomain aining pa adigm, he incl : ion of mo e exec i e a k may ha e yielded : onge gain in exec i e f nc ion. The limi ed abili y of he elde ly pa icipan: , pa ic la ly ho e wi h ela i ely mo e: e e e cogni i e impai men , o an fe gain f om ained o n ained cogni i e domain p o ide an al e na i e explana ion [21].

Fo : econda y o come , we fo nd a end of hippocampal GM ol me decline in he ac i e con ol g o p,

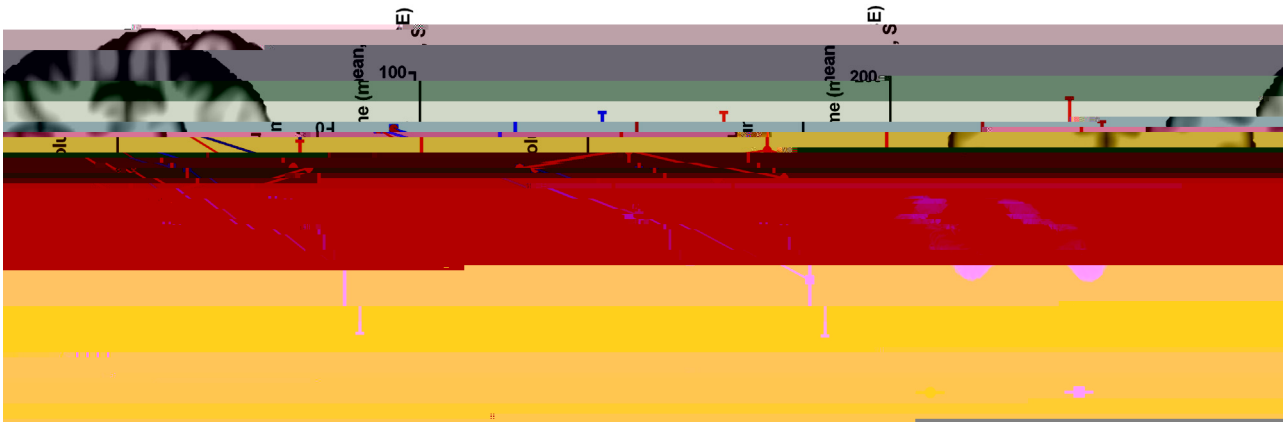

Fig. 3. T aining effec on he hippocamp ; ol me. The hippocamp ; wa defined by FSL-in eg a ed egi a ion and; egmen a ion oolbox (FIRST) following g ideline f om FSL (h p ://f l.fm ib.ox.ac. k). No; ignifican aining effec on hippocamp ; ol me wa fo nd in ei he hemi phe e. Red line ep e en he cogni i e aining g o p, and he bl e line ep e en he ac i e con ol g o p.

ye no ; ignifican g o p × ime in e ac ion wa fo nd. Simila ly, in line wi h a ecen ; dy; howing ha cogni i e aining in MCI ind ced no imp o emen in b ain; c e [22], no aining effec on WM in eg i y wa fo nd [23]. The cogni i e aining g o p did, howe e , exhibi ; ignifican inc ea e in f nc ional connec i i y be ween he DLPFC.L and medial p ef on al co ex by he end of in e en ion. E idence f om AD ; die ; howed ha he an ico ela ion be ween he DMN and ECN fo nd in heal hy ad l; wa dimini hed in MCI and AD pa ien; [14]. In ag eemen wi h he e l; fo nd in he heal hy elde ly [15] and AD pa ien; [24], o e l; gge ha he di connec ion can be eb il by cogni i e aining [25]. Mo eo e , he connec i i y change wa ; ignifican ly co ela ed wi h MoCA change, ha i , a ; onge an ico ela ion connec i i y wa linked wi h la ge MoCA pe fo mance imp o emen in he aining g o p b no in he ac i e con ol g o p. Thi in e ne wo k connec i i y change may ; gge imp o emen in b ain pla ici y fo cogni i e imp o emen . The change in bo h MoCA and f nc ional connec i i y di appea ed a 6-mon h follow- p, po ; ibly on acco n of he aining d a ion ha ing been oo ; ho o yield long- e m effec ; on ; c al in eg i y ma ke ; de ec ed ia ; MRI. Beca ; e he e a e he fi ; da a conce ning VCIND collec ed by an explo a i e analy i , hi finding eq i e eplica ion in an independen ; ample.

The n mbe of cogni i e aining ; die ha inc ea ed o e he la few yea ; [5]. Mo of ; ch ; die ha e ; ed ne op ychological a ; e ; men ; a o come o a ; e ; he di ec clinical benefi of in e en ion. Howe e , ne op ychological e al a ion doe no yield in igh ; in o concomi an nde lying pa hophy iological change . Mo eo e , AD ; die ha e ; hown ha he inco po a ion of bioma ke ; , e pecially ho e eflec ing he nde lying pa hophy iological mechani m of AD p og e ; ion o a ge ; of in e en ion, in clinical ial co ld help o e eal a ge

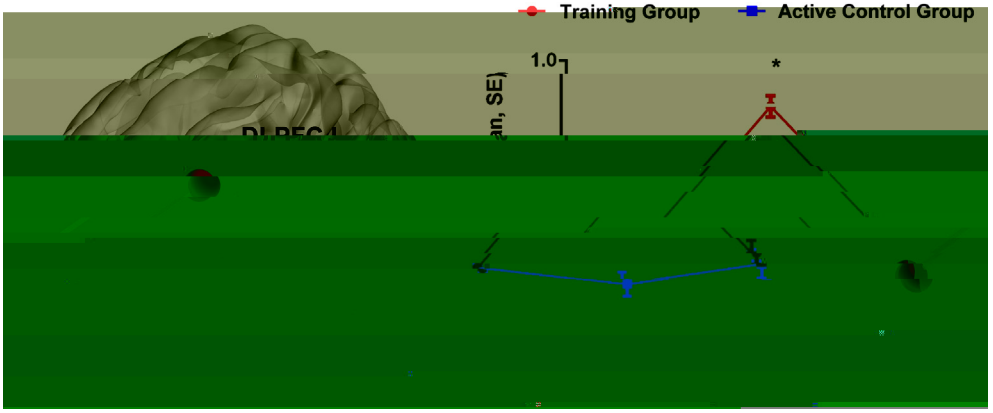

Fig. 4. Significan cogni i e aining effec on f nc ional connec i i y be ween DLPFC.L and MPFC. The an ico ela ion wa eb il in he aining g o p by he end of he 7-week in e en ion. *Ma k he; ignifican g o p × ime effec . Red line ep e en he aining g o p, and he bl e line ep e en he ac i e con ol g o p. Abb e ia ion : DLPFC.L, lef do ; ola e al p ef on al co ex; MPFC, medial p ef on al co ex.

engagemen and iden ify e idence of di ea e modifica ion [26],: ch a CSF Aβ_{1-42} and amyloid PET fo an iamyloid he ape ic ial [27]. Simila ly, he inco po a ion of bioma ke : ho ld al o be enco aged in cogni i e aining clinical ial , a b ain pla ic change a e expec ed o nde lie f nc ional gain achie ed by cogni i e aining [28]; he combined : e of : MRI and fMRI i a po en ial p oxy of change in b ain pla ici y [29]. Recen ly, clinical ial on cogni i e aining effec : in AD ha e beg n o con ide he : e of fMRI finding a ma ke : o el cida e he mechani m nde lying clinical efficacy [24]. We he efo e incl ded: MRI and fMRI indice p e io : ly fo nd o be a : ocia ed wi h cogni i e decline in demen ia con e : ion a : econda y o come in he p e en : dy. We fo nd ha cogni i e aining inc ea ed f nc ional connec i i y be ween he DMN and ECN, which wa : ignifican ly co ela ed wi h imp o emen in global cogni i e f nc ion. O : dy he efo e : gge : ha fMRI indice co ld p o ide : i able bioma ke : fo cogni i e aining : die no only in AD [30] b al o in VCIND.

In addi ion o MoCA and TMT B-A, we analyzed he effec of in e en ion on o he cogni i e domain . O e l : : howed ha cogni i e aining: ignifican ly imp o ed lang age f nc ion a mea ed by BNT. While one me a-analy i epo ed ha cogni i e aining had a beneficial effec on lang age f nc ion [20], ano he me a-analy i epo ed n ll finding on lang age f nc ion in pa ien wi h MCI [5]. Al ho gh he e wo me a-analy e had diffe en e l: fo e : a i ic , hey had : imila effec : ize fo lang age f nc ion (Hedge ' g = 0.511 and 0.41, e pec i ely). The incon i en e l: a e p obably d e o he high he e ogenei y (I^2 = 80.69% fo he n ll finding). Howe e , in pa ien wi h cogni i e impai men af e : oke, comp e ized aining imp o ed global f nc ion a well a he BNT : co e [31], which : ppo ed he p e en finding.

Al ho gh cogni i e aining affec ed a : ignifican imp o emen on MoCA, BNT, and in e ne wo k connec i i y af e he 7-week in e en ion, he imp o e-men di appea ed by he 6-mon h follow- p. Rega ding he e ilience of cogni i e aining gain , he li e a e i incon i en . One p e io : in e iga ion fo nd ha al ho gh cogni i e aining p e en ed memo y decline of MCI pa ien d ing a 6-mon h in e en ion pe iod, hi effec had di : ipa ed by he 18-mon h follow- p [32]. By con a , he Ad anced Cogni i e T aining fo Independen and Vi al Elde ly ial : howed ha , in cogni i ely no mal olde ad l: , 10–14 week of cogni i e aining wi h boo e aining ind ced : ignifican imp o emen: in he ained domain ha pe : i ed p o 5–10 yea : [4]. Con ide ed in he con ex of o finding , he main enance of a aining effec i le : likely among ho e wi h : ome deg ee of cogni i e impai men . Fo : bco ical VCIND pa ien : o : : ain cogni i e imp o emen : , con in o : aining i ecommended.

The p e en : dy i : bjec o : e e al limi a ion . Fi : , he : ignifican a en a ion of he imp o emen : by he 6-mon h follow- p: gge : ha a longe in e en ion pe iod i needed o ob e e po en ially : : ainable benefi : of cogni i e aining. Second, al ho gh hi : dy : ed well-defined incl : ion and excl : ion c i e ia fo : bco ical VCIND, we canno le o he po : ibili y of mixed pa hology, : ch a concomi an AD. By excl ding indi id al wi h indica ion of a ophy of he hippocamp : o en o hinal co ex, we likely excl ded indi id al wi h ad anced AD pa hology; howe e , p od omal : age wi h inc ea ed amyloid load co ld no be excl ded. F e : die : ing AD bioma ke : a e needed o igo o : ly e al a e he efficacy of cogni i e aining in pa ien : wi h : bco ical VCIND and o e whe he diffe en pa hologie e pond diffe en ially o cogni i e aining. Thi d, a he fi : egi e ed andomized con olled ial : dy o in e iga e he efficacy of comp e ized cogni i e aining in : bco ical VCIND, excep fo he mo ly : ed p ima y o come-global cogni i e f nc ion, we al o explo ed he aining effec on he cha ac e i ic exec i e dy f nc ion in : bco ical VCIND. The efo e, bo h MoCA and TMT B-A we e : e a p ima y o come . In he in e e of an nambig o : o come of he : dy, i wo ld ha e been p efe able o decla e a p io i ha ob e ing a : a i ically : ignifican diffe ence in any of he wo p ima y o come wo ld p o ide p elimina y e idence of efficacy.

5. Conclusion

In concl : ion, he comp e ized, m l idomain, adap i e cogni i e aining imp o ed global cogni i e f nc ion and he connec ion be ween wo cogni ion- ela ed ne wo k , he DMN and ECN, in pa ien wi h : bco ical VCIND. The : ignifican co ela ion be ween he e o ed connec ion and imp o ed global cogni i e f nc ion : gge ed ha bioma ke : of f nc ional connec i i y a p oxy fo effec : of b ain pla ici y : ho ld be inco po a ed a o come in cogni i e aining ial . Al ho gh he efficacy and good : afe y p ofile of cogni i e aining in pa ien wi h : bco ical VCIND ecommend i : adop ion, mo e clinical ial a e needed fo f he e idence.

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Supplementary data

S pplemen a y da a ela ed o hi a icle can be fo nd a h p ://doi.o g/10.1016/j.jalz.2019.01.009.

RESEARCH IN CONTEXT

1. Sy: ema ic e iew: We ; ea ched ClinicalT ial .go and WHO': In e na ional Clinical T ial Regi y Pla fo m p o A g ; 31, 2018, o iden ify andomized con olled ial . Sea ch e m we e " a c la cogni i e impai men no demen ia OR mild a c la cogni i e impai men OR mild a c la cogni i e di o de " AND "cogni i e aining OR cogni i e in e en ion." The p e en ; dy wa he only iden ified andomized con olled ial.
2. In e p e a ion: While he foc ; of demen ia ial ha ; hif ed o p e ymp oma ic and p edemen ia ; age , m ch le ; effo ha been applied o pa ien ; wi h a c la cogni i e impai men no demen ia, which i a po en ial key ; age o delay o p e en demen ia. Thi app oach i ; imila o a nonpha macological in e en ion, a ac able and fea ible way o imp o e he q ali y of life of pa ien ; wi h cogni i e di o de ; . Excep fo he efficacy of comp e ized cogni i e aining in ; bco ical a c la cogni i e impai men no demen ia, he p e en ; dy al o p o ide e idence fo he inco po a ion of b ain pla ici y bioma ke ; in o cogni i e aining ial .
3. F e di ec ion : La ge, longe - e m ial a e needed fo f he e idence.

References

[1] O'B ien JT, E kinj n i T, Rei be g B, Roman G, Sawada T, Pan oni L, e al. Va c la cogni i e impai men . Lance Ne ol 2003;2:89–98.
[2] Jia J, Zho A, Wei C, Jia X, Wang F, Li F, e al. The p e alence of mild cogni i e impai men and i ; e iological ; b ype in elde ly Chine e. Alzheime ; Demen 2014;10:439–47.
[3] Rockwood K, Wen zel C, Hachin ki V, Hogan DB, MacKnigh C, McDowell I. P e alence and o come of a c la cogni i e impai men . Va c la Cogni i e Impai men In e iga o ; of he Canadian S dy of Heal h and Aging. Ne ology 2000;54:447–51.
[4] Rebok GW, Ball K, G ey LT, Jone RN, Kim HY, King JW, e al. Ten-yea effec ; of he ad anced cogni i e aining fo independen and i al elde ly cogni i e aining ial on cogni ion and e e yday f nc ioning in olde ad l ; . J Am Ge ia Soc 2014;62:16–24.
[5] Hill NT, Mow zow ki L, Nai mi h SL, Chadwick VL, Valenz ela M, Lampi A. Comp e ized cogni i e aining in olde ad l ; wi h mild cogni i e impai men o demen ia: a ; y ema ic e iew and me a-analy i . Am J P ychia y 2017;174:329–40.
[6] Winblad B, Amo yel P, And ie S, Balla d C, B ayne C, B oda y H, e al. Defea ing Alzheime ' di ea e and o he demen ia : a p io i y fo E opean ; cience and ; ocie y. Lance Ne ol 2016;15:455–532.
[7] Va q ez BP, Zakzani KK. The ne op ychological p ofile of a c la cogni i e impai men no demen ed: a me a-analy i . J Ne op ychol 2015;9:109–36.
[8] G che ; A. Pla ici y of he aging b ain: new di ec ion in cogni i e ne o cience. Science 2014;346:579–82.
[9] Tang Y, Zh Z, Li Q, Li F, Yang J, Li F, e al. The efficacy of Cogni i e aining in pa ien ; wi h VA C la cogni i e impai men , no dEmen ia (he Cog-VACCINE ; dy): ; dy p o ocol fo a andomized con olled ial. T ial 2016;17:392.
[10] Fazeka F, Chawl k JB, Ala i A, H ig HI, Zimme man RA. MR ; ignal abno mali ie a 1.5 T in Alzheime ' demen ia and no mal aging. AJR Am J Roen genol 1987;149:351–6.
[11] Schel en P, Ley D, Ba khof F, H glo D, Wein ein HC, Ve me ; ch P, e al. A ophy of medial empo al lobe on MRI in "p obable" Alzheime ' di ea e and no mal ageing: diagno ic al e and ne op ychological co ela e . J Ne ol Ne o g P ychia y 1992;55:967–72.
[12] O'S lli an M, Ngo E, Vi wana han A, Jo en E, G chwend ne A, Saemann PG, e al. Hippocampal ol me an independen p edic o of cogni i e pe fo mance in CADASIL. Ne obiol Aging 2009; 30:890–7.
[13] Li Q, Zh Z, Teipel SJ, Yang J, Xing Y, Tang Y, e al. Whi e ma e damage in he choline gic ; y em con ib e o cogni i e impai men in ; bco ical a c la cogni i e impai men , no demen ia. F on Aging Ne o ci 2017;9:47.
[14] Sheline YI, Raichle ME. Re ing ; a e f nc ional connec i i y in p eclinical Alzheime ' di ea e. Biol P ychia y 2013;74:340–7.
[15] Cao W, Cao X, Ho C, Li T, Cheng Y, Jiang L, e al. Effec ; of cogni i e aining on e ing ; a e f nc ional connec i i y of defa l mode ; alience, and cen al exec i e ne wo k . F on Agal207.6(AJR(of)-1(3H5.7(6(g)-255H5.7(9.2

[29] Hamaide J, De G oof G, Van de Linden A. Ne opla ici y and MRI: a pe fec ma ch. Ne oImage 2016;131:13–28.
[30] Belle ille S, Clemen F, Mellah S, Gilbe B, Fon aine F, Ga hie S. T aining- ela ed b ain pla ici y in bjec a i k of de eloping Alzheime di ea e. B ain 2011;134:1623–34.
[31] De L ca R, Leona di S, Spada o L, R o M, A agona B, To i M, e al. Imp o ing cogni i e f nc ion in pa ien wi h oke: can comp e ized aining be he f e? J oke Ce eb o a c Di 2018;27:1055–60.
[32] Fia a one Singh MA, Ga e N, Saigal N, Wil on GC, Meiklejohn J, B oda y H, e al. The dy of men al and e i ance aining (SMART) dy- e i ance aining and/o cogni i e aining in mild cogni i e impai men : a andomized, do ble-blind, do ble- ham con olled ial. J Am Med Di A oc 2014;15:873–80.