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PERFILS COGNITIUS EN LA DEPRESSIÓ I DESENVOLUPAMENT D'UNA ESTRATÈGIA D'INTERVENCIÓ NEUROCOGNITIVA

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PERFILS COGNITIUS EN LA DEPRESSIÓ I DESENVOLUPAMENT D'UNA ESTRATÈGIA D'INTERVENCIÓ NEUROCOGNITIVA

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A tu, que sempre estàs amb mi

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Psicòloga

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ÍNDEX

Pròleg

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and subjective cognition in major depressive disorder. *European* Neuropsychopharmacology, 29, 46–56. https://doi.org/10.1016/j.euroneuro.2018.11.1104

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Draganov, M., Vives-Gilabert, Y., de Diego-Adeliño, J., Vicent-Gil, M., Puigdemont, D., & Portella, M. J. (2020). Glutamatergic and GABA-ergic abnormalities in first-episode depression. A 1-year follow-up 1H-MR spectroscopic study. *Journal of Affective Disorders*, *266*, 572–577. https://doi.org/10.1016/j.jad.2020.01.138

López-Solà, C., Subirà, M., Serra-Blasco, M., Vicent-Gil, M., Navarra-Ventura, G., Aguilar, E., Acebillo, S., Palao, D. J., & Cardoner, N. (2020). Is cognitive dysfunction involved in difficult-to-treat depression? Characterizing resistance from a cognitive perspective. *European Psychiatry, 63*(1), 1–8. https://doi.org/10.1192/j.eurpsy.2020.65

De la Serna, E., Montejo, L., Solé, B., Castro-Fornieles, J., Camprodon-Boadas, P., Sugranyes, G., Rosa-Justicia, M., Martinez-Aran, A., Vieta, E., Vicent-Gil, M., Serra-Blasco, M., Cardoner, N., & Torrent, C. (2021). Effectiveness of enhancing cognitive reserve in children, adolescents and young adults at genetic risk for psychosis: Study protocol for a randomized controlled trial. *Revista de Psiquiatría y Salud Mental*. https://doi:10.1016/j.rpsm.2021.02.003

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Glossari

BDI: Beck Depression Inventory

DSM: Diagnostic and Statistical Manual of Mental Disorders

ECC: Entrenament Cognitiu Computeritzat

ECP: Estimulació Cerebral Profunda

FAST: Functioning Assessment Short Test

HDRS: Hamilton Depression Rating Scale

ICD: International Classification of Diseases

INCREM: INtegral Cognitive REMediation

MADRS: Montgomery-Asberg Depression Rating Scale

MSM: Maudsley Staging Method

RC: Remediació Cognitiva

RF: Rehabilitació Funcional

SCIP: Screening for Cognitive Impairment in Psychiatry

TEC: Teràpia Electroconvulsiva

EMT: Estimulació Magnètica Transcranial

1. Introducció

1.1. Breu aproximació

La disminució en la capacitat per a pensar o concentrar-se, i les dificultats per a prendre decisions són dues de les característiques necessàries per a complir els criteris diagnòstics d'un episodi de depressió major inclosos en els manuals diagnòstics anomenats Diagnostic and Statistical Manual of Mental Disorders (DSM) i International Classification of Diseases (ICD). Existeix suficient evidència científica que demostra la presència de dificultats d'atenció, de memòria, de velocitat de processament i de funcionament executiu en fases actives de la malaltia, inclús en períodes de major estabilitat clínica (Rock et al., 2014). Però, tot i contemplar-se com un criteri diagnòstic i existir un coneixement científic que hi dóna suport, la disfunció cognitiva no està contemplada com un dels objectius principals dels tractaments antidepressius més comuns. És més, les dificultats cognitives no s'acostumen a avaluar ni tractar de forma rutinària en la majoria d'entorns clínics, tot i saber-se que aquest dèficit es relaciona amb un detriment a nivell psicosocial i laboral (Evans et al., 2014), amb una pitjor qualitat de vida (Bo et al., 2019), amb una major probabilitat de noves recaigudes (Hammar & Ardal, 2009; Lee et al., 2012) i amb baixes taxes de recuperació (IsHak et al., 2016).

Tot i estar ben acceptat que existeix una disfunció cognitiva en la depressió, no hi ha un acord entre l'especificitat dels dominis cognitius implicats i el grau d'afectació d'aquests dèficits. Els estudis han reportat mides de l'efecte que van de petites a moderades del dèficit cognitiu, la qual cosa ha comportat deixar en segon lloc el tractament de la cognició i haver donat prioritat als símptomes depressius en la cerca de tractaments antidepressius. A més, la majoria d'aquests estudis basen els seus resultats en les diferències envers un altre grup, és a dir, comparant el rendiment cognitiu de forma grupal sense tenir en compte que no tots els pacients han de presentar dèficits cognitius. Factors com la barreja de pacients inclosos en les mostres dels estudis, diferents etapes de la malaltia, la trajectòria de cadascun dels pacients o els efectes de la medicació podrien explicar les inconsistències observades entre els diferents estudis.

Quant a les intervencions portades a terme en la depressió, ni la farmacoteràpia ni la psicoteràpia han estat efectives per a resoldre les dificultats cognitives i funcionals en la majoria dels pacients. És a dir, tot i la disminució de la simptomatologia clínica, les dificultats psicosocials i la falta de percepció de recuperació completa per part dels pacients continuen presents. En els darrers anys, s'han portat a terme intervencions de remediació cognitiva en altres trastorns neuropsiquiàtrics mostrant millores significatives en el rendiment cognitiu dels pacients. Ara bé, en depressió són pocs els estudis al respecte; la diferència en els dissenys i les mostres utilitzades han fet difícil obtenir resultats concloents. Però, i si l'heterogeneïtat cognitiva, és a dir, la presència de pacients amb afectació cognitiva i sense, és una de les causes de l'escassetat d'evidència d'eficàcia en aquests estudis? És possible estudiar aquesta heterogeneïtat? Existeix alguna intervenció que permeti als pacients retornar a nivells previs de funcionament i recuperar una bona qualitat de vida?

1.2. Disfunció cognitiva en la depressió

1.2.1. Introducció al concepte de disfunció cognitiva en la depressió

La depressió és un dels trastorns psiquiàtrics més comuns arreu del món, sent així la tercera causa de discapacitat mundial (Malhi & Mann, 2018). Es creu que aproximadament una de cada set persones patirà un episodi depressiu al llarg de la seva vida (Kessler et al., 2012). Aquesta malaltia està associada a altes taxes de recurrència i falta de recuperació entre episodis depressius, fet que comporta gran impacte en el consum de recursos sanitaris i greus dificultats en el funcionament psicosocial, específicament a nivell de productivitat laboral. Tot i existir prou evidència científica sobre la neurobiologia de la depressió, aquesta continua sent diagnosticada a través del compliment de diferents criteris diagnòstics recollits en els manuals de classificació dels trastorns mentals DSM i ICD, amb les seves respectives versions actualitzades. D'una banda, l'estat d'ànim deprimit i la incapacitat per a sentir plaer són els principals símptomes per al diagnòstic d'un episodi depressiu major. De l'altra, el dèficit cognitiu conjuntament amb la pèrdua o guany de pes, l'augment o disminució de la gana, el retràs psicomotor o l'agitació, el sentiment d'inutilitat o de culpa inapropiada, formen part dels símptomes que poden estar presents o no en un episodi depressiu. Específicament, la disfunció cognitiva es descriu com una disminució en la capacitat per a pensar o concentrar-se, o per a prendre decisions (DSM-5; American Psychiatric Association, 2013). No obstant, les dificultats cognitives van més enllà de les descrites en els criteris diagnòstics més usats. Moltes vegades els dèficits cognitius no són valorats en els entorns clínics a causa de la manca de queixa per part dels pacients, al poc valor diagnòstic que se li atribueix a les queixes cognitives subjectives dels pacients o degut a la falta de marcadors objectius de cognició que siguin de fàcil implementació en la pràctica clínica. A més a més, aquestes dificultats cognitives no es contemplen de forma extensa en les escales de depressió estàndards tipus *Hamilton Depression Rating Scale* (HDRS; Hamilton, 1960), *Montgomery-Asberg Depression Rating Scale* (MADRS; Montgomery & Asberg, 1979) o *Beck Depression Inventory* (BDI; Beck et al., 1961) usualment utilitzades per a valorar la simptomatologia d'un episodi depressiu. Aquestes presenten un única pregunta sobre el funcionament cognitiu, sempre relacionada amb el grau de dificultat en la concentració i en l'alentiment en el pensament i llenguatge, sense tenir en compte altres dificultats com són les mnèsiques, les atencionals o les executives.

Les alteracions cognitives en la depressió es caracteritzen per dèficits en els dominis d'atenció, memòria, velocitat de processament i funcions executives (**Taula 1**). Aquests dominis cognitius afectats no s'observen únicament en pacients deprimits, sinó també en altres trastorns psiquiàtrics com en l'esquizofrènia i en el trastorn bipolar, però en aquests casos el grau d'afectació sembla ser més greu.

Taula 1. Dominis cognitius en la depressió

Domini cognitiu	Descripció
ATENCIÓ	Capacitat de concentració, habilitat de focalitzar i mantenir l'atenció en el temps
MEMÒRIA DE TREBALL	Manteniment temporal i manipulació de la informació
MEMÒRIA VERBAL	Inclou aprenentatge, codificació, retenció i recuperació d'informació verbal
MEMÒRIA VISUAL	Capacitat de mantenir i recuperar informació visual
VELOCITAT DE PROCESSAMENT	Habilitat de percebre i respondre ràpidament a un estímul
FUNCIONS EXECUTIVES	Habilitat d'organització, planificació i resolució de problemes. Flexibilitat cognitiva. Presa de decisions. Habilitat d'inhibició de respostes.

Nota. Adaptat de "Cognitive Dysfunction in Major Depressive Disorder: Assessment, Impact and Management", per T. Chakrabarty, 2016, Focus, 14, 194-206 (Chakrabarty et al., 2016).

La magnitud de l'efecte entre els estudis de cognició en depressió és molt variable (amb mides de l'efecte de 0.3 a 0.5 en la Cohen's *d*), fet que fa considerar la possible influència de certs factors en el rendiment cognitiu que podrien donar lloc a aquesta heterogeneïtat. Per una banda, característiques clíniques com la gravetat, el número d'episodis depressius, la resposta al tractament antidepressiu, símptomes psicòtics o melancòlics o el fet de patir una depressió resistent s'han relacionat amb dèficits cognitius més greus (López-Solà et al., 2020; Murrough et al., 2015; Pimontel et al., 2016; Schatzberg et al., 2000; Semkovska et al., 2019; Serra-Blasco et al., 2015; Withall et al., 2010). Altres variables sociodemogràfiques com l'edat, la capacitat intel·lectual o els anys d'escolaritat també han estat vinculats a una major o menor afectació cognitiva. Per l'altra banda, la mescla de pacients inclosos en els estudis també podria explicar les dificultats per a detectar diferències en el rendiment cognitiu dels pacients en comparació als controls sans. Tenint en compte la possible influència dels anteriors factors esmentats, la recerca actual es centra en la investigació del funcionament cognitiu utilitzant mostres amb característiques més homogènies quant a càrrega de malaltia (ex. fase aguda vs. fase de remissió clínica, controlant els efectes de la medicació, rangs d'edat, etc.) (**Figura 1**).

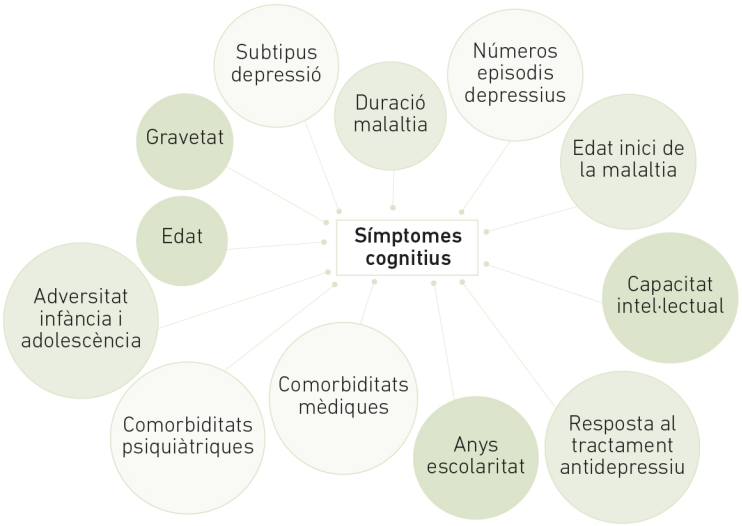

Figura 1. Possibles factors que poden influir en els símptomes cognitius en la depressió.
Nota. Adaptat de "Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder", per H. Zuckerman, 2018, Frontiers in Psychiatry, 9: 655 (Zuckerman et al., 2018)

La majoria de la recerca en l'última dècada sobre les dificultats cognitives en la depressió s'ha centrat en investigar si la disfunció cognitiva és independent o és conseqüència de la manifestació clínica de la depressió (Hammar & Ardal, 2009). Alguns estudis reporten millores en el rendiment cognitiu en fase de remissió clínica (Biringer et al., 2007), mentre d'altres assenyalen una persistència del deteriorament cognitiu en fases de major estabilitat clínica (Bora et al., 2013; Hasselbalch et al., 2011). Una possible explicació a aquesta divergència de resultats entre estudis, és que un percentatge de pacients no presentin cap afectació cognitiva al llarg de la malaltia, i que altres presentin una disfunció cognitiva marcada inclús en fases de major estabilitat clínica. Però, tot i l'augment considerable d'estudis científics al voltant del concepte de la disfunció cognitiva en depressió, fins el moment no hi ha hagut un trasllat suficient de tot el coneixement a la pràctica clínica, ja sigui en la detecció o en el tractament d'aquest tipus de simptomatologia.

1.2.2. En un primer episodi depressiu

Els dèficits cognitius no han estat mai un dels objectius principals en el tractament de la depressió, i menys en les fases inicials de la malaltia (Fiorillo et al., 2018). Segurament els pocs estudis en pacients amb un primer episodi depressiu en les últimes dues dècades no han ajudat a millorar el maneig a nivell clínic d'aquest simptomatologia. Si més no, existeixen suficients estudis els quals confirmen la presència de dificultats cognitives significatives ja en un primer episodi depressiu (Lee et al., 2012; Vicent-Gil & Portella, 2021)

L'any 2010, Kaymak i col·laboradors van estudiar el rendiment cognitiu en una mostra de 20 dones amb un primer episodi depressiu sense tractament farmacològic en comparació a una mostra control de

dones sanes. Es van observar dificultats significatives en atenció, memòria de treball, memòria verbal i visual, velocitat psicomotora i funcions executives conjuntament amb un menor volum del hipocamp (Kaymak et al., 2010). Schmid i Hammar, en una mostra de 30 pacients amb un primer episodi en relació a una mostra control, van detectar dificultats en inhibició i fluïdesa verbal semàntica ja en l'inici de la malaltia. No es van observar dificultats en flexibilitat cognitiva, fluència fonètica, planificació i resolució de problemes. Un any més tard, aquests pacients tot i trobar-se la majoria en remissió clínica, continuaven mostrant les mateixes dificultats cognitives (Schmid & Hammar, 2013b). A més, van observar com aquells pacients que havien patit una nova recaiguda durant l'any de seguiment mostraven una disfunció en la capacitat d'inhibició més greu a nivell basal (Schmid & Hammar, 2013a). Posteriorment, l'any 2014, Trivedi and Greer van portar a terme una revisió sistemàtica dels estudis previs en cognició i depressió, i van descriure la presència de dèficits cognitius en memòria i presa de decisions ja en l'inici de la malaltia conjuntament amb anormalitats estructurals del hipocamp i de l'escorça prefrontal (Trivedi & Greer, 2014). Continuant en aquesta línia d'investigació sobre la neurobiologia de la depressió, Hansson i coautors, van estudiar la relació entre el funcionament cognitiu i els nivells de cortisol abans i després de la prova de supressió de dexametasona en una mostra de 21 pacients amb un primer episodi depressiu. Els resultats no van mostrar associacions significatives entre la memòria verbal i el rendiment executiu amb els nivells de cortisol, tot i mostrar alteracions en el funcionament de l'eix hipotalàmic-pituïtari-adrenal (Hansson et al., 2015). Anys més tard, Chen i col·laboradors, van comparar el rendiment cognitiu de pacients amb un primer episodi depressiu sense tractament farmacològic amb una mostra de pacients depressius amb medicació i una altra de controls sans. Els pacients amb un primer episodi sense medicació mostraven dificultats en memòria verbal i visual i en memòria de treball, remarcant la importància de detectar els símptomes cognitius ja des del primer episodi depressiu (Chen et al., 2018).

La progressió de les dificultats cognitives des d'un primer episodi depressiu ha estat investigada mitjançant dissenys on es comparaven mostres de pacients amb un primer episodi i pacients amb diversos episodis (recurrents). En l'estudi de Roca i coautors es va comparar el rendiment cognitiu abans i després de sis mesos de tractament farmacològic entre 26 pacients amb un primer episodi depressiu i 53 pacients recurrents. A nivell basal no es van observar diferències en el rendiment cognitiu entre els dos grups. Passats els sis mesos, quan els pacients es trobaven en remissió clínica, es van detectar millores en velocitat de processament, en flexibilitat cognitiva, fluència semàntica i en el temps de resolució de problemes, independentment de l'etapa de la malaltia en què es trobessin (Roca et al., 2015a). Serra-Blasco i col·laboradors també van comparar una mostra de pacients crònics seleccionats per a ser intervinguts amb estimulació cerebral profunda amb una mostra de primers episodis depressius. Després d'un any de tractament, es va observar una millora en la memòria verbal en els dos subgrups (Serra-Blasco et al., 2015). Recentment, Lin i coautors han comparat una mostra de 433 pacients amb un primer episodi depressiu amb 206 pacients depressius recurrents, tots en fase aguda, i

s'ha observat com tot i mostrar dificultats cognitives ambdós grups, els pacients recurrents mostren dèficits més accentuats en memòria verbal i visual (Lin et al., 2021).

Fins a l'actualitat, són pocs els estudis que han seguit en aquesta línia de recerca enfocada al seguiment dels símptomes cognitius en pacients amb un primer episodi depressiu (Roca et al., 2015a; Schmid & Hammar, 2013a; Serra-Blasco et al., 2015). L'any 2012, Maeshima i col·laboradors van portar a terme un estudi comparant el rendiment en memòria verbal i visual entre 30 pacients amb un primer episodi depressiu, 38 pacients recurrents i 57 controls sans, durant el període de remissió clínica. En el moment inicial de remissió, les puntuacions en les proves de memòria eren similars entre els grups de pacients, i inferiors al grup control. En el seguiment, la disfunció cognitiva en memòria en el grup de primers episodis va desaparèixer (Maeshima et al., 2012). Anys més tard, l'equip de Gu van seguir una mostra de 100 pacients amb un primer episodi depressiu durant dos anys i van observar dos perfils cognitius on el rendiment en atenció, velocitat de processament i les funcions executives diferenciava el grup de pacients preservat del grup afectat (Gu et al., 2016). Més recentment, Ronold i coautors va portar a terme el primer estudi de seguiment publicat a cinc anys de pacients amb un primer episodi depressiu i van observar un manteniment dels dèficits cognitius en velocitat de processament i funcions executives, sense senyals d'empitjorament al llarg dels anys (Ronold et al., 2020).

La diversitat de resultats en els estudis sobre disfunció cognitiva en primers episodis depressius ha estat analitzada en dues metaanàlisis (Ahern & Semkovska, 2017; Lee et al., 2012), per tal d'aclarir quin és el patró real de disfunció cognitiva en la fase inicial de la malaltia. En la primera (13 estudis amb 644 pacients), es van identificar dèficits cognitius significatius de lleus a moderats en velocitat de processament, memòria visual i funció executiva com fluïdesa verbal, flexibilitat cognitiva i canvi en l'atenció. En la segona (31 estudis amb 944 pacients), es van observar dificultats (lleus a greus) en el rendiment cognitiu en la majoria dels dominis cognitius durant un primer episodi depressiu, concretament en atenció, memòria de treball, memòria visual i verbal, velocitat de processament, capacitat d'inhibició, raonament i abstracció, flexibilitat cognitiva i fluència verbal. L'heterogeneïtat en les variables neuropsicològiques incloses en els estudis i les diferències entre els pacients inclosos en les mostres podrien ser dues possibles explicacions de l'ampli ventall de dificultats cognitives observades. Aquests autors van concloure que donada la varietat de resultats observats es feia difícil interpretar i determinar quina és la disfunció cognitiva específica a l'inici de la malaltia.

Tanmateix, existeixen diferents factors sociodemogràfics i clínics que podrien estar afectant a aquest rendiment neuropsicològic dels pacients. D'una banda, variables com l'edat o el nivell educatiu sembla que influeixen en l'abast del deteriorament cognitiu. De fet, els pacients de major edat presentaven un pitjor rendiment en les proves que avaluen velocitat psicomotora, memòria visual i funcionament executiu, mentre que els pacients amb menys educació mostraven pitjors resultats en memòria verbal i visual, i en canvi de focus atencional. Quant a variables clíniques, es va observar com algunes

característiques com ara la gravetat de la simptomatologia depressiva o períodes d'hospitalització influïen en el rendiment de velocitat psicomotora, memòria de treball i, memòria verbal i visual. La medicació antidepressiva també es va relacionar amb una pitjor memòria verbal, però a la vegada amb una major flexibilitat cognitiva (Lee et al., 2012). Tot i així, és necessari que s'investigui més sobre l'associació entre medicació i cognició en primers episodis depressius ja que la majoria dels estudis estan realitzats amb mostres de pacients amb tractament antidepressiu, sent pocs els estudis de pacients sense intervenció farmacològica (Ahern & Semkovska, 2016)

Així doncs, la veritable magnitud de la disfunció cognitiva en un primer episodi depressiu és una qüestió no resolta fins el moment. La majoria dels estudis actuals calculen quina és la disfunció cognitiva d'un primer episodi depressiu a través d'una mitjana aritmètica del rendiment neuropsicològic de tots els pacients en conjunt. Realitzant aquest tipus d'anàlisi és probable que els resultats es puguin veure afectats per la presència de valors extrems, donada la gran heterogeneïtat que hi pot existir. És a dir, no tots els pacients manifestaran el mateix grau d'afectació cognitiva o fins i tot, n'hi pot haver que no mostrin disfunció cognitiva tot mantenint un rendiment cognitiu preservat des de l'inici de la malaltia. Així doncs, les anàlisis realitzades fins el moment en els diversos estudis no han estat prou fructíferes per comprendre què és el que està passant a nivell cognitiu en un primer episodi depressiu.

1.2.3. En fase activa de la malaltia

Prèviament a la recerca centrada en els primers episodis depressius, la majoria dels estudis es van focalitzar en determinar si hi havien dificultats cognitives objectives en les fases actives de la malaltia. Actualment, està àmpliament acceptat que la depressió comporta dèficits cognitius en les períodes de major inestabilitat anímica. Aquestes dificultats s'han objectivat en la majoria de dominis cognitius; en atenció, en memòria verbal i visual, en velocitat de processament i en les funcions executives (Hammar & Ardal, 2009; Marazziti et al., 2010; Murrough et al., 2011; Rock et al., 2014; Snyder, 2013; Wagner et al., 2012). Però de nou, no s'ha pogut identificar un patró de disfunció cognitiva que representi a la majoria de pacients amb un episodi depressiu actiu, com tampoc quin és el seu grau d'afectació cognitiva.

Una limitació important a l'hora d'identificar quin és el perfil cognitiu durant la fase activa de la depressió, és el fet que els diferents estudis mesclen pacients amb cursos de la malaltia molt variables. Per exemple, en un estudi del grup de l'autor Reppermund es va comparar el rendiment cognitiu de pacients amb un primer episodi depressiu amb pacients recurrents i es van observar dèficits en velocitat de processament/atenció, memòria i funcions executives. El fet d'analitzar els símptomes cognitius de forma conjunta sense distingir entre pacients fa difícil la interpretació dels resultats (Reppermund et al., 2009). En un altre estudi, Roca i coautors, van examinar si existien diferències en el rendiment cognitiu dels pacients durant un episodi depressiu segons la presència o absència de simptomatologia melancòlica. Els resultats van mostrar que els pacients melancòlics mostraven un rendiment inferior en

atenció, velocitat de processament de la informació, velocitat psicomotora, resolució de problemes i memòria de treball (Roca et al., 2015b). Recentment, en un estudi amb l'objectiu de determinar la discrepància entre cognició objectiva i subjectiva en la depressió (Serra-Blasco et al., 2019) es va comparar el rendiment cognitiu entre tres grups de pacients depressius: durant un episodi actiu, en remissió parcial i en remissió clínica. Es van trobar diferències significatives entre els tres grups, mostrant un major perfil d'afectació en atenció, memòria i executives en el grup de pacients amb un episodi depressiu actiu. La disparitat metodològica entre tots aquests estudis ha dificultat notablement el poder determinar de forma clara quin és el rendiment neuropsicològic dels pacients durant un episodi depressiu actiu.

No només és interessant esbrinar quins dominis cognitius es troben afectats durant un episodi depressiu, sinó també és rellevant identificar factors, sociodemogràfics o clínics, que puguin estar afectant al rendiment cognitiu d'aquests pacients. En un estudi recent, l'any 2019, Schwert i coautors van realitzar un estudi amb 103 pacients amb depressió recurrent durant episodi depressiu actiu i 103 controls sans. Els pacients van mostrar afectació cognitiva de moderada a greu en els dominis cognitius de velocitat de processament, atenció, memòria, memòria de treball i funcions executives. A més, es va observar que característiques clíniques, com la severitat de la depressió, la medicació, l'edat d'inici de la malaltia, la duració de l'episodi actual, la ruminació, i característiques sociodemogràfiques com l'edat, d'intel·ligència premòrbida i el nivell educatiu influenciaven el grau d'afectació cognitiva (Schwert et al., 2019). Així doncs, és important tenir en compte no només el perfil d'afectació cognitiva dels pacients durant un episodi depressiu sinó també totes aquelles variables que podrien estar afectant el grau d'aquesta disfunció.

Un altre concepte important a tenir en compte en aquells pacients que es troben en fase activa de la malaltia, és el nivell de resistència al tractament antidepressiu. En altres paraules, aquest concepte es refereix a aquells pacients que no han tingut una resposta adequada o no hi ha hagut resposta terapèutica després de varis tractaments antidepressius (entenent com a resposta adequada: dosis farmacològiques adequades, duració òptima de tractament i compliment satisfactori del tractament). Malauradament existeixen pocs estudis que determinin el perfil cognitiu de pacients amb resistència al tractament, tot i conèixer que una major persistència de símptomes depressius pot comportar una major presència de símptomes cognitius, donant lloc a majors dificultats per a aconseguir una recuperació completa de l'episodi depressiu. Gupta i coautors, van observar dificultats cognitives moderades en tots els dominis cognitius explorats en una mostra de 33 pacients resistents al tractament. A més, es va observar com els dèficits cognitius estaven directament relacionats amb la competència funcional, és a dir, amb tot allò que els pacients es veien capaços de fer (Gupta et al., 2013). En l'estudi del grup de Serra-Blasco també van descriure el rendiment neuropsicològic de pacients resistents al tractament (n=8) en front a pacients amb un primer episodi depressiu (n=8), observant-se majors dificultats en memòria, funcionament executiu, i velocitat de processament

cognitiu en aquells pacients crònics (Serra-Blasco et al., 2015). Més recentment, es va publicar un nou estudi que intenta identificar factors clínics i cognitius associats a la resistència al tractament, observant-se que els pacients resistents presenten un major dèficit cognitiu en memòria verbal, i que un rendiment inferior en memòria verbal conjuntament amb una major severitat de la simptomatologia depressiva s'associa a un major risc de presentar resistència als tractaments antidepressius (López-Solà et al., 2020). Així doncs, sembla oportú tenir en compte la resposta dels pacients als tractaments antidepressius ja que acostumen a anar lligat a un dèficit cognitiu significatiu.

1.2.4. En període de remissió

La disfunció cognitiva durant la fase activa de la depressió és un fet ben establert. No obstant, l'evolució d'aquestes dificultats al llarg del temps continua sent una qüestió de debat. En un inici, la millora de la simptomatologia depressiva havia estat relacionada amb una millora en el rendiment cognitiu dels pacients (Biringer et al., 2007; Preiss et al., 2009). Però en les dues últimes dècades, s'ha evidenciat la persistència de dificultats cognitives en períodes de major estabilitat clínica, inclús en períodes de remissió clínica (Bora et al., 2013; Hasselbalch et al., 2011).

L'any 2011, Conradi i col·laboradors van portar a terme un estudi longitudinal de tres anys on 267 pacients deprimits d'atenció primària van ser entrevistats cada tres mesos. Se'ls preguntava sobre la presència de símptomes depressius residuals durant els següents episodis depressius i en períodes de remissió clínica parcial. Van observar com la simptomatologia depressiva residual era substancial durant els períodes de major estabilitat anímica. A més a més, els problemes cognitius conjuntament amb la falta d'energia i les dificultats en la son eren els tres símptomes més reportats en un 40% del temps durant els períodes en remissió clínica (Conradi et al., 2011). Així doncs, els anteriors autors van evidenciar la necessitat de portar a terme investigació clínica al respecte, ja que els símptomes cognitius semblaven persistir en remissió clínica impedint aconseguir una remissió completa. Prèviament i durant els següents anys, es va portar a terme varis estudis que van objectivar les dificultats cognitives descrites pels pacients. Behnken i col·laboradors, en una mostra de 30 pacients depressius en remissió i 30 controls sans, van observar persistència de dèficits en memòria no verbal en remissió clínica (Behnken et al., 2010). L'any successiu, Maeshima i col·laboradors van portar a terme un estudi amb 30 pacients amb un únic episodi depressiu i 38 pacients amb múltiples episodis recurrents amb l'objectiu de comparar-los en remissió clínica. Els pacients depressius recurrents continuaven mostrant dificultats en memòria verbal i visual, inclús després de 3 anys en remissió clínica, en front dels pacients amb un primer episodi depressiu on aquestes dificultats desapareixien (Maeshima et al., 2012). Tal i com s'ha comentat anteriorment, el treball de Roca i altres (2015) també van comparar una mostra de 26 pacients amb un primer episodi depressiu i 53 pacients recurrents, abans i després de seguir un tractament farmacològic. Després de sis mesos, els pacients en remissió clínica puntuaven millor en la majoria de proves neuropsicològiques en comparació als pacients no remesos, però tot i així les diferències no eren significatives estadísticament (Roca et al., 2015a). Anys més tard, en un estudi

també comentant prèviament, Serra-Blasco i coautors van comparar el rendiment neuropsicològic entre 57 pacients en remissió clínica, 90 pacients en remissió parcial i 81 pacients durant un episodi depressiu actiu. Van observar presència de dèficits cognitius en atenció, memòria i funcions executives tant en remissió clínica total com en remissió clínica parcial (Serra-Blasco et al., 2019).

De nou, degut a les diferències metodològiques entre estudis i a la rellevància de la simptomatologia cognitiva residual en el curs de la malaltia, s'han portat a terme diverses metaanàlisis i revisions sobre la disfunció cognitiva en remissió. En una primera revisió sistemàtica amb 11 estudis (500 pacients depressius en remissió i 471 controls sans), es van identificar dèficits en atenció sostinguda i selectiva, en memòria i en funció executiva, o en tests d'estimació cognitiva global, en nou dels 11 estudis inclosos (Hasselbalch et al., 2011). L'any 2013, Bora i coautors van portar a terme la primera metaanàlisi al respecte, on es van incloure 895 pacients en remissió i 997 controls sans de 27 estudis diferents. Els resultats evidencien la presència de dèficits cognitius en períodes de major estabilitat clínica. A més, observen com els pacients amb una edat d'inici més tardana de la malaltia presenten un pitjor rendiment cognitiu en memòria verbal, en velocitat de processament i en funcions executives (Bora et al., 2013). L'any següent, l'equip de recerca de Rock (2014) van realitzar una revisió sistemàtica i una metaanàlisi de pacients depressius, tant en fase activa com en remissió, per tal d'investigar quin era el veritable grau de disfunció cognitiva en la depressió en les diferents etapes de la malaltia. Es van identificar dèficits moderats significatius en atenció i funció executiva, i dèficits de lleu a moderats en memòria (amb tendència significativa) en aquells pacients en remissió clínica. Els resultats de l'estudi posen de manifest la necessitat de tenir en compte els dèficits cognitius com una característica principal de la depressió, ja que aquests no són exclusivament secundaris a un baix estat d'ànim (Rock et al., 2014). A continuació, els autors Cardoner i Serra-Blasco van portar a terme una revisió de la literatura sobre cognició en remissió amb l'objectiu de definir el patró simptomàtic de la disfunció cognitiva en la depressió, i van determinar la presència de d'alteracions en atenció, memòria i funcions executives (Cardoner & Serra Blasco, 2016). Donat que els resultats entre estudis eren inconsistents quant a importància dels dèficits, perfils cognitius diferents, severitat de la simptomatologia cognitiva i els possibles factors moderadors de la disfunció cognitiva en remissió, l'autora Semkosvka i coautors van portar a terme l'última revisió sistemàtica i metaanàlisi que s'ha publicat fins el moment sobre el funcionament cognitiu després d'un episodi depressiu. Es van incloure 252 estudis, dels quals es van analitzar les dades de 11882 pacients depressius amb remissió. Els resultats van mostrar dèficits en 55 de les 75 variables cognitives estudiades. A més, es va observar dèficits de lleu a moderats en velocitat de processament, atenció selectiva visual, memòria de treball, aprenentatge verbal i funcions executives, i dificultats greus en memòria verbal a llarg termini. Tanmateix, es va relacionar el nombre d'episodis depressius amb l'heterogeneïtat cognitiva, és a dir, a major número d'episodis depressius pitjor rendiment en capacitat cognitiva global, velocitat de processament, atenció, memòria, fluència verbal i flexibilitat cognitiva. Altres variables com el gènere, anys d'educació formal, durada de la malaltia, temps en eutímia, severitat de la simptomatologia depressiva residual semblen no tenir un

impacte significatiu en la gravetat de la disfunció cognitiva en els pacients depressius en remissió clínica (Semkovska et al., 2019).

1.3. Disfunció cognitiva i psicosocial

La depressió sempre ha estat associada a dificultats en el funcionament diari dels pacients. De fet, un dels criteris diagnòstics de la depressió es basa en què la simptomatologia depressiva ha de causar un malestar clínicament significatiu i/o un deteriorament social, laboral o en altres àrees d'activitat importants en la vida dels pacients (DSM-V; American Psychiatric Association, 2013). Existeixen suficients estudis els quals demostren presència de disfunció psicosocial en les fases actives de la depressió. Aquests dèficits funcionals no només han estat reportats a nivell laboral, sobretot en productivitat laboral, sinó també en les relacions interpersonals, en l'autonomia i en el funcionament global dels pacients (Bortolato et al., 2015; Evans et al., 2014; Hammar & Ardal, 2009; Lam et al., 2014). Tradicionalment, es pensava que la millora en aquesta simptomatologia clínica depressiva portaria la millora de les dificultats de funcionament en la vida diària. No obstant, els resultats dels estudis van indicar que una millora de la depressió no sempre anava lligada a una millora funcional en el mateix grau. Dit d'una altra manera, el funcionament psicosocial podia continuar afectat en períodes de remissió clínica.

A partir d'aquest moment la recerca es va enfocar a entendre quins factors estaven relacionats amb aquesta manca de recuperació funcional dels pacients en remissió de la simptomatologia depressiva. Així doncs, varis estudis van mostrar com els dèficits cognitius, conjuntament amb la simptomatologia depressiva residual, eren els factors que s'associaven i podien afectar a la intensitat de les dificultats funcionals dels pacients en períodes de major estabilitat anímica (Cambridge et al., 2018; Zuckerman et al., 2018). Per exemple, Jaeger i col·laboradors van fer el seguiment d'una mostra de 48 pacients deprimits hospitalitzats i van observar com la majoria dels pacients després de sis mesos de l'ingrés continuaven mostrant dificultats funcionals. A més, un baix rendiment en atenció, velocitat de processament, funcions executives i coneixement verbal es va relacionar amb aquesta disfunció psicosocial (Jaeger et al., 2006). Seguint aquesta línia d'investigació i uns anys més tard, Daniel i altres van analitzar les associacions entre el perfil cognitiu i el funcionament global en pacients eutímics amb depressió i trastorn bipolar. Els resultats indicaven com els pacients amb un millor rendiment en funcions executives presentaven un millor funcionament, sense diferències entre els trastorns afectius (Daniel et al., 2013). Seguit l'any 2014, Fried & Nesse, van estudiar una mostra de 3703 pacients depressius de l'estudi STAR*D amb l'objectiu de relacionar els diferents símptomes depressius amb la magnitud de les dificultats funcionals. Els resultats van mostrar que els únics símptomes que es relacionaven amb el funcionament psicosocial eren un estat d'ànim trist i la presència de dificultats en la concentració, suggerint la importància de tenir en compte aquests dos símptomes a l'hora de comprendre l'evolució de la malaltia (Fried & Nesse, 2014). De fet, en un estudi l'any 2016 dels autors Cléry-Melin & Gordwood, van demostrar com el rendiment en una prova atencional pot funcionar com a factors predictor del funcionament psicosocial a llarg termini en pacients depressius en tractament

farmacològic (Cléry-Melin & Gorwood, 2016). Posteriorment, Knight i coautors van portar a terme un estudi amb 72 pacients depressius en remissió clínica en front a 110 controls sans per tal d'explorar la relació entre cognició i funcionament psicosocial. Els resultats van mostrar que el funcionament psicosocial dels pacients en remissió del funcionament executiu. Més específicament, el rendiment executiu explicava el funcionament ocupacional, la cognició subjectiva i el temps d'oci dels pacients. En canvi, en el grup de controls sans el predictors cognitius del funcionament psicosocial eren més heterogenis, observant-se relacions entre el funcionament executiu, atenció i fluència semàntica entre varis dominis del funcionament psicosocial. Aquests resultats reforcen la importància de les funcions executives en el desenvolupament de les activitats diàries, quant a responsabilitats personals, relacions interpersonals, en la presa de decisions, en la planificació i resolució de problemàtiques (Knight et al., 2018).

Un altre punt a tenir en compte en relació al funcionament psicosocial dels pacients en depressió en les diferents etapes de la malaltia és la cognició subjectiva. Buist-Bouwman i col·laboradors (2008) a través d'un estudi epidemiològic basat en una entrevista poblacional va mostrar com la percepció de dèficits en atenció i de concentració estaven correlacionats amb el grau de funcionament (Buist-Bouwman et al., 2008)(Buist-Bouwman et al., 2008). Anys més tard, Cha i coautors van publicar els resultats d'un estudi on, un cop més, aquesta autopercepció sobre el rendiment cognitiu i la simptomatologia depressiva residual s'associaven al funcionament psicosocial dels pacients amb una depressió amb gravetat de moderada a severa. Més específicament, la cognició subjectiva es relacionava amb el funcionament laboral o escolar, amb dies laborals perduts i amb les dificultats per a portar a terme les responsabilitats familiars. Aquestes estudis recolzen el concepte que no només la cognició objectiva té un paper en el grau de disfunció psicosocial, sinó que també és important tenir en compte la percepció del pacient sobre la seva pròpia disfunció cognitiva ja que aquesta pot tenir un efecte directe sobre el seu funcionament (Cha et al., 2018).

La reducció de la simptomatologia depressiva sempre havia estat l'objectiu del tractament durant els episodis depressius, però en observar-se que les dificultats funcionals no milloraven en alleugerir-se la simptomatologia depressiva, es va produir un canvi en l'enfocament de la intervenció en la depressió. En altres paraules, es va decidir incloure la **recuperació funcional**, conjuntament amb la clínica, com a objectius principals dels tractaments de la depressió (Sheehan et al., 2017).

Relacionat amb aquest concepte, és interessant tenir en compte que el fet de no recuperar els nivells previs de funcionament pot arribar a ser frustrant pels pacients i pot donar lloc a una sensació de falta de recuperació completa dels episodis depressius. De fet, Zimmerman i coautors van portar a terme un estudi amb 535 adults que havien estat tractats per depressió on se'ls va administrar un qüestionari amb diferents afirmacions sobre el què significava per a ells està en remissió. Aconseguir una salut mental positiva (optimisme, confiança i vitalitat), sensació de benestar i el retorn la normalitat personal,

conjuntament amb l'absència de simptomatologia depressiva, eren els factors essencials per experimentar una recuperació completa (Zimmerman et al., 2006). Recentment, es va publicar un estudi on van explorar quins eren els millors indicadors de remissió, tant per a pacients com per als professionals en salut mental. Tant els pacients com els professionals creien que la recuperació del funcionament psicosocial i de les relacions interpersonals, la qualitat de vida i el fet d'aconseguir fites personals eren els indicadors més rellevants per poder aconseguir una recuperació completa. No obstant, els professionals també van identificar que la reducció de la simptomatologia depressiva i la satisfacció amb el tractament eren importants per aconseguir resultats significatius del tractament (Kan et al., 2020) Aquestes diferències evidencien la necessitat de tenir en compte les necessitats dels pacients en el disseny de les intervencions, ja que posen de manifest quin és l'impacte real de la depressió en la vida quotidiana dels pacients.

1.4. Tractament dels símptomes cognitius

Donada la relació que existeix entre la disfunció cognitiva i les dificultats en el funcionament psicosocial, hi ha un gran interès en desenvolupar estratègies d'intervenció enfocades a la millora dels símptomes cognitius. Però tot i el gran esforç científic al respecte, i que moltes d'aquestes estratègies procognitives (**Figura 2**) s'utilitzen ja en la pràctica clínica, no acaben de ser del tot eficaces en la millora del funcionament, ni en la recuperació de la qualitat de vida dels pacients (Lam & McIntyre, 2014; Miskowiak et al., 2016; Zuckerman et al., 2018).

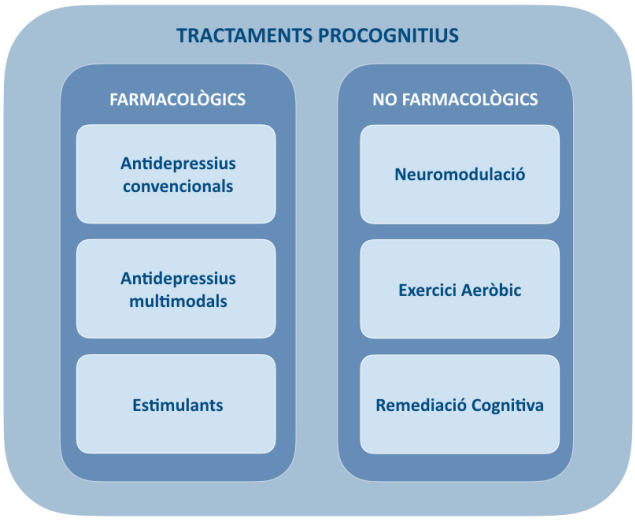

Figura 2. Esquema resum tractaments procognitius en la depressió

1.4.1. Intervencions procognitives farmacològiques

Les dificultats funcionals persistents en els pacients depressius en remissió clínica justifiquen la necessitat de desenvolupar fàrmacs antidepressius, que no només millorin la simptomatologia clínica depressiva, sinó que també tinguin efectes procognitius. Tot i la falta d'estudis recents focalitzats en avaluar la funció cognitiva, existeix cert evidència científica que confirma que els fàrmacs antidepressius

convencionals (ISRS, ISRN, duals) i els d'acció multimodal podrien tenir un efecte positiu sobre el funcionament cognitiu dels pacients (Salagre et al., 2017a; Zuckerman et al., 2018).

Respecte a fàrmacs inhibidors selectius de la recaptació de serontonina (ISRS), es va observar com les funcions cognitives de velocitat psicomotora, funció executiva i memòria verbal milloraven després d'un tractament amb sertralina (Constant et al., 2005; Culang-Reinlieb et al., 2012; Schrijvers et al., 2009). Tanmateix, Wroolie i col·laboradors (2006) en un estudi en dones amb depressió també van observar millores en memòria lògica verbal, memòria visual i flexibilitat cognitiva després de 12 setmanes de tractament amb escitalopram (Wroolie et al., 2006). Pel que fa a fàrmacs d'acció dual, tant a nivell serotoninèrgic com noradrenèrgic, es va observar una millora significativa a nivell atencional i en memòria de treball en pacients depressius amb tractament amb venlafaxina i desvenlafaxina, respectivament (Reddy et al., 2016; Tian et al., 2016). Un altre fàrmac dual que també ha estat associat a millores cognitives significatives ha estat la duloxetina. L'any 2014, Greer i coautors van mostrar millores en velocitat psicomotora, memòria verbal i visual i presa de decisions després de 12 setmanes de tractament amb duloxetina. A més, la majoria d'aquestes millores observades eren totalment independents a la reducció de la simptomatologia depressiva, excepte en memòria verbal i visual (Greer et al., 2014). Quant a fàrmacs Inhibidors Selectius de la Recaptació de la Noradrenalina (ISRN) també s'han assenyalat efectes beneficiosos sobre la simptomatologia cognitiva. En concret, en un estudi de Ferguson i col·laboradors, es van mostrar mostrant millores en atenció sostinguda i en velocitat de processament cognitiu mitjançant reboxetina (Ferguson et al., 2003). Un altre fàrmac a tenir en compte és el bupropión amb efecte dopaminèrgic i noradrenèrgic. En un estudi de l'any 2014, on es comparava el tractament amb bupropion i amb escitalopram, es va observar una millora en memòria verbal i no verbal, millores en el funcionament global, i específicament en la productivitat laboral, en ambdós grups (Soczynska et al., 2014). Per últim, un fàrmac nou que ha suscitat molt interès en l'última dècada pel seu mecanisme d'acció multimodal ha estat la vortioxetina (Al-Sukhni et al., 2016). Aquesta s'ha associat a millores en atenció, memòria verbal, velocitat de processament i funció executiva (Harrison et al., 2016; Katona & Katona, 2014; Mahableshwarkar et al., 2015; Mcintyre et al., 2014). A més, els estudis previs suggereixen que l'efecte sobre la cognició és independent als efectes antidepressius de la medicació. En altres paraules, sembla ser que la vortioxetina contribueix directament a la millora de la simptomatologia cognitiva. Així doncs, alguns antidepressius podrien tenir un efecte procognitiu en els pacients depressius, però donada les diferències metodològiques entre estudis, la mida petita de les mostres d'estudi i que l'objectiu dels fàrmacs és la millora de l'estat d'ànim es fa difícil determinar l'abast d'aquesta millora cognitiva. No obstant, convé ressaltar tant la duloxetina com la vortioxetina ja que el seu impacte procognitiu és independent a la reducció de la simptomatologia depressiva.

A banda dels fàrmacs antidepressius, també s'ha investigat si fàrmacs estimulants com el modafinil podrien tenir un impacte sobre la cognició en els pacients depressius. En una revisió i metanàlisi de Goss i col·laboradors (2013), es va determinar com el modafinil era efectiu com a estratègia d'augment

durant un episodi depressiu, i que donat el seu efecte modulador del sistema dopaminèrgic i noradrenèrgic podia tenir efectes procognitius (Goss et al., 2013). Uns anys més tard, Kaser i coautors, van realitzar un estudi amb 60 pacients en remissió clínica on van observar un millora cognitiva en memòria episòdica i memòria de treball (Kaser et al., 2017). Més recentment, en una revisió sistemàtica sobre l'eficàcia del modafinil i el seu potencial efecte procognitiu, es va observar millores en el funcionament executiu després de quatre setmanes de tractament en pacients amb un episodi depressiu actiu (Vaccarino et al., 2019). Tot i que l'evidència sobre els seus efectes procognitius és limitada, el modafinil sembla ser un fàrmac prometedor per a la millora cognitiva dels pacients depressius. Per últim, també s'hauria de tenir present l'eritropoietina com a candidat terapèutic en la depressió. Donada les seves propietats neurotròfiques s'han portat a terme varis estudis on s'ha observat com l'administració d'eritropoietina es relaciona amb un augment del rendiment en memòria verbal en pacients amb depressió resistent (Miskowiak et al., 2014, 2015). En la **Figura 2**, es mostra un esquema dels efectes de les teràpies farmacològiques sobre la cognició, així com els seus mecanismes d'acció.

Taula 2. Resum dels efectes procognitius de les intervencions farmacològiques més habituals

Fàrmac	Tipus de fàrmac	Mecanisme d'acció	Evidència clínica dels efectes sobre la cognició
Sertralina	ISRS	Inhibidor selectiu de la recaptació de 5-HT a la membrana neuronal presinàptica augmentant la concentració sinàptica de 5-HT en el Sistema Nerviós Central (SNC)	Memòria verbal, velocitat psicomotora, funció executiva
Escitalopram	ISRS	Inhibidor Selectiu de la Recaptació de 5-HT. Augmenten els nivells de 5-HT en les sinapsis neuronals donat que impedeixen la recaptació de 5-HT a les terminals presinàptiques de les neurones serotoninèrgiques	Memòria lògica verbal, memòria visual, flexibilitat cognitiva
Venlafaxina i Desvenlafaxina	Dual: ISRS + ISRN	Inhibidor Selectiu de la Recaptació de 5-HT i NA. Bloqueig dels transportadors que intervenen en la recaptació de 5-HT i NA	Atenció, memòria de treball
Duloxetina	Dual: ISRS + ISRN	Inhibidor Selectiu de la Recaptació de 5-HT i NA. Potent inhibidor de la recaptació neuronal de 5-HT i NA, i inhibidor menys potent de la recaptació de DA	Memòria verbal, memòria visual, velocitat psicomotora, presa de decisions
Reboxetina	ISRN	Inhibidor altament selectiu i potent de la recaptació de NA	Atenció sostinguda, velocitat de processament
Bupropion	IRDN	Inhibidor de la recaptació de DA i NA, inhibint de forma dèbil les enzimes implicades en la recaptació de DA i NA des de l'esquerda sinàptica, perllogant la durada d'acció dins de la sinapsi neuronal i els seus efectes descendents d'aquests neurotransmissors.	Memòria verbal, memòria visual
Vortioxetina	Multimodal	Inhibidor transportador de recaptació de Serotonina, acció agonista sobre receptors 5-HT1A, acció agonista parcial sobre receptors 5-HT1B i acció antagonista dels receptors 5-HT3, 5-HT1D i 5-HT7	Atenció, memòria verbal, velocitat de processament, funció executiva
Modafinil	Estimulant	Mecanisme exacte d'acció no especificat. Possiblement es tracta d'una inhibició directe de la recaptaciO de DA i una inhibició indirecte de la recpatació de NA.	Memòria episòdica, memòria de treball
Eritropoietina	Propietats neurotròfiques	Factor de creixement produït pels ronyons que estimula la producció de glòbuls vermells. El producte conté la mateixa seqüència d'aminoàcis i la mateixa activitat biològica que l'eritropoietina biològica.	Memòria verbal

Basat en:
"Treatment of neurocognitive symptoms in unipolar depession: A systematic review and future perspectives", per E. Salagre, 2017, Journal of Affective Disorders, 221: 205-221 (Salagre et al., 2017); "Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder", per H. Zuckerman, 2018, Frontiers in Psychiatry, 9: 655 (Zuckerman et al., 2018).
Nota. ISRS: Inhibidors Selectius Recaptació Serotonina; ISRN: Inhibidors Selectius Recaptació i Noradrenalina; IRDN: Inhibidor Recaptació Dopamina i Noradrenalina; 5-HT: Serotonina; NA: Noradrenalina; DA: Dopamina.

1.4.2. Intervencions procognitives no farmacològiques

- Tècniques de neuromodulació:

Les intervencions basades en la neuromodulació, com ara *l'Estimulació Cerebral Profunda* (ECP), la *Teràpia Electroconvulsiva* (TEC) i *l'Estimulació Magnètica Transcranial* (EMT), són estratègies habitualment utilitzades en la pràctica clínica, sobretot en aquells casos de pacients amb episodis depressius greus o en pacients amb depressió resistent. Tanmateix, no són tants els estudis focalitzats en determinar si hi ha un efecte procognitiu en l'ús d'aquestes estratègies (Miskowiak et al., 2016; Salagre et al., 2017a; Zuckerman et al., 2018)

En el cas de la intervenció basada en ECP, els resultats entre els diferents estudis són força contradictoris. Per exemple, l'any 2017, Bergfeld i coautors van portar a terme un estudi amb 25 pacients amb depressió resistent que es van sotmetre a una intervenció d'ECP i 21 controls sans. Els resultats van mostrar com l'ECP no tenia un efecte positiu en la cognició, i hipotetitzaven que aquesta intervenció podia tenir efectes negatius temporals en la memòria verbal (Bergfeld et al., 2017). No obstant, altres estudis longitudinals refutaven aquesta idea i donaven suport a que l'ECP és una tècnica segura sense perjudici en la cognició dels pacients. Serra-Blasco i coautors (2015) van realitzar un estudi exploratori per avaluar la funció cognitiva abans i després d'una intervenció d'ECP en el gir subgenual cingulat i van mostrar com el rendiment cognitiu dels pacients no empitjorava amb l'estimulació, i que la memòria verbal millorava al cap d'un any de tractament (Serra-Blasco et al., 2015). Així doncs, encara que la tècnica d'ECP sigui eficaç a nivell clínic, encara és necessari portar a terme més investigació per a determinar el seu efecte a nivell cognitiu. En una recent revisió de l'equip de Sullivan s'exposa la necessitat de fer un canvi en els objectius de l'ECP, des de l'estimulació de *targets* locals cap a l'estimulació de xarxes cognitives. Els autors suggereixen que per tal de produir efectes positius en la cognició, no és suficient d'estimular una sola àrea, sinó que és necessari fer un pas més i estimular xarxes neuronals, és a dir, estimular àrees del cervell connectades entre si (Sullivan et al., 2021).

Quant als efectes de TEC en la cognició, està ben establert que aquesta tècnica de neuromodulació produeix efectes secundaris a curt termini en el rendiment cognitiu dels pacients depressius. En una revisió sistemàtica i metaanàlisi de l'any 2010, Semkovska i McLoughlin van determinar que després del tractament amb TEC es donava un dèficit cognitiu de tres dies d'evolució. Però, al cap de 15 dies, s'observava una millora en el rendiment cognitiu dels pacients a nivell de velocitat de processament, memòria de treball, memòria anteròrgrada i alguns aspectes de la funció executiva (Semkovska & McLoughlin, 2010). Una dècada més tard, es va publicar una nova revisió i metaanàlisi sobre els efectes secundaris cognitius del TEC en pacients resistents al tractament. Les anàlisis van mostrar presència de dificultats d'aprenentatge verbal immediatament després del tractament, però que aquestes milloraven amb el pas dels dies, o si més no, tornaven al nivell basal de rendiment dels pacients. A més, van suggerir que intervencions basades en TEC causaven dèficits en la memòria autobiogràfica persistents (Porter et al., 2020). No obstant, les diferències metodològiques entre estudis i la manca de

monitorització d'aquesta simptomatologia en les rutines mèdiques, fa difícil clarificar els efectes secundaris cognitius, i si amb el temps es produeix una millora cognitiva significativa o si els dèficits cognitius es mantenen presents.

Per últim, l'EMT és un mètode de neuromodulació menys invasiu que les anteriors tècniques i produeix efectes favorables sobre el rendiment cognitiu dels pacients depressius. Diferents estudis han provat la seva eficàcia en la millora de la memòria verbal (Fitzgerald et al., 2009), en atenció (Begemann et al., 2020; Naim-Feil et al., 2016), velocitat psicomotora (Höppner et al., 2003) i en flexibilitat cognitiva (Moser et al., 2002).

- Exercici aeròbic:

Una altra intervenció no farmacològica a tenir en compte pels seus possibles efectes procognitius és l'exercici aeròbic. L'any 2017, es va portar a terme una metanàlisi de 637 pacients amb depressió per tal d'avaluar els efectes de l'exercici físic en els símptomes cognitius de la depressió. Els resultats van determinar que l'exercici físic no millorava els dèficits cognitius en la depressió i que variables com la duració de l'exercici, el número de sessions per setmana i la intensitat d'aquestes sessions no tenien rellevància en el resultat final (Brondino et al., 2017). Un any més tard es va publicar una nova metaanàlisi amb 642 pacients depressius, on de nou, els resultats van mostrar que l'exercici físic no produïa un impacte significatiu en la cognició, però que la combinació d'exercici físic i activitats cognitives sí que milloraven el rendiment cognitiu global dels pacients. Malgrat aquests últims resultats esperançadors, és necessari continuar investigant en aquest camp ja que no està clar el paper que juga l'exercici aeròbic en la cognició en pacients amb depressió (Sun et al., 2018).

- Remediació cognitiva:

La ***Remediació Cognitiva*** **(RC)** és una intervenció psicoterapèutica que té com a objectiu la millora del funcionament cognitiu, i a la vegada, el traspàs d'aquestes millores a la vida quotidiana dels pacients depressius (Kim et al., 2018). Per tal de demostrar l'eficàcia d'aquestes intervencions s'han portat a terme diferents estudis basant-se en dos tipus d'enfocs diferents: la restauració i la compensació. Les estratègies de restauració es basen en el principi bàsic de plasticitat neuronal en el qual la repetició d'exercicis ("*drill and practice"*) porta a una millora cognitiva. En canvi, les estratègies compensatòries utilitzen estratègies conductuals i modificacions de l'entorn per tal de compensar aquests dèficits cognitius i així millorar el funcionament diari dels pacients. Aquests estudis han portat a terme diferents programes de RC quant a tècniques utilitzades, els software aplicats, la freqüència i duració de les sessions, el dominis cognitius treballats o les mesures de resultats utilitzades. Però tots ells, tenen com a resultat una millora significativa de la simptomatologia cognitiva en els pacients (Motter et al., 2016; Porter et al., 2013).

L'any 2007, Elgamal i coautors van portar a terme un estudi en una mostra de 12 pacients amb depressió recurrent en remissió parcial en comparació a una mostra control de pacients depressius i una mostra de controls sans. L'objectiu de l'estudi era implementar un programa d'entrenament cognitiu computeritzat 'PSSCogReHab' basat en la repetició d'exercicis durant deu setmanes (dues sessions/setmana) per tal de millorar els dominis cognitius de memòria, atenció, funció executiva i velocitat psicomotora. Els resultats van mostrar una millora en el rendiment cognitiu dels pacients, sense observar-se canvis en la simptomatologia depressiva, suggerint que la millora cognitiva no estava determinada per la millora en altres variables clíniques. Donada la mida de la mostra i la falta d'aleatorització en el procés d'assignació dels pacients és difícil determinar l'eficàcia de la intervenció tot i els resultats favorables que es van observar (Elgamal et al., 2007). En un altre estudi similar, Naismith i col·laboradors, en una mostra de 16 pacients depressius en remissió parcial (vuit en el grup d'intervenció i vuit en llista d'espera), van detectar millores en memòria verbal utilitzant el programa 'Neuropsychological Educational Approach to Remediation' (NEAR). Aquest programa es basava en la utilització d'estratègies de restauració i compensació dos cops per setmana durant 10 setmanes d'entrenament. De nou, la mida petita de la mostra, la falta d'aleatorització i la falta de grup control no actiu limitava la interpretació dels resultats (Naismith et al., 2010). Posteriorment, Bowie i coautors van examinar els resultats d'implementar una estratègia de RC en una mostra de 33 pacients depressius resistents al tractament, aleatoritzats al grup de tractament o al grup d'espera. La intervenció es basava en deu sessions durant deu setmanes, on es realitzaven exercicis en format de repetició a través del programa d'entrenament cognitiu computeritzat 'Scientific Brain Training Pro' conjuntament amb una discussió sobre les estratègies de resolució utilitzades exercicis i sobre els objectius de la vida quotidiana dels pacients, a nivell laboral, oci i interpersonal. A més a més, els pacients realitzaven exercicis d'entrenament cognitiu online cada dia durant 20 minuts. Els resultats van mostrar una millora en atenció, velocitat de processament i memòria, i en la simptomatologia depressiva (Bowie et al., 2013). Recentment, es va publicar un estudi pilot desenvolupat per Hammar i coautors on també es mostraven millores cognitives en pacients en remissió clínica, en aquest cas a nivell de memòria de treball. L'entrament cognitiu estava totalment focalitzat en millorar la memòria de treball a través de 25 sessions a través del programa computeritzat 'Cogmed Working Memory Traininig'. Així doncs, els diferents estudis van demostrar que la RC semblava ser una estratègia eficaç per a la millora de la simptomatologia cognitiva present en períodes de major estabilitat clínica (Hammar et al., 2020).

Però amb el propòsit d'investigar si aquesta estratègia també podia ser útil durant un episodi depressiu, Semkovska i altres van realitzar un estudi pilot amb una mostra de 24 pacients depressius hospitalitzats amb simptomatologia depressiva greu. Aquests pacients van ser aleatoritzats en dos grups de tractament: 'RehaCom' o jocs online (durant cinc setmanes, quatre sessions setmanals). L'entrenament cognitiu computeritzat 'RehaCom' es basava en un conjunt d'exercicis focalitzats en millorar atenció dividida, memòria verbal, memòria figurativa, compra i planificació. Es van observar millores en el rendiment cognitiu, específicament en atenció dividida, record visual immediat, memòria de treball i

planificació (Semkovska et al., 2015). Seguint aquesta línia d'investigació, Trapp i coautors, van examinar els efectes d'un grup de RC tipus joc 'X-Cog' en una mostra de 46 pacients depressius ingressats al hospital, però amb una menor simptomatologia depressiva respecte l'anterior estudi. En aquest cas, es van mostrar millores significatives en memòria verbal i no verbal, memòria de treball i en funció executiva en aquells pacients que havien seguit les 12 sessions d'entrenament cognitiu computeritzat (Trapp et al., 2016).

Tenint en compte que l'objectiu de la RC no només és la millora de la simptomatologia cognitiva, sinó també la millora del funcionament psicosocial dels pacients, és interessant destacar la falta d'ús de mesures que avaluïn la funcionalitat dels pacients en les anteriors publicacions esmentades. Fins el moment, únicament s'han publicat tres estudis que incloguin el funcionament psicosocial com una mesura d'eficàcia de les intervencions de RC. Lee i col·laboradors (2013) van observar millores en la memòria i en el funcionament psicosocial en una mostra de 55 pacients amb un primer episodi depressiu o psicòtic després del programa de RC anomenat 'NEAR'. Aquest consistia en una intervenció basada en la psicoeducació de la simptomatologia cognitiva i l'aprenentatge d'estratègies compensatòries, activitats d'entrenament cognitiu basades en la repetició en format grupal i un entrenament cognitiu computeritzat individualitzat durant deu setmanes (Lee et al., 2013). De forma similar, Listunova i altres van implementar una intervenció formada per un entrenament cognitiu computeritzat i sessions de transferència amb l'ús d'estratègies compensatòries en una mostra de pacients depressius en remissió. Com a resultat s'observen millores atencionals i millores en l'escala d'autopercepció de funcionament psicosocial en el dos grups d'estudi, tant a nivell grupal com individual (Listunova et al., 2020). Per últim, en l'estudi de Hagen i coautors van aleatoritzar a 63 pacients amb depressió actual o prèvia, lleu o moderada, a rebre vuit sessions d'una intervenció metacognitiva de RC anomenada 'Goal Management Training' o un entrenament cognitiu computeritzat a través de la plataforma BrainHQ. Es van observar millores significatives en la funció executiva, i disminució en la simptomatologia depressiva en les dues opcions d'intervenció (Hagen et al., 2020).

En resum, els estudis sobre RC en la depressió semblen ser les intervencions convenients per a tractar la simptomatologia cognitiva, i a la vegada, millorar el funcionament psicosocial dels pacients. No obstant, per tal d'aconseguir una recuperació completa de la depressió, tenint en compte aspecte com la qualitat de vida o la salut mental positiva, és necessari optimitzar les estratègies utilitzades i avaluar els resultats a nivell longitudinal.

2. Hipòtesis

En aquesta tesi s'estudia la possible heterogeneïtat cognitiva en les diferents etapes clíniques de la depressió, i es desenvolupa una estratègia de remediació cognitiva dirigida als pacients amb dèficits cognitius i funcionals que no aconsegueixen una recuperació completa. Així doncs, les hipòtesis del treball són les següents:

Hipòtesi 1:

Els pacients amb un primer episodi depressiu presenten diferents nivells d'afectació cognitiva.

Hipòtesi 2:

El rendiment cognitiu en un primer episodi depressiu conjuntament amb altres factors, són predictors de la gravetat de la simptomatologia clínica depressiva, tant a l'inici del quadre com al cap d'un any de seguiment.

Hipòtesi 3:

Les característiques cognitives, clíniques i sociodemogràfiques defineixen diferents grups de pacients depressius durant un episodi agut.

Hipòtesi 4:

El grup de pacients depressius en fase activa amb majors dificultats cognitives presenten una pitjor adaptació funcional.

Hipòtesi 5:

Els pacients depressius en remissió clínica que reben la intervenció INtegral Cognitive REMediation (INCREM; estratègia d'intervenció dissenyada per aquest estudi i que està basada en la unió d'una rehabilitació funcional i un entrenament cognitiu computeritzat), milloren el funcionament psicosocial i cognitiu després de la intervenció.

3. Objectius

La finalitat general d'aquesta tesi és l'estudi de la possible heterogeneïtat en el rendiment cognitiu dels pacients amb depressió i el desenvolupament d'una estratègia d'intervenció dirigida a aquells pacients amb dificultats cognitives i funcionals. Per un costat, aquesta tesi presenta dos estudis específicament pensats per a estudiar els possibles diferents perfils de rendiment cognitiu dels pacients, tenint en compte no només variables neuropsicològiques sinó també característiques sociodemogràfiques, clíniques i de funcionament psicosocial. Per l'altre, presenta el desenvolupament d'una estratègia d'intervenció neurocognitiva integral i la seva posterior aplicació en una mostra de pacients depressius en remissió clínica total o parcial.

Heterogeneïtat cognitiva

El primer estudi es va portar a terme per explorar la presència de diferents perfils cognitius en una mostra de pacients amb un primer episodi depressiu. Fins el moment, els estudis previs en depressió s'havien centrat en determinar si els dèficits cognitius eren independents o eren una conseqüència de la manifestació clínica de la malaltia, sense tenir en compte la possible presència d'heterogeneïtat cognitiva ja en els inicis de la malaltia. De forma afegida, es va estudiar el paper del rendiment cognitiu en la manifestació clínica de la malaltia, tant a nivell basal com a llarg termini.

Els objectius van ser:

Objectiu 1:

Determinar el rendiment cognitiu dels pacients amb un primer episodi depressiu per tal d'explorar la presència de diferents perfils cognitius ja en l'inici de la malaltia.

Objectiu 2:

Investigar si els dèficits cognitius ja a l'inici de la malaltia ens poden ajudar a determinar el perfil clínic dels pacients a nivell basal, i l'evolució clínica d'aquests pacients.

Existeixen variables clíniques i sociodemogràfiques que han estat relacionades amb el rendiment cognitiu dels pacients, així doncs, aquests també podrien estar influenciant en el diferents perfils cognitius dels pacients al llarg de la malaltia. De manera que el segon estudi dirigides va dissenyar per resoldre quin era el grau de relació entre aquestes variables en pacients depressius durant la fase activa de la malaltia.

Així doncs, els següents objectius de la tesi van ser:

Objectiu 3:

Identificar clústers de pacients depressius en fase aguda utilitzant variables cognitives, clíniques i sociodemogràfiques.

Objectiu 4:

Comparar els diferents clústers de pacients per tal d'observar diferències en característiques clíniques, cognitives i funcionals entre els diferents grups de pacients depressius.

Remediació cognitiva

De forma paral·lela, es va desenvolupar una nova estratègia d'intervenció procognitiva (INCREM) específica per als pacients depressius amb un perfil cognitiu afectat. Aquest programa es basa en la combinació de tècniques de rehabilitació funcional i d'entrenament cognitiu computeritzat, amb el qual es pretén millorar no només el rendiment cognitiu dels pacients, sinó també el seu funcionament psicosocial i la seva qualitat de vida.

Finalment, l'últim objectiu va ser:

Objectiu 5:

Examinar l'eficàcia de la intervenció INCREM en la millora del funcionament psicosocial i cognitiu en una mostra de pacients depressius en remissió parcial, en comparació a un grup control actiu de psicoeducació i un grup no actiu amb el tractament habitual.

4. Mètodes

Aquesta tesi està formada per a quatre articles, tres de publicats a les revistes *European Neuropsychopharmacology*, *Psychological Medicine* i *BMC Psychiatry,* i un altre que es troba en revisió en una revista internacional. Tot i que la metodologia de cadascun dels articles es troba extensament detallada en cada un dels treballs, en aquest apartat s'exposen els aspectes més rellevants de manera resumida:

ESTUDI 1:

La mostra del primer treball està formada per un grup de 50 pacients amb un primer episodi depressiu i un grup de 40 controls sans. Els pacients van ser reclutats en els serveis de Salut Mental del Hospital de la Santa Creu i Sant Pau (Barcelona) i del Hospital Parc Taulí (Sabadell). Es va portar a terme una entrevista clínica i una bateria neuropsicològica completa a l'inici de l'estudi. Els dominis cognitius explorats van ser: llenguatge, atenció, memòria verbal i visual i funció executiva. A l'any de tractament, es va avaluar la simptomatologia clínica depressiva en tots els pacients depressius.

Per tal d'aconseguir una base de dades completa, es va fer un estudi de la quantitat i del patró dels valors que faltaven (*missings*), i tot seguit es va portar a terme una imputació múltiple d'aquelles variables que presentaven menys d'un 5% de valors perduts. A continuació, es van analitzar les diferències sociodemogràfiques i clíniques entre les dues submostres d'estudi, utilitzant proves t per a les variables quantitatives i proves xi quadrada per a les variables categòriques. Les diferències neuropsicològiques entre grups també van ser explorades mitjançant una anàlisi multivariant de la variància (MANOVA). Amb l'objectiu de reduir el nombre de variables neuropsicològiques, es va realitzar una anàlisi de components principals donant lloc a la creació de quatre components (dominis cognitius). Aquests components van ser utilitzats en el model de clúster jeràrquic amb l'objectiu d'identificar grups de pacients amb un rendiment neuropsicològic similar (clústers). Tot seguit, es van comparar les característiques sociodemogràfiques, clíniques i neuropsicològiques entre els clústers a nivell basal i al cap de l'any de tractament. En darrer lloc, es van construir dos models lineals generalitzats utilitzant la simptomatologia depressiva basal i el canvi en aquesta a l'any de tractament, com a variables dependents. Com a possibles factors predictors, es van entrar en el model aquelles variables sociodemogràfiques i clíniques que mostraven una correlació significativa amb les variables dependents. Les anàlisis estadístiques es van realitzar amb el programa estadístic R.

ESTUDI 2:

La mostra del segon treball està formada per 174 participants amb un episodi actual de depressió major, reclutats en el servei de Salut Mental del Hospital Parc Taulí (Sabadell). Es tracta d'un estudi transversal amb única avaluació sociodemogràfica, clínica, neuropsicològica i funcional a l'inici de l'estudi.

L'entrevista clínica va incloure l'avaluació del nivell de resistència al tractament a través de l'escala *Maudsley Staging Method* (MSM; Fekadu et al., 2009)). És a dir, fa un recull d'informació relativa al tractament, com és: la duració i gravetat de la simptomatologia depressiva, els tractaments antidepressius, les estratègies de potenciació i l'ús de teràpia electroconvulsiva. L'avaluació neuropsicològica va incloure una bateria extensa de proves per tal de cobrir tots els dominis cognitius. Per tal de mesurar el funcionament psicosocial dels participants es va utilitzar l'escala *Functioning Assessment Short Test* (FAST), àmpliament utilitzada en salut mental, específicament en el trastorn bipolar.

Les anàlisis estadístiques es van portar a terme mitjançant el programa *Statistical Package for Social Sciences* (SPSS). Les dades neuropsicològiques van ser transformades a puntuacions Z a través dels barems poblacionals normatius. Seguit, per tal de reduir la quantitat de proves neuropsicològiques, es van definir diferents dominis cognitius a través d'una anàlisi de components principals. Amb l'objectiu d'identificar grups homogenis de pacients, es va aplicar una anàlisi d'agrupació en dos passos (*two-step clustering*). En aquest cas, no només es van utilitzar els dominis cognitius extrets de l'anterior anàlisi, sinó que també es van utilitzar variables clíniques i sociodemogràfiques; com la resistència al tractament (MSM), la simptomatologia depressiva (HDRS-17), el número d'episodis depressius, l'edat i els anys d'escolaritat. Aquesta anàlisi permet incloure variables categòriques i contínues en mostres grans. En últim lloc, es van analitzar les diferències sociodemogràfiques, clíniques i funcionals (FAST) entre els clústers resultants a través d'anàlisis de variància (ANOVA) o xi-quadrada, i també es van reportar les mides de l'efecte.

ESTUDI 3:

El tercer treball de la present tesi va ser el desenvolupament d'una nova estratègia d'intervenció neurocognitiva integral anomenada **INtegral Cognitive REMediation (INCREM)** amb l'objectiu de millorar el funcionament psicosocial a través de la millora del rendiment cognitiu dels pacients. Aquesta estratègia està formada per 12 sessions de 110 minuts, un cop per setmana, en la que s'inclou un programa de **Rehabilitació Funcional (RF)** i un programa d'**Entrenament Cognitiu Computeritzat (ECC).** El programa funcional es porta a terme en format grupal durant 90 minuts. Aquest es basa en la psicoeducació dels símptomes cognitius, en l'ús de tècniques neurocognitives i en l'aprenentatge de tècniques de compensació sempre utilitzant com a exemple situacions o activitats quotidianes en la vida dels pacients. De forma seguida, es realitza l'entrenament cognitiu computeritzat durant 20 minuts en format individual a través del software CogniFit (https://www.cognifit.com) (**Figura 3**)**.** Les diferents sessions consten de diferents activitats tipus joc en les quals s'entrenen les habilitats cognitives d'atenció, memòria i funcions executives. Aquesta bateria de tasques cognitives s'adapten al perfil cognitiu del pacient, reajustant els paràmetres de les diferents activitats en base al propi rendiment del pacient en les diferents sessions. La unió entre estratègies de remediació basades en la restauració i en

la compensació podria suposar una diferència significativa respecte els estudis previs, donant lloc a una possible millor recuperació funcional dels pacients depressius.

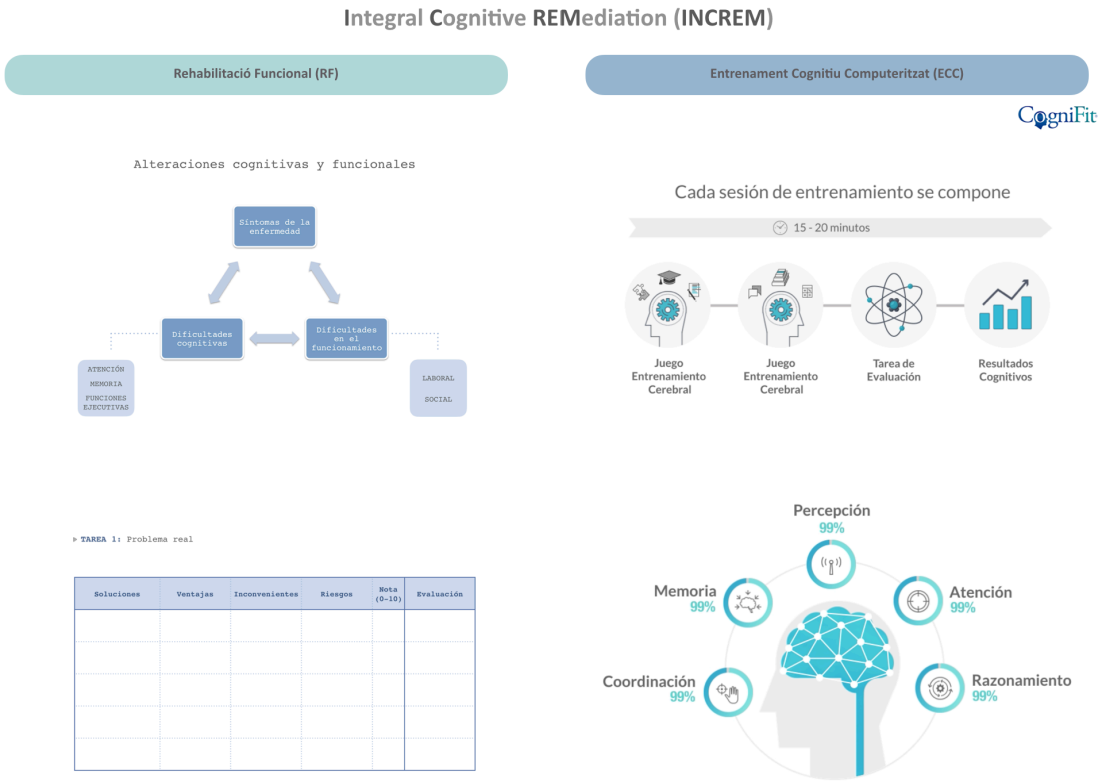

Figura 3. Esquema sessió d'INCREM (programes de Rehabilitació Funcional i d'Entrenament Cognitiu Computeritzat).

Un cop creada la nova intervenció procognitiva, es va dissenyar un assaig clínic aleatoritzat en pacients depressius en remissió clínica total o parcial per tal de valorar-ne l'eficàcia. Segons el disseny de l'estudi, els pacients serien aleatoritzats a una de les tres branques de tractament possible: programa INCREM, programa de Psicoeducació (Portella et al., 2020) o al tractament habitual, i serien avaluats (a nivell sociodemogràfic, clínic, neuropsicològic i funcional) en tres moments temporals diferents (basal, post-intervenció i longitudinalment) (**Figura 4**). Segons la bibliografia, el present estudi és el primer estudi que combina dues estratègies de remediació cognitiva (RF i ECC) a la vegada, amb l'objectiu de no només tractar els símptomes cognitius, sinó de traslladar aquestes millores a la vida quotidiana dels pacients.

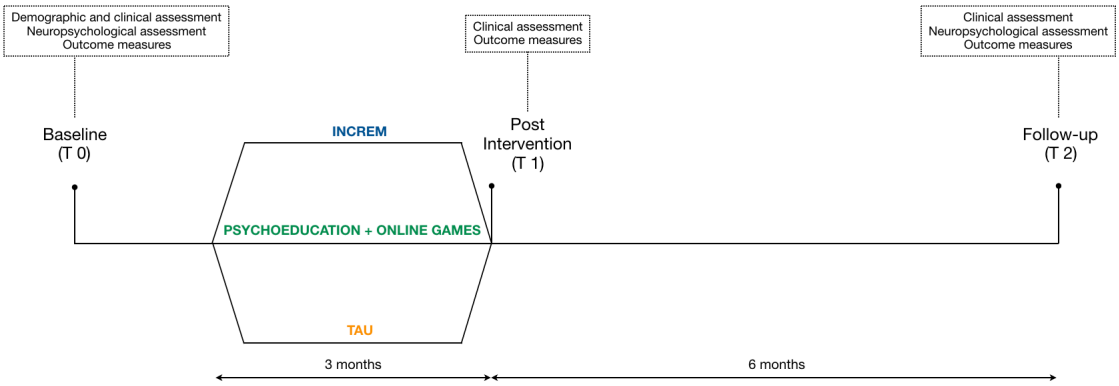

Figura 4. Diagrama de l'estudi INCREM.
Nota. INCREM: INtegral Cognitive REMediation; TAU: Treatment As Usual (Tractament habitual).

ESTUDI 4: *(en revisió)*

Per últim, es va portar a terme l'estudi 3. Així doncs, el quart estudi és un assaig clínic aleatori cec amb tres branques de tractament, i amb seguiment longitudinal. Es tracta d'una mostra de 52 pacients depressius en remissió clínica total o parcial, reclutats en el servei de Salut Mental del Hospital de la Santa Creu i Sant Pau. A banda d'estar en període de remissió (avaluat a través de l'escala HDRS-17), els participants havien de presentar dèficits cognitius objectius (valorat amb l'escala *Screening for Cognitive Impairment in Psychiatry* – SCIP) i mostrar dificultats en el funcionament psicosocial (a través de l'escala FAST). A l'inici de l'estudi i després del reclutament, es va portar a terme una avaluació sociodemogràfica, clínica, neuropsicològica i funcional dels participants. Seguit, els participants van ser aleatoritzats (seguint un mètode d'aleatorització per blocs) a una de les tres branques de tractament: programa INCREM, programa de psicoeducació o tractament habitual (TAU). Just en finalitzar els tres mesos de tractament (12 sessions, una per setmana) es va realitzar una nova avaluació utilitzant totes les mesures d'eficàcia (excepte la bateria neuropsicològica). I de nou, sis mesos després d'aquesta avaluació post-intervenció, es va dur a terme una nova avaluació completa.

Les anàlisis estadístiques es van executar mitjançant el programa SPSS i el programa estadístic R. Les variables neuropsicològiques van ser transformades a puntuacions T a través dels barems normatius de la població de referència. A partir d'aquestes, es van formar cinc dominis cognitius diferents: Atenció/Memòria de Treball, Memòria Verbal, Memòria Visual, Velocitat de processament i Funció Executiva. Per comprovar les diferències a nivell basal entre els grups de tractament es van realitzar ANOVAs i xi quadrada, en funció de la naturalesa de les variables sociodemogràfiques, clíniques, neuropsicològiques i funcionals. La distribució de la normalitat es va comprovar per a les mesures de resultat a través de la prova Kolmogorov-Smirnov. Amb l'objectiu d'avaluar l'eficàcia de la nova intervenció INCREM a través dels canvis en l'escala de funcionalitat FAST, es van portar a terme un model d'anàlisi de variància (ANOVA) amb mesures repetides. A més, també es van calcular els percentatges de canvi en les puntuacions de la FAST respecte a la línia base en les diferents línies de

tractament, les taxes de recuperació de les puntuacions FAST i una anàlisi d'interacció entre les puntuacions de FAST, branca de tractament i edat (en tres categories: adults joves, adults mitjana edat i adults majors). De manera similar a l'anàlisi del funcionament psicosocial, es van realitzar models d'anàlisi de variància (ANOVA) amb mesures repetides del funcionament cognitiu, tant amb l'escala SCIP com en els diferents dominis cognitius. L'única diferència, és que en el cas dels dominis cognitius, les mesures repetides només eren en dos moments temporals (basal i a llarg termini). Per últim, es van portar a terme models d'anàlisi de variància (ANOVA) amb mesures repetides per la resta de mesures de resultat i es van realitzar anàlisis descriptives d'aquestes mesures.

5. Resultats

5.1. Cognitive predictors of illness course at 12 months after first-episode of depression

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ABSTRACT

Background

Major Depressive Disorder (MDD) entails cognitive dysfunction in many cognitive domains, but it is still uncertain whether such deficits are present in the early stages. The purpose of the study is to determine the cognitive performance in first episode depression (FED) exploring the presence of different cognitive profiles, and the role of cognition in FED at baseline and long- term.

Methods

Ninety subjects (18–50 years) were included, 50 patients with a FED and 40 healthy controls. Participants were assessed with a neuropsychological battery, covering language, attention, verbal memory, processing speed and executive domains. Neuropsychological group comparisons were performed with MANOVAs. A hierarchical cluster analysis was run to identify clusters of patients with similar neuropsychological performance. Two generalized linear models were built to predict baseline HDRS-17 and changes at 12 months.

Results

Patients performed significantly worse than healthy controls in language, attention/working memory, verbal memory, processing speed and executive functioning, with moderate to large effect sizes (0.5 - 1). Two clusters were found: cognitively preserved patients (n=37) and cognitively impaired patients (n=13). Large effect sizes of cognitive impairment in FED were observed between the two cognitive clusters (preserved and impaired). Depressive symptoms at baseline were predicted by verbal memory (p=0.003), while 12-month changes were predicted by executive function (p=0.041) and language (p=0.037).

Conclusions

Cognitive performance predicted depressive symptoms at baseline and at follow-up, pointing to the usefulness of cognitive assessment even at the commencement of the illness.

KEYWORDS

Cognition; first-episode; major depression; cognitive predictors

INTRODUCTION

Cognitive dysfunction is considered a central characteristic of Major Depressive Disorder, MDD (Bortolato et al., 2015). Diminished ability to think or to concentrate or to make decisions is part of the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) for MDD. Currently, there is sufficient scientific evidence that proves the existence of cognitive impairment not only in the acute phase of the disease, but even in periods of remission of clinical symptoms (Rock et al., 2014). Cognitive dysfunction has been correlated with poorer occupational and psychosocial functioning, as well as with an increased risk of relapse (Evans et al., 2014; Hammar & Ardal, 2009). Despite it is well accepted that MDD entails cognitive dysfunction in attention, processing speed, memory and executive function, there is a lack of agreement on the specificity or the degree of such cognitive deficits.

Among the factors related with the inconsistencies in cognitive impairment, the mixture of patients included in previous studies could be the most relevant one, given that cognitive deficits may depend on the stage of the illness and on different depression trajectories (Hammar & Ardal, 2009), making it difficult to ascertain whether cognitive symptoms arise together with the rest of depressive symptoms. Therefore, a more adequate approach to disentangle this issue is to investigate cognitive functioning in a homogeneous sample with similar illness burden as for instance patients with a first episode of depression (FED). The scarce literature of cognitive functioning in FED shows that cognitive impairment is already observable in early stages of MDD (Ahern & Semkovska, 2017; Lee et al., 2012). But again, there still exists some controversy upon the degree of impairment, given that the majority of these studies base their conclusions on group differences, considering that patients would have a unique neuropsychological profile (i.e., averaging neurocognitive performance of all patients). Therefore, it might be necessary to define subgroups of patients taking into account their cognitive characteristics, as some patients could present cognitive deficits while others could not.

Yet, current literature on cognitive dysfunction in FED has not provided any evidence on the usefulness of assessing cognition at the commencement of the illness. Although nowadays research findings point towards a holistic perspective of major depressive symptomatology (i.e., including the core depressive symptoms and the cognitive ones), we are far from seeing that cognitive evaluation will help clinicians and psychotherapists when treating patients. Previous works have already determine that cognitive symptoms, in particular executive dysfunction, can remain beyond the acute episode (Ahern & Semkovska, 2017), as well as they can represent vulnerability factors for further relapses (Lee et al., 2012). Therefore, cognitive performance may be used as a predictive factor of long-term clinical manifestations, but no studies have been carried out on this regard.

The aims of this study were to determine the cognitive performance of patients with a first episode depression in order to explore the presence of different cognitive profiles; and to investigate whether

cognitive deficits at illness onset could predict baseline clinical profile and follow-up clinical outcomes. The first hypothesis is that there will be different levels of cognitive impairment in the group of FED patients. The second hypothesis is that cognitive performance together with other known factors will be predictive of initial and future depressive symptoms.

METHODS

Participants

Ninety subjects aged between 18 and 50 years were included in the present study, 50 patients fulfilling criteria for a first episode of depression (FED; DSM-IV-TR criteria) and 40 healthy controls. FED patients were recruited from the emergency psychiatric services of the Hospital Sant Pau in Barcelona and Hospital Parc Taulí in Sabadell, and healthy controls, from the community. Patients were antidepressant treatment-naïve or had taken antidepressants for less than two weeks prior of the study inclusion. Treatment regimens were homogeneous for all patients and included a Selective Serotonin Reuptake Inhibitor -SSRI- (mainly escitalopram 20mg/day or citalopram 40mg/day, and in five cases fluoxetine) plus benzodiazepines if needed. Depressive symptoms were evaluated using the 17-item Hamilton Depression Rating Scale (HDRS-17; Bobes et al., 2003; Hamilton, 1960) at the beginning of the study and twelve months after. Patients were required to have a total score ≥14 on the HDRS-17 for inclusion. Exclusion criteria for all participants were axis I comorbidity according DSM-IV-TR, significant physical or neurological illnesses or intelligence quotient (IQ) <80. Lifetime psychiatric diagnoses and first-degree relatives with psychiatric diagnoses were exclusion criteria for healthy controls. The study was approved by the Research Ethics Board of Hospital de Sant Pau and permission was obtained from the Ethics Committee of Hospital Parc Taulí to use coded information of their sample. The study was carried out in accordance with the Declaration of Helsinki. After a full explanation of the study protocol all subjects gave written informed consent.

Neuropsychological assessment

A comprehensive neuropsychological battery was administered to all participants at the beginning of the study. Neuropsychological testing covered the domains of language, attention, verbal and visual memory, and executive functions. Premorbid intelligence was estimated with Vocabulary subtest of the Wechsler Adult Intelligence Scale version III (WAIS-III; Wechsler, 1997). Language was measured by the semantic verbal fluency test (Category fluency; Benton & Hamsher, 1976) and Boston Naming Test (BNT; Kaplan et al., 1983). Attention and verbal short-term memory were assessed using the Digit Forward of the WAIS-III. Digit Backward (WAIS-III) was used to assess attention and verbal working memory performance. Continuous Performance test version II (CPT-II; Conners, 2000) was used to evaluate sustained attention. Verbal learning memory was tested by means of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964); using immediate recall (sum of trial 1 to 5) and delayed recall. Processing speed was evaluated using Digit Symbol Substitution subtest (DSST; WAIS-III) and Trail Making Test Part A (TMT-A; Reitan, 1958). Executive functioning was tested with Tower of London (TOL;

Portella et al., 2003), Trail Making Test Part B (TMT-B), categories and perseverative errors of Wisconsin Card Sorting Test (WCST; Heaton, 1981) and phonemic verbal fluency (Controlled Oral Word Association Test, COWAT; Benton & Hamsher, 1976). Performance of patients and healthy controls was compared at baseline, and it was then used to predict clinical outcomes after one year.

Data Analyses

The full dataset was inspected in order to assess the number and pattern of missing values. Variables with more missing values than a threshold of 5% were discarded. Imputation of below threshold missing data was done using plausible values drawn from a distribution specifically designed for each missing data point, as implemented in the Multivariate Imputation by Chained Equations R package (MICE; Van Buuren & Groothuis-Oudshoorn, 2011), using 100 imputations and 100 reiterations for each variable by means of a predictive matrix. The imputed data was then graphically analyzed to check consistency between the imputed and the raw data. Demographics and clinical variables were analyzed with the statistical software R using t-test for quantitative variables, and χ^2 and exact Fisher's test for categorical variables. Level of statistical significance was set at $p<0.05$ (two-tailed). Neuropsychological raw scores were transformed into z-scores. Group comparisons were performed with multivariate ANOVAs, which were carried out for each cognitive domain to analyze differences between patients and healthy controls. Before carrying out the MANOVAs, normal distribution was checked by means of Kolmogorov-Smirnov test. Those variables that did not fulfill normality were log-transformed or discarded. Effect sizes of differences between patients and healthy controls were calculated by means of Cohen's *d*.

To investigate cognitive characteristics of FED patients, a principal component analysis (PCA) was used for dimensionality reduction of neuropsychological data. The number of retained components was based on the scree plot, admitting eigenvalues above 1 (or close to 1 based on theoretical coherence of the model). The data used in the PCA were adjusted by IQ and age. The obtained components were then rotated and used to further create a hierarchical model using Ward's clustering criteria (Ward, 1963), so as to identify clusters (i.e. groups of patients with similar neuropsychological performance). New comparisons were then carried out to assess differences in demographic, clinical and neuropsychological variables among cluster groups at baseline. Clinical outcomes after one year were also compared among clusters, and effects sizes were also calculated. Finally, to determine cognitive, demographic and clinical predictors of clinical outcomes, two generalized linear models (least squares regression for continuous variables) were built using the HDRS-17 scores at baseline and the change in HDRS-17 at 12 months (Δ score= baseline HDRS-17 minus follow-up HDRS-17) as dependent variables. To limit the number of independent factors, only those clinical and demographic variables showing significant correlations with the dependent variables were entered into the models. This method was chosen to explore interactions between predictive variables. These analyses were run with the R statistics package (www.r-project.org).

RESULTS

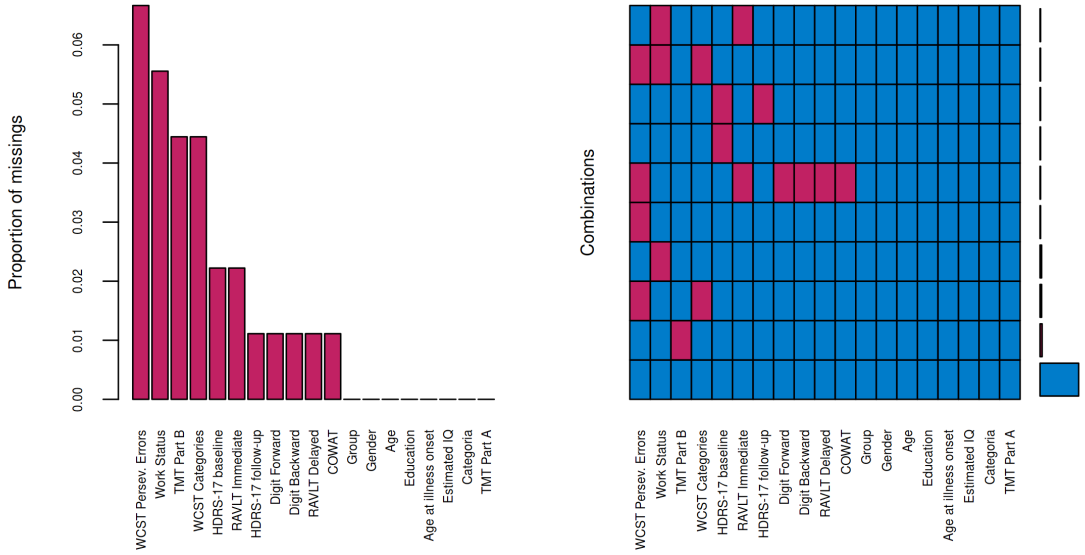
Table 1 displays mean and standard deviation for all demographics and clinical variables. There were no differences in gender and years of schooling between FED patients and healthy controls. By contrast, there was a significant difference in age (patients were older than HC), in baseline and 12 months HRDS-17 scores (patients had higher scores), in work status (patients were more unemployed or in sick-leave), and in premorbid IQ (patients had a lower IQ, within normal range). Most of the patients were on remission (HDRS-17<8) at the end of the follow-up (74% of patients).

Table 1. Mean scores (standard deviation) for demographic and clinical variables of all participants

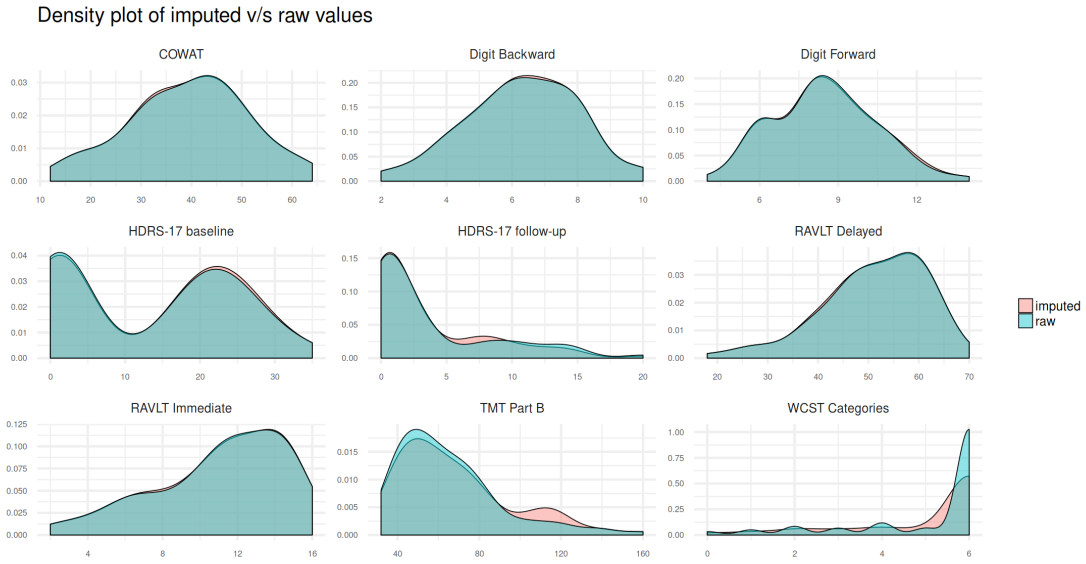
	FED (n=50)	**Healthy Controls** (n=40)	**Statistic**	**p**	**Cohen's *d***
Age, years	43.86 (10.61)	39.7 (9.05)	-2.01	.048	.42
Gender, *n (% females)*	30 (60)	24 (60)	0	.999	1*
Education, *years*	12.9 (3.73)	13.15 (3.02)	0.35	.726	.07
Work status, *n*			11.92	.018	2.2*
Active	24	30			
Unemployed	12	5			
Sick leave	11	1			
Students	3	4			
Estimated IQ	102.4 (11.7)	107.2 (9.19)	2.20	.030	.46
Clinical variables					
Age at illness onset	40.22 (10.46)				
HDRS-17 (baseline)	22.95 (4.71)	1.38 (1.53)	-30.45	<.001	6.16
HDRS-17 (12 months)	4.66 (5.2)	1.71 (2.66)	-3.48	<.001	.71

Note.
FED= First Episode Depression, HDRS= Hamilton Depression Rating Scale.
*Risk ratio

Observation of missingness pattern revealed that missing data points followed a random distribution (MAR; see graph of missingness pattern in **supplementary material 1**). BNT, CPT-II, DSST, TOL and perseverative errors of WCST were discarded because of non-normal distribution even after log-transformation or due to a percentage of missing data greater than 5%. Imputation of data was performed with baseline HDRS-17 scores (2% of missing values), follow-up HDRS-17 scores (1%), COWAT (1%), Digit Forward (1%) and Backward (1%), RAVLT immediate (1%), RAVLT delayed (2%), TMT part B (4%) and WCST Categories (4%). The imputed dataset analysis brought out that the imputed data followed the original distribution in all imputed variables (**Supplementary material 2** with graphs of probability density function with imputed and raw data).



Supplementary material 1. Graph of missingness pattern.



Supplementary material 2. Graphs of probability density function with imputed and raw data.

Table 2 displays neuropsychological tests' performance with the univariate effects for each test. The analyses revealed that patients performed significantly worse than healthy controls in Category fluency, COWAT, Digit forward, RAVLT immediate and delayed recall and TMT Part A and B with moderate to large effect sizes ranging between 0.5 to 1.

Table 2. Results of neuropsychological assessment for first-episode Major Depressive Disorder and controls

	FED (n=50)	**Healthy Controls** (n=40)	**t**	**p**	**Cohen's *d***
Language					
Semantic fluency (Category fluency)	18.86 (5.05)	24.12 (5.46)	4.70	<.001	1.00
Phonemic fluency (COWAT)	34.54 (10.97)	45.4 (10.08)	4.88	<.001	1.03
BNT	53.42 (5.36)	55.83 (2.76)	2.75	.007	.57
Attention / Working Memory					
Digit forward (WAIS-III)	8.13 (1.79)	8.98 (2.12)	2.02	.047	.43
Digit backward (WAIS-III)	6.29 (1.54)	6.33 (1.95)	.08	.935	.02
CPT Omissions	4.11 (2.58)	2.18 (2.67)	-3.46	<.001	.74
CPT Commissions	12.49 (4.96)	8.7 (5.98)	-3.22	<.001	.69
CPT Reaction Time	400.2 (56.61)	424.8 (65.37)	1.88	.064	.40
CPT Detectability	.86 (.32)	.99 (.55)	1.29	.201	.29
Verbal Memory					
RAVLT (Immediate recall)	47.96 (11.28)	55 (7.6)	3.53	<.001	.73
RAVLT (Delayed recall)	9.87 (3.95)	12.55 (1.97)	4.20	<.001	.86
Processing Speed					
TMT Part A	49.19 (18.29)	33.55 (11.31)	-4.96	<.001	1.03
DSST (WAIS-III)	64.11 (20.51)	73.13 (13.43)	2.51	.014	.52
Executive Function					
TMT Part B	75.38 (31.73)	59.5 (18.63)	-2.96	.004	.61
WSCT Categories	4.86 (1.83)	5.3 (1.34)	1.29	.200	.27
WCST Perseverative Errors	8.99 (8.28)	13.21 (11.36)	1.97	.005	.42
TOL	32.4 (6.32)	33.92 (5.57)	1.21	0.23	.26

Note.
FED= First Episode Depression, COWAT= Controlled Oral Word Association Test, BNT= Boston Naming Test, WAIS= Wechsler Adult Intelligence Scale, CPT= Continuous Performance Test, RAVLT= Rey Auditory Verbal Learning Test, TMT= Trail Making Test, DSST= Digit Symbol Substitution Test, WCST= Wisconsin Card Sorting Test, TOL= Tower of London.

Principal Component Analysis (PCA) of adjusted neuropsychological data offered four orthogonal dimensions which corresponded to four identifiable cognitive domains. The components were then rotated using a varimax rotation for an easier interpretation. The four retained components explained a cumulative variance of 71.19%. The variables included in component 1 were Digit forward and backward ("attention/working memory"); in component 2, immediate and delayed recall of RAVLT ("verbal memory"); in component 3, TMT Part A, TMT Part B, and WCST categories ("executive functioning") and in component 4, semantic and phonetic fluency ("language").

The hierarchical cluster analysis revealed a two-cluster solution, and patients were classified as cognitively preserved (37 patients) and cognitively impaired (13 patients). Patients with cognitive deficits showed subtle impairments in executive function (≤1SD) and significant impairment in attention/working memory and verbal memory (>1SD).

Comparisons of demographics and clinical variables between the preserved and impaired cluster are shown in **Table 3**. There were differences in age at illness onset and in years of education, whereas the rest of variables did not show significant differences. Regarding cognitive performance, **Figure 1** plots distribution of clusters by the four components solution of neuropsychological performance, where the

two clusters differed significantly in attention/working memory, verbal memory, and executive functioning components, where patients in the cognitively impaired cluster showed worse performance in most of the components. **Table 4** displays pair-wise comparisons of the tests included in the four cognitive components between the two clusters. The magnitude of differences between clusters ranged from 0.8 to 2.2, indicating large effect sizes.

Table 3. Mean scores (standard deviation) for demographic and clinic assessment across the clusters (only patients)

	Preserved Cluster (n=37)	**Impaired Cluster** (n=13)	**Statistic**	**p**	**Cohen's *d***
Age, years	42.24 (9.54)	48.46 (12.46)	-1.64	.12	.56
Gender, *n (% females)*	25 (68)	5 (38)	2.29	.130	.56*
Education, *years*	14.24 (2.64)	9.08 (3.8)	4.54	<.001	1.58
Work status, *n*			7.02	.071	.04*
Active	21	3			
Unemployed	7	5			
Sick leave	6	5			
Students	3	0			
Estimated IQ	103.8 (11.69)	98.46 (11.25)	1.45	.161	.47
Clinical variables					
Age at illness onset	38.81 (9.37)	44.23 (12.63)	-1.42	.017	.49
HDRS-17 (baseline)	22.53 (4.04)	24.15 (6.28)	-.872	.396	.31
HDRS-17 (12 months)	4.41 (5.36)	5.39 (4.84)	-.61	.548	.19

Note.
HDRS= Hamilton Depression Rating Scale.
*Risk ratio

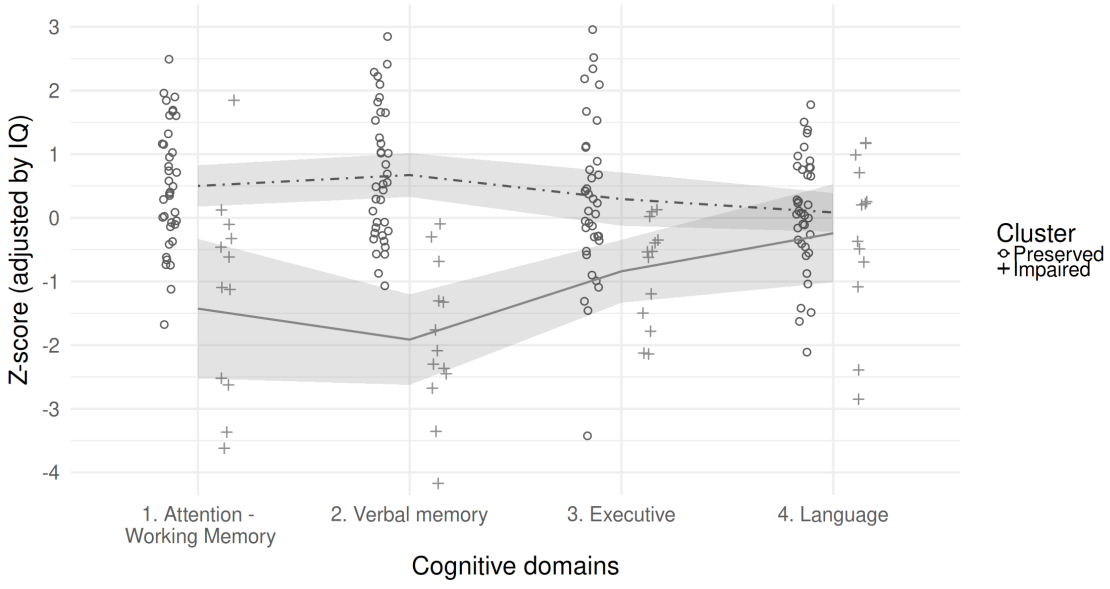


Figure 1. Graph illustrating mean z-scores of each cluster in each cognitive component (four-dimension solution in principal component analysis).

Note. The dash line represents preserved patients, and the continuous line represents impaired patients. Shaded areas represent standard deviation of means. Circles represent patients of preserved cluster and crosses represent patients of impaired cluster.

Table 4. Mean scores (standard deviation) for neuropsychological assessment across the clusters (only patients)

	Preserved Cluster (n=37)	**Impaired Cluster** (n=13)	**t**	**p**	**Cohen's *d***
Attention / Working Memory - Component 1					
Digit forward (WAIS-III)	8.49 (1.64)	7.11 (1.85)	2.38	.028	.79
Digit backward (WAIS-III)	6.73 (1.33)	5.05 (1.47)	3.63	.002	1.2
Verbal Memory - Component 2					
RAVLT (Immediate recall)	52.16 (8.4)	35.99 (9.92)	5.25	<.001	1.76
RAVLT (Delayed recall)	11.41 (3.15)	5.48 (2.35)	7.13	<.001	2.13
Executive Function - Component 3					
TMT Part A	43.32 (11.77)	65.89 (23.27)	-3.35	.005	1.22
TMT Part B	62.23 (23)	112.8 (21.73)	-7.11	<.001	2.26
WCST Categories	5.67 (.91)	2.58 (1.85)	5.78	<.001	2.12
Language - Component 4					
Semantic fluency (Category fluency)	19.73 (4.78)	16.38 (5.16)	2.05	.054	.67
Phonemic fluency (COWAT)	36.16 (10.81)	29.92 (10.5)	1.83	.081	.59

Note.
WAIS-III= Wechsler Adult Intelligence Scale-III, RAVLT= Rey Auditory Verbal Learning Test, TMT= Trail Making Test, WCST= Wisconsin Card Sorting Test, COWAT= Controlled Oral Word Association Test

The generalized linear models used to predict HDRS-17 at baseline and change at follow-up included the 4 cognitive components of PCA (i.e., attention/working memory, verbal memory, executive functioning and language), years of schooling and age at illness onset. Depressive symptoms at baseline were significantly predicted only by verbal component (β=–1.44; p=0.003). When predicting change in the HDRS-17 at 12 months, the model showed that executive (β=0.055; p=0.041) and language components β=0.06; p=0.037) were significant predictors.

DISCUSSION

The present study shows that FED patients displayed a moderate cognitive impairment as compared to healthy controls across different cognitive domains, particularly in language, attention/working memory, verbal memory, processing speed and executive functioning. The moderate effect may be explained by the presence of two different clusters within patients' performance: the preserved cluster, which was comprised by patients with non-impairment of any cognitive domain; and the impaired cluster, which was constituted by patients with reduced cognitive performance on most of the cognitive components. These findings indicate that there are a 26% of FED patients who display significant cognitive deficits, affecting attention/working memory and verbal memory, while there are other patients with a subtle or even absent cognitive impairment. On the other hand, the results show that cognitive performance at illness onset can predict initial and follow up depressive symptoms. In particular, the findings showed that greater baseline depressive symptoms were predicted by verbal memory. Clinical changes after twelve months were predicted by executive functioning and language. Therefore, cognitive assessment should be included in clinical settings so as to better capture the characteristics of a FED that may further determine the course of the illness.

FED patients displayed cognitive disturbances in the cognitive domains commonly altered in MDD (Lee et al., 2012). These findings give support to the hypothesis that cognitive impairment is present across illness, even at early stages. Moreover, patients with similar clinical characteristics could present different degrees of cognitive affectation, indicating that cognitive impairment is not necessarily a consequence of depressive symptomatology (Reppermund et al., 2009; Rock et al., 2014). Effect sizes in the current study were still moderate to large when compared to healthy controls. Perhaps, cognitive deficits may not be a global characteristic of all patients with MDD, but of a particular subgroup of patients. In this regard, when exploring the cognitive performance with clustering analysis, the results revealed two different profiles, where some patients were cognitively preserved while others were impaired. It is reasonable that the existence of different cognitive profiles occur in any stage of the illness, underlying the moderate effect sizes of previous studies, as well as the lack of agreement on the specific cognitive deficits. This neurocognitive variability has already been observed in depressed and bipolar patients (Burdick et al., 2014; Cotrena et al., 2017; Iverson et al., 2011; Solé et al., 2016). Therefore, these findings reflect an important issue to bear in mind so as to establish more adequate treatments, given that cognitive impairment is closely related to psychosocial functioning (Lam et al., 2014; McIntyre et al., 2013).

Patients in the impaired cluster showed significant deficits in attention/ working memory and verbal memory and subtle deficits in executive function. These cognitive domains are the most replicated in studies of cognitive performance of depressed population (Ahern & Semkovska, 2017; Gorwood et al., 2017; Lee et al., 2012), suggesting a key role in the clinical manifestation of depression, as well as in the clinical course. In this regard, deficits in attention/working memory have been considered as a trait marker for a first episode of MDD, which persists in remission (Lee et al., 2012; Paelecke-Habermann et al., 2005). Similarly, memory dysfunction has been extensively studied across first-episode and recurrent MDD (Lee et al., 2012; Reischies & Neu, 2000). The majority of studies have shown persistent memory deficits even in remitted patients (Gorwood et al., 2008; Maeshima et al., 2012; Neu et al., 2012), but the findings also suggest that memory is the most sensitive domain to clinical state, as improvement in mood has been strongly related to improved verbal memory (Ahern & Semkovska, 2017; Douglas et al., 2009; Lee et al., 2012), especially after successful treatment (Douglas & Porter, 2009; Serra-Blasco et al., 2015). In fact, it has been described that verbal memory impairment worsens with subsequent depressive episodes (Douglas & Porter, 2009; gorwood et al., 2008). With regard to executive functioning, a meta-analysis suggests a permanent impairment across stages of the illness and even in remission (Snyder, 2013). Verbal memory also appears to be useful in predicting depressive symptoms at baseline, pointing out the value of cognitive assessment at illness onset. The link between depressive symptoms and verbal memory impairment is well known in MDD (Preiss et al., 2009), but few works have determined this association at illness onset.

However, patients in the impaired cluster showed less years of education and older age at onset. Level of education has already been related to cognitive dysfunction in FED (Hermens et al., 2011; Lee et al., 2012; Porter et al., 2007), which could be mirroring the impact of cognitive reserve (CR) on depressive symptoms, as lower CR has been related with more severe clinical expression and worse psychosocial functioning (Barnett et al., 2006). Our findings on age at onset are in line with a previous study by Xu and colleagues, where later age at onset in patients with either MDD or bipolar disorder was associated with worse cognitive performance (Xu et al., 2012). In any case other works have failed to find such association (Daniel et al., 2013; Neu et al., 2005).

Longitudinal approaches have shown that cognitive performance can be predictive of illness trajectories in MDD (Dawson et al., 2017; Rock et al., 2014), and a previous work showed that neuropsychological impairments could identify subjects at risk of developing a first episode of depression and be predictors of clinical and functional remission (Cléry-Melin & Gorwood, 2016; Mannie et al., 2009). However, longitudinal studies in FED patients are still scarce (Roca et al., 2015a). Our findings provide new evidence of the usefulness of cognitive data to predict illness outcomes. In particular, executive dysfunction and language at illness onset were relevant predictors of depressive symptoms at long-term also in a sample of FED patients, while attention/working memory and verbal memory were not. These findings indicate that fronto-temporal functioning may be a stronger factor of illness trajectories. Indeed, the association of executive functioning and language with change in depressive symptoms after one year may show the implication of the fronto-temporal circuit in the clinical manifestation along time. However, other relevant factors were not included in the model, and this may be explained by the high remission rates observed in our sample, which could have prevented to find other associations, including verbal memory as it is known that improvements in mood are associated with improvements in memory (Preiss et al., 2009). In any case, treatment interventions for depression should therefore be directed to those individuals with impaired cognitive functioning so as to reach a global remission, which in turn, may improve psychosocial functioning, even at the onset of the disease (Lam et al., 2014; McIntyre et al., 2013). Possibly, an early intervention may improve patient's quality of life and even prevent new episodes, although no evidence is available yet.

Some limitations should be noted in this study. First, the study involved a small sample of FED and some findings could have been missed. Future studies with larger samples are needed to identify cognitive clusters accounting for the relationship between clinical/demographic characteristics and cognitive and psychosocial functioning. Psychotic symptoms were not specifically explored in this sample. The high rates of treatment response and remission of the present sample might not be representative of FED patients, but the findings still provide useful information about good response. A further limitation is a lack of follow-up of neuropsychological tests. However, as previous studies identified practice effects (Reppermund et al., 2009), neuropsychological performance in this study was used as a cognitive predictor in order to avoid these effects. In fact, other works have suggested that a cognitive

assessment at baseline can help in identifying vulnerable patients to suffer further episodes or to have worse responses (Dawson et al., 2017). Missing data was another limitation of this study. Although a Multivariate Imputation by Chained Equations in R (MICE; Van Buuren & Groothuis-Oudshoorn, 2011) was used, as it is one of the most valid approaches to deal with missing data, the resulting sample could have entailed non-controlled effects on the results. Finally, our conclusions arise from group differences which might not be completely useful for clinical practice, but the findings show that it is important to bear in mind whether a patient does present cognitive deficits at illness onset because this may determine treatment response, future relapses and functional outcomes.

In conclusion, FED patients showed a moderate cognitive impairment across different domains. Among patients, two different clusters were identified: preserved and impaired, indicating that only some patients displayed a cognitive dysfunction in the early stages. Interestingly, cognitive performance predicted depressive severity both at baseline and long-term, pointing the necessity of prevention (through boosting cognitive reserve) and individualized treatment of cognitive functioning (through procognitive agents or remediation programs) even in these very early stages of the illness.

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CONFLICTS OF INTEREST

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CONTRIBUTORS

MJP, EA and VP conceived the idea and designed the protocol for the present study. Authors MCS, JDA, EA and MM performed the selection of the patients, and were responsible of their treatment and follow-up. Authors MVG and AKG managed data collection and analyses under the supervision of JT. MVG and MSB manage the literature searches and clinical/neuropsychological data collection. Authors MSB and NC helped in the interpretation of the results. MVG wrote the first version of the manuscript under the supervision of MJP. All authors contributed to the writing of the final version of the manuscript and gave their approval to it.

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5.2. Dealing with heterogeneity of cognitive dysfunction in acute depression: a clustering approach

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ABSTRACT

Background

Heterogeneity in cognitive functioning among major depressive disorder (MDD) patients could have been the reason for the small-to-moderate differences reported so far when it is compared to other psychiatric conditions or to healthy controls. Additionally, most of these studies did not take into account clinical and sociodemographic characteristics that could have played a relevant role in cognitive variability. This study aims to identify empirical clusters based on cognitive, clinical and sociodemographic variables in a sample of acute MDD patients.

Methods

In a sample of 174 patients with an acute depressive episode, a two-step clustering analysis was applied considering potentially relevant cognitive, clinical and sociodemographic variables as indicators for grouping.

Results

Treatment resistance was the most important factor for clustering, closely followed by cognitive performance. Three empirical subgroups were obtained: cluster 1 was characterized by a sample of non-resistant patients with preserved cognitive functioning (n = 68, 39%); cluster 2 was formed by treatment-resistant patients with selective cognitive deficits (n = 66, 38%) and cluster 3 consisted of resistant (n=23, 58%) and non-resistant (n=17, 42%) acute patients with significant deficits in all neurocognitive domains (n = 40, 23%).

Conclusions

The findings provide evidence upon the existence of cognitive heterogeneity across patients in an acute depressive episode. Therefore, assessing cognition becomes an evident necessity for all patients diagnosed with MDD, and although treatment resistant is associated with greater cognitive dysfunction, non-resistant patients can also show significant cognitive deficits. By targeting not only mood but also cognition, patients are more likely to achieve full recovery and prevent new relapses.

KEYWORDS

Acute episode; analysis; cluster; cognition; heterogeneity; major depressive disorder

INTRODUCTION

Research over the last decade has been mainly focused on cognitive performance after a depressive episode (Semkovska et al., 2019) so as to explore difficulties in cognition as an independent facet of clinical manifestation of major depressive disorder (MDD). Some studies report improvements in cognitive performance upon remission of depression (Biringer et al., 2007) whereas others suggest that cognitive impairment persists during clinical remission (Bora et al., 2013; Hasselbalch et al., 2011). The disparity in these results might be explained by the fact that a number of patients do not show any cognitive impairment over the course of the disorder, and others display significant cognitive difficulties even in a non-symptomatic phase. In this regard, a recent study has even found discrete neurocognitive subgroups suggesting the presence of substantial heterogeneity in neurocognitive performance in MDD patients with current affective stability (Pu et al., 2018). It is noteworthy to mention that although patients were in clinical remission, some of them were classified as globally impaired showing moderate to severe cognitive impairment. Therefore, it would be reasonable to think that unresolved cognitive deficits were already present during the acute phase of MDD, from which it could be inferred that different cognitive profiles existed among patients. Despite such a heterogeneity being frequently proposed as an explanation for disparate findings in cognitive performance during a depressive episode (Hammar & Ardal, 2009; Lee et al., 2012), it has scarcely been investigated. A recent study by our group has already found two distinguishable cognitive profiles in first-episode patients (Vicent-Gil et al., 2018), whereas other reports used mixed samples of mood disorders (Cotrena et al., 2016; Iverson et al., 2011).

Previous studies have described that cognitive dysfunction could be associated with more severe manifestations of the disease (Serra-Blasco & Lam, 2019), such as early/late illness onset, symptom severity (McDermott & Ebmeier, 2009), number of previous depressive episodes (Semkovska et al., 2019) and a higher level of resistance to antidepressant strategies (Murrough et al., 2015; Pimontel et al., 2016; Serra-Blasco et al., 2015). All these studies did not take into account the possible heterogenic cognitive profiles among the included patients, which could have explained the small-to-moderate effect sizes reported so far. Apart from that, other sociodemographic variables, such as years of schooling (Venezia et al., 2018) and age (Dotson et al., 2008), could also be associated with lower cognitive performance. In fact, two recent studies on clustering analysis of cognitive functioning have shown that the most affected cognitive profile was characterized by poorer general functioning (i.e. poorer intellectual ability; Pu et al., 2018; Vicent-Gil et al., 2018).

Recent studies have reported an association of cognitive dysfunction with worse psychosocial functioning, both at work performance and in social relationships (Clark et al., 2016; Cotrena et al., 2016; Evans et al., 2014). Considering the above, it might be useful to identify those patients with cognitive impairment during an acute episode of depression, to try to cope with cognitive deficits while at the same time improving the patients' psychosocial functioning without having to wait to treat those deficits after clinical remission. So far, only one of the studies mentioned in a sample of first episode of

depression has analyzed neuropsychological heterogeneity in the acute stage of the illness revealing two distinguishable cognitive profiles (preserved and impaired clusters) (Vicent-Gil et al., 2018). Some patients were classified as cognitively impaired showing significant deficits in attention/working memory and verbal memory and subtle impairment in executive function, whereas the rest did not show any cognitive deficit. Unfortunately, cognition is not routinely evaluated in all MDD patients [as reported by McAllister-Williams et al. (2017) in the UK], and the presence of cognitive dysfunction in a non-negligible percentage of them still represents an unresolved problem, which derives in increased social and health costs.

Even though there seems to be some evidence about the heterogeneity in cognitive functioning among MDD patients (see Douglas et al., 2018), no studies have attempted to identify subgroups of acute patients considering the factors mentioned above. The aim of the current study is to identify clusters of MDD patients with an acute episode using cognitive, clinical and sociodemographic measures as indicators of grouping. We hypothesize that different cluster groups will emerge based on their cognitive, clinical and sociodemographic characteristics. In addition, we also expect that most cognitively affected patients will show worse psychosocial adaptation.

METHODS

Participants

A sample of 174 participants aged 18 to 65 years old was selected from the outpatient unit at the Psychiatry Department of the Hospital Universitari Parc Taulí, from part of a broader project studying the cognitive functioning in major depression (Serra-Blasco et al., 2019). The patients fulfilled the inclusion criteria of a current episode of Major Depressive Disorder (MDD; DSM-IV-TR criteria). Diagnosis was double-checked by two experienced psychiatrists and validated through clinical reports. Exclusion criteria for all participants was the following: (i) presence of any neurological disease, (ii) medical illness with a known impact on cognitive functioning, (iii) intelligence quotient (IQ) <85, (iv) presence of a comorbid axis I diagnosis with the exception of anxiety disorders and dysthymia, (v) past or current substance abuse or (vi) any axis II diagnosis according to the DSM-IV-TR. Participants were on medication at the time of evaluation. Patients were invited to participate in this cross-sectional study, which included a clinical and neuropsychological assessment conducted by experienced research neuropsychologists. The study was set following the principles of the Declaration of Helsinki and was approved by the Research Ethics Board of the Institut d'Investigació i Innovació Parc Taulí (I3PT) at Hospital Universitari Parc Taulí. All participants gave their written informed consent after a full and comprehensive explanation of the study.

Clinical and demographic assessment

Clinical and demographic variables were obtained during a semi-structured interview, which covered age, sex, years of schooling, age at illness onset, number of episodes and duration of illness. Medication use at the time of evaluation was categorized as: no medication, monotherapy with antidepressants,

antidepressants plus benzodiazepines, and combination of antidepressants with one or more psychotropic drugs (e.g., antipsychotics, lithium, anticonvulsants). Depressive symptomatology was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960; bobes et al., 2003). The Maudsley Staging Method (MSM; Fekadu et al., 2009) was administered to assess the level of treatment-resistance. MSM includes information about duration and severity of depression, antidepressant treatments, augmentation strategies and electroconvulsive therapy (ECT) providing two categories: non-resistant (scores 3-6) and resistant (scores 7-15).

Neuropsychological assessment

The neuropsychological battery included the following tests: Digit Span of the Wechsler Adult Intelligence Scale version IV (WAIS-IV; Wechsler, 2008); Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941); Digit Symbol Substitution Test (DSST; WAIS-IV); Trail Making Test Part A (TMT-A), and Trail Making Test Part B (TMT-B; Tombaugh, 2004); Wisconsin Card Sorting Test (WCST; Heaton, 1981); Similarities subtest (WAIS-IV); semantic verbal fluency test (Category fluency; Benton & Hamsher, 1976; Peña-Casanova et al., 2009) and phonemic verbal fluency (PMR, adapted for Spanish speaking population; Peña-Casanova et al., 2009; Casals-Coll et al., 2013). Premorbid intelligence (estimated IQ) was assessed with Vocabulary Subtest of the WAIS-IV and it was used to compare cognitive profiles after the clustering analysis.

Functional assessment

Functioning Assessment Short Test (FAST; Rosa et al., 2007) was used to evaluate autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The scores range from 0-72 with higher values indicating more disability. A score of ≥12 represents a mildly to severe functional impairment (Bonnín et al., 2018).

Data Analyses

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 21. Neuropsychological raw scores were converted to z-scores using normative data. In order to reduce the number of neuropsychological variables (Mur et al., 2007; Miskowiak et al., 2017), cognitive domains were defined using a principal component analysis (PCA). The number of retained components was decided upon the resulting scree plot, admitting eigenvalues above or close to 1 (based on theoretically-driven decision). These components (cognitive domains) were then rotated and used for a cluster analysis.

To identify homogeneous subgroups of patients, a two-step clustering analysis was carried out based on cognitive domains, stage of treatment-resistance (MSM), depressive symptomatology (HDRS-17), number of depressive episodes, age and years of schooling. This two-step analysis is designed to use categorical and continuous variables in large samples. It represents an extra value to previous works as

other relevant variables such as treatment response can be included. During the first step, subjects are preclustered into small subgroups using a sequential clustering approach. In the second step, subclusters from the first are entered as inputs and grouped into the best number of clusters according to a hierarchical clustering method (Norusis, 2011). The determination of the optimal numbers of clusters is based on the Akaike Information Criterion (AIC) and the log-likelihood distance, taking as the best solution the large ratio of AIC changes and the large ratio of distance measures. The final model is based on different criteria (Nylund et al., 2007): (i) the highest cohesion and separation of the resulted clusters measured with the Silhouette's index, (ii) the best clinical coherence and (iii) an adequate number of patients in each cluster to facilitate statistical analyses of comparison. Also, as a final result, the analyses provide a ranking of the importance of each predictor entered in the model. The greater the importance measure, the more relevant the variable is considered in the formation of the cluster.

Demographic, clinical and functional variables were analysed among resulting clusters in each group of patients by means of one-way ANOVAs or chi-square when appropriate, and effect-sizes were reported, as well.

RESULTS

The principal component analysis of neuropsychological data extracted four orthogonal dimensions that corresponded to four cognitive domains and explained a 74% of cumulative variance. The four cognitive domains were: (i) Attention/Working Memory domain, which included the forward and backward Digit Span; (ii) Verbal Memory domain, composed by RAVLT first trial, immediate recall and delayed recall; (iii) Executive Function domain, with TMT Part A, TMT Part B, DSST and number of categories from WCST; and (iv) Verbal Ability domain which included PMR, semantic fluency and Similarities. See **supplementary Table 1** with a brief summary of outcome measures for each test.

Supplementary Table 1. Neuropsychological Assessment

Cognitive Domains*	Neuropsychological Test	Subtest	Outcome measure	Cognitive Function
ATTENTION WORKING MEMORY	Digit Test (Wechsler Adult Intelligence Scale, version-IV)	Digit forward	Sum of correct responses	Selective attention
		Digit backward	Sum of correct responses	Verbal Working Memory
VERBAL MEMORY	Rey Auditory Verbal Learning Test (RAVLT)	First Trial	Sum of trial 1	Short term auditory-verbal memory
		Immediate recall	Sum of trial 1 to 5	Verbal learning
		Delayed recall	Sum of trial 6, after 25-30'	Long-term auditory-verbal memory
EXECUTIVE FUNCTION	Trail Making Test (TMT)	Part A (TMT-A)	Time taken to complete the test	Cognitive processing speed
		Part B (TMT-B)	Time taken to complete the test	Set-shifting ability
	Digit Symbol Substitution Test (DSST; WAIS-IV)	-	Sum of correct responses	Motor speed, attention and visuoperception
	Wisconsin Card Sorting Test (WCST)	-	Number of categories completed	Categorization and shifting abilities
VERBAL ABILITY	Category Fluency	Animals	Sum of correct responses	Semantic verbal fluency
	Phonemic Fluency	PMR	Sum of correct responses	Phonemic verbal fluency
	Similarities subtest (WAIS-IV)	-	Sum of correct responses	Logical thinking and verbal abstract reasoning

Note. *Cognitive domains were based on a Principal Component Analysis (PCA).

The two-step clustering analysis resulted in a three-cluster solution, which was selected as being the most optimal one based on a fair Silhouette's index (equal to 0.3, see **supplementary Figure 1**), on the clinical interpretability from previous studies, and on the number of patients in each cluster. As can be observed in **Figure 1**, the stage of treatment-resistance obtained the highest relevance for clustering with a predictor importance of 1.0, followed by verbal ability, executive function, attention/ working memory and verbal memory with values ranging between 0.8 and 0.5. Depressive symptomatology, years of schooling, age and number of depressive episodes obtained the lowest relevance for clustering. **Table 1** presents the centroids for the predictors, mean values of quantitative variables and percentage distribution for the categorical variable treatment resistance.

Supplementary Figure 1. Silhouette measure of cohesion and separation

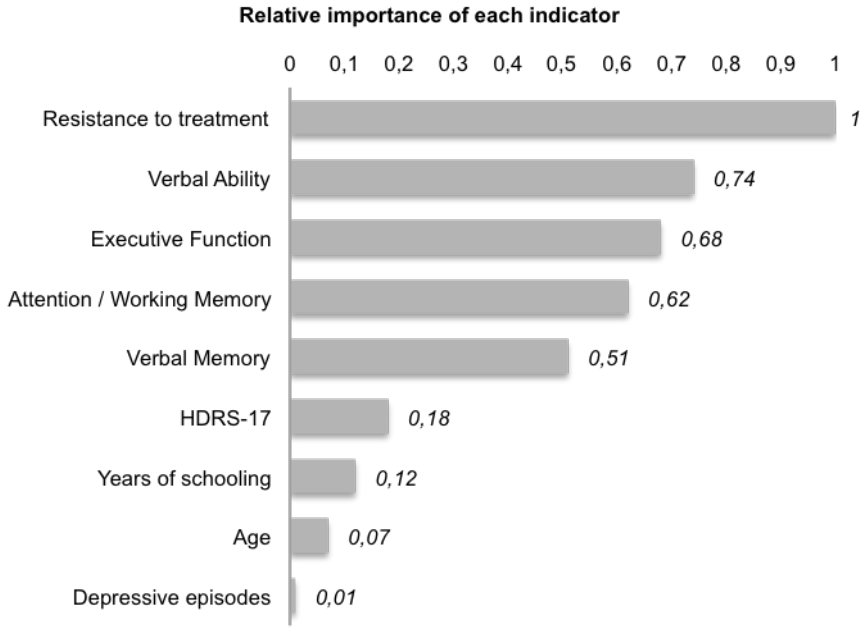


Figure 1. Clustering summary: relative importance of each indicator

Table 1. Clustering summary: centroids

	C1	C2	C3	Combined
Categorical indicators				
MSM non-resistant*	80%	0%	20%	100%
MSM resistant*	0%	74.2%	25.8%	100%
Quantitative indicators (means)				
Verbal Ability	-.46	-.71	-1.86	-.88
Executive function	-.45	-.79	-1.83	-.9
Attention / Working Memory	-.51	-.74	-1.71	-.88
Verbal Memory	-.49	-1.07	-1.92	-1.04
HDRS-17	17.15	19.33	23.25	19.38
Years of schooling	10.5	9.97	8.05	9.74
Age	52.16	54.97	51.95	53.18
Depressive episodes	2.19	2.41	2.43	1.35

Note. MSM: Maudsley Staging Method, HDRS: Hamilton Depression Rating Scale.
*MSM non-resistant (scores 3-6), MSM resistant (scores 7-15).

Figure 2 illustrates a radar chart that shows the profile of the clusters within the different predictors of the model (quantitative variables were transformed into z-scores for a better comprehension of the figure). The first cluster (C1) was classified as cognitively preserved (n=68, 39%) and it was characterized by a sample of non-resistant patients. The second cluster (C2) included 66 patients (38%) classified as selectively impaired and all patients were treatment-resistant. And cluster 3 (C3) included globally impaired patients (n=40, 23%) with significant deficits in all neurocognitive domains, being 23 patients classified as resistant (58%) and 17 as non-resistant (42%).

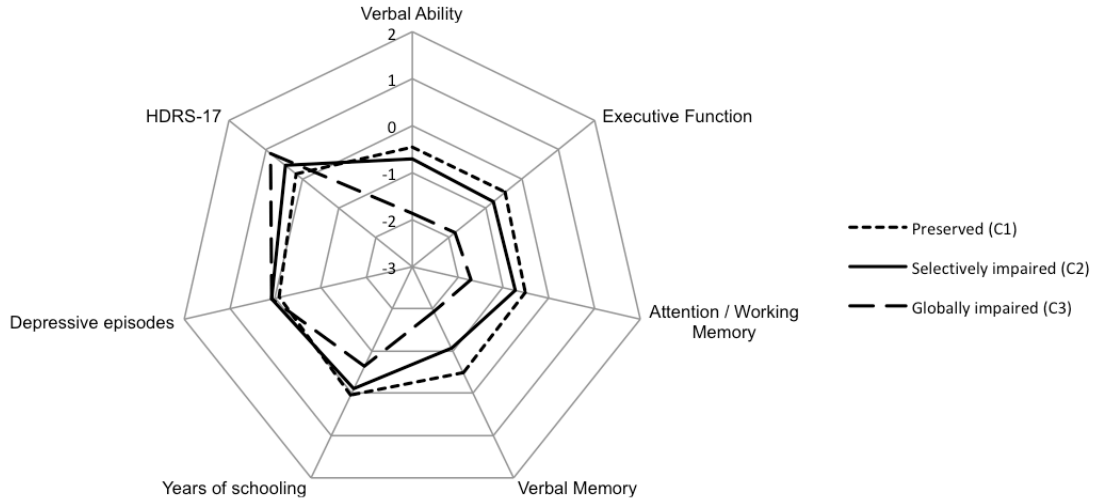


Figure 2. Radar chart for the distribution of the indicators of the model.

*HDRS-17: Hamilton Depression Rating Scale

Tables 2 and **3** display comparisons among the three clusters for demographic, clinical and functional variables and for cognitive tests. The three clusters differed in terms of cognitive performance (see **supplementary Figure 2**), in which C1 patients (cognitively preserved) scored within normal range in almost all the tests (with the exception of number of categories). C2 patients (selectively impaired) obtained scores below 1SD in specific tests evaluating memory and executive functioning. And C3 patients (globally impaired) showed significant alterations in almost all the neuropsychological tests (with z-scores ranging between -1 to -2). *Posthoc* comparisons of C3 (globally impaired patients) to C1 and C2 showed large effect sizes in all cognitive variables (Cohen's $d > 0.8$, with the exception of first trial in RAVLT in the contrast C2 vs. C3). With regard to functional assessment, significant differences were also observed, in which globally impaired patients showed the worst outcomes.

Table 2. Mean scores (standard deviation) for demographic and clinical variables across clusters.

	Clusters			Statistics		Post-hoc			Cohen's *d**		
	C1 Preserved (n=68)	**C2** Selectively impaired (n=66)	**C3** Globally impaired (n=40)	F or X^2	p	C1 vs C2	C1 vs C3	C2 vs C3	C1 vs C2	C1 vs C3	C2 vs C3
Age, *years*	52.16 (8.62)	54.97 (6.22)	51.95 (7.97)	2.94	.056	.104	1.0	.150	.37	.03	.42
Sex, *female n (%)*	49 (72.1)	40 (60.6)	33 (82.5)	5.9	.052	.16	.22	.018	.12	.12	.23
Educational level, *years*	10.5 (3.36)	9.97 (3.29)	8.05 (2.03)	8.29	<.001[a]	.96	<.001[a]	.006	.16	.88	.7
Estimated IQ, *T-score*	51.68 (8.27)	49.52 (7.49)	43.3 (3.67)	17.63	<.001[a]	.246	<.001[a]	<.001[a]	.27	1.31	1.05
Age at illness onset, *years*	42.13 (12.12)	42.17 (9.76)	38.8 (12.23)	1.35	.262	1.0	.423	.418	.00	.27	.30
Number of episodes, *n*	2.19 (1.42)	2.41 (1.2)	2.43 (1.47)	.57	.566	1.0	1.0	1.0	.17	.17	.01
Illness duration, *months*	127.3 (122.07)	171.68 (110.38)	171.63 (145.52)	2.67	.073	.118	.221	1.0	.38	.33	.00
HDRS-17, *total score*	17.15 (6.03)	19.33 (6.56)	23.25 (4.9)	12.99	<.001[a]	.110	<.001[a]	.004	.35	1.11	.68
Comorbidities, *n (%)*	20 (29.4)	21 (31.8)	18 (45.0)	.294	.230	.762	.101	.173	.03	.16	.13
Anxiety disorders, n (%)	3 (4.4)	6 (9.1)	6 (15.0)	.361	.164	.279	.055	.352	.09	.19	.09
Dysthymia, n (%)	17 (25.0)	17 (25.8)	12 (30.0)	.349	.840	.920	.571	.635	.01	.05	.05
MSM, *resistant n (%)*	0 (0)	66 (100)	23 (58)	134.9	<.001[a]	<.001[a]	<.001[a]	<.001[a]	1.0	.68	.56
FAST, *total score*	36.49 (13.39)	42.68 (14.19)	47.93 (13.48)	9.17	<.001[a]	.03	<.001[a]	.176	.45	.85	.38
Current medication, *n (%)*				18.98	<.001[a]	<.001[a]	.01	.482	.38	.29	.07
AD	30 (44.1)	7 (10.6)	8 (20)								
AD + BZD	22 (32.4)	22 (33.3)	11 (27.5)								
AD + Others	14 (20.6)	37 (56.1)	20 (50)								
Medication-free	2 (2.9)	0 (0)	1 (2.5)								

IQ: Intelligence quotient, HDRS: Hamilton Depression Rating Scale, MSM: Maudsley Staging Method, FAST: Functional Assessment Short Test, AD: Antidepressant, BZD: Benzodiazepines, Others: Antipsychotics, Lithium or Anticonvulsants.

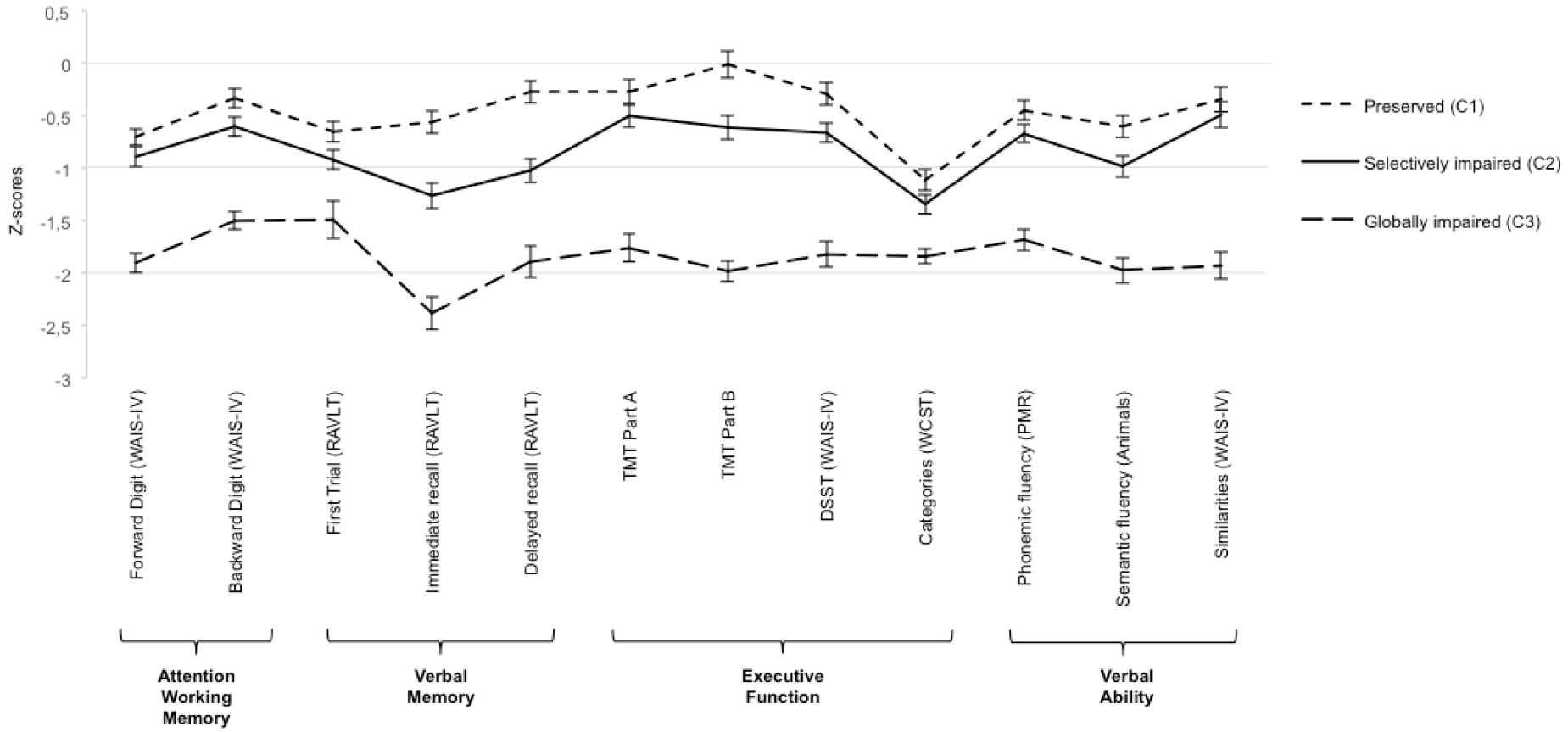
* Cramer's *V* for categorical variables. [a] Analysis of variance or χ2 tests statistically significant after applying Bonferroni correction for multiple comparisons (p<.004)

Table 3. Mean scores (standard deviation) for cognitive variables across clusters.

	Clusters			Statistics		Post-hoc			Cohen's *d*		
	C1 Preserved (n=68)	**C2** Selectively impaired (n=66)	**C3** Globally impaired (n=40)	F	p	C1 vs C2	C1 vs C3	C2 vs C3	C1 vs C2	C1 vs C3	C2 vs C3
ATTENTION / WORKING MEMORY	-.51 (-.88)	-.74 (.62)	-1.71 (.45)	54.41	<.001[a]	.071	<.001[a]	<.001[a]	.30	1.72	1.79
Forward Digit (WAIS-IV)	-.7 (.66)	-.89 (.77)	-1.9 (.59)	41.32	<.001[a]	.331	<.001[a]	<.001[a]	.26	1.92	1.47
Backward Digit (WAIS-IV)	-.33 (.79)	-.6 (.75)	-1.5 (.54)	34.80	<.001[a]	.091	<.001[a]	<.001[a]	.35	1.73	1.38
VERBAL MEMORY	-.49 (.74)	-1.07 (.72)	-1.92 (.85)	44.52	<.001[a]	<.001[a]	<.001[a]	<.001[a]	2.14	1.79	1.08
First Trial (RAVLT)	-.65 (.81)	-.92 (.78)	-1.49 (1.14)	11.22	<.001[a]	.251	<.001[a]	.005	.34	.85	.58
Immediate recall (RAVLT)	-.56 (.87)	-1.26 (1.0)	-2.38 (.98)	46.42	<.001[a]	<.001[a]	<.001[a]	<.001[a]	.75	1.96	1.13
Delayed recall (RAVLT)	-.27 (.88)	-1.02 (.92)	-1.89 (.96)	40.53	<.001[a]	<.001[a]	<.001[a]	<.001[a]	.83	1.76	.93
EXECUTIVE FUNCTION	-.45 (.72)	-.79 (.63)	-1.83 (.48)	60.9	<.001[a]	.007	<.001[a]	<.001[a]	.50	2.26	1.86
TMT Part A	-.27 (.97)	-.5 (.87)	-1.76 (.82)	37.61	<.001[a]	.426	<.001[a]	<.001[a]	.25	1.66	1.49
TMT Part B	-.01 (1.05)	-.61 (.93)	-1.98 (.62)	38.66	<.001[a]	.003	<.001[a]	<.001[a]	.60	2.28	1.73
DSST (WAIS-IV)	-.29 (.88)	-.66 (.74)	-1.82 (.76)	47.01	<.001[a]	.022	<.001[a]	<.001[a]	.46	1.86	1.55
Categories (WCST)	-1.11 (.82)	-1.34 (.76)	-1.84 (.44)	12.01	<.001[a]	.240	<.001[a]	.003	.29	1.11	.81
VERBAL ABILITY	-.46 (.64)	-.71 (.67)	-1.86 (.48)	68.06	<.001[a]	.06	<.001[a]	<.001[a]	.38	2.47	1.97
Phonemic fluency (PMR)	-.45 (.77)	-.67 (.73)	-1.68 (.66)	37.58	<.001[a]	.255	<.001[a]	<.001[a]	.29	1.72	1.45
Semantic fluency (Animals)	-.6 (.86)	-.98 (.83)	-1.97 (.78)	34.31	<.001[a]	.025	<.001[a]	<.001[a]	.45	1.67	1.23
Similarities (WAIS-IV)	-.34 (1.0)	-.49 (1.02)	-1.93 (.82)	37.12	<.001[a]	1.0	<.001[a]	<.001[a]	.15	1.74	1.56

WAIS: Wechsler Adult Intelligence Scale, RAVLT: Rey Auditory Verbal Learning Test, TMT: Trail Making Test, DSST: Digit Symbol Substitution Test, WCST: Wisconsin Card Sorting Test.

[a] Analysis of variance or $\chi 2$ tests statistically significant after applying Bonferroni correction for multiple comparisons ($p<.003$)



Supplementary Figure 2. The graph displays neuropsychological assessment across clusters. Whiskers indicate SEM.

WAIS-IV: Wechsler Adult Intelligence Scale 4th edition, RAVLT: Rey Auditory Verbal Learning Test, TMT: Trail Making Test, DSST: Digit Symbol Substitution Test, WCST: Wisconsin Card Sorting Test.

DISCUSSION

This work explores the existence of empirical clusters for MDD taking into account patients' cognitive performance, stage of treatment resistance, depressive symptomatology, number of depressive episodes, age and years of schooling. Treatment resistance was the variable with the highest importance of clustering, closely followed by cognitive performance (verbal ability, executive function, attention/working memory and verbal memory). The rest of variables obtained the lowest importance on identifying distinct subgroups of patients. Three empirical clusters were determined: Cluster 1, characterized by non-resistant patients with preserved cognitive performance; Cluster 2, composed by resistant patients with selective impairment; and Cluster 3, grouped by resistant and non-resistant patients with a global cognitive impairment. As hypothesized, the latest was related with worse clinical and psychosocial outcomes. These findings may indicate the existence of different subgroups of patients, determined by clinical variables –as well-established in the literature– and by cognitive symptoms, which have not received enough attention for decades and may be underlying poor outcomes.

To our knowledge, this study is the first to show different cognitive profiles during an acute phase of the illness, considering not only cognitive performance but also clinical and sociodemographic factors, which are likely to have contributed to divergent results in the last decades. Hammar and Ardal (2009) already suggested that no single cognitive functioning profile could characterize all depressed patients, and that not all patients were to be impaired in the same degree during the acute phase (Hammar & Ardal, 2009). The existence of such heterogeneity among mood disorders' cognitive functioning is supported by previous cluster analyses, especially in bipolar disorder (Burdick et al., 2014; Cotrena et al., 2017; Lima et al., 2019; Solé et al., 2016). These studies found three-cluster solutions based on cognitive performance, corresponding to intact or preserved, selectively impaired and globally impaired patients. Only two studies have been carried out clustering analysis with exclusively MDD patients, and their findings point towards cognitive heterogeneity along the different stages of the disorder. One included patients in partial remission and reported three clusters (Pu et al., 2018) in accordance with the above-mentioned works, and the other was centered into first episode patients and showed two clusters, one preserved and one impaired (Vicent-Gil et al., 2018). These last studies, except the one with first episode patients, endorse our current findings of a subgroup of intact or mostly preserved patients, of a globally impaired subgroup with a general cognitive affectation, and of a subgroup with specific domains impaired. Although some of the works (Burdick et al., 2014; Pu et al., 2018) claim to have found "discrete neurocognitive subgroups", this may be straightforward for preserved and globally impaired patients, because these individuals can be easily detected even in clinical settings. By contrast, the selectively impaired subjects may not constitute a clearly discrete neurocognitive subgroup given that other characteristics may interact with cognition making difficult to detect specific cognitive alterations. At this point, our current study highlights the importance of adding clinical information to the clustering,

as it may be crucial for a more comprehensive classification of patients, by capturing other factors that may blur those patients in C2.

Treatment resistance was the most important variable in the clustering process, which embraces lack of response (and/or remission) and greater severity of clinical symptoms. The totality of participants in the cognitively preserved cluster was non-resistant and likewise, the 100% of the participants in the selectively impaired cluster were ~~non-~~resistant. In the group of globally impaired patients, however, up to 42% of patients were non-resistant. A possible explanation is that alterations of memory and executive function are more specifically related to treatment resistance (Pimontel et al., 2016; Rao et al., 2019), as observed in C2, in consistence with previous evidence of hippocampus and prefrontal cortex alterations in treatment resistant depression (Ge et al., 2019). Thus, a global alteration of cognitive function may be reflecting a different phenotype, in which the main characteristic would be cognitive impairment and not exclusively linked to treatment resistance –this may not be unreasonable as the majority of antidepressant treatments do not target cognitive symptoms–. These results might indicate that although treatment resistance would be associated with greater cognitive impairment, the existence of various cognitive profiles has to be taken into account beyond the usual clinical variables, as non-resistant patients can still display cognitive symptoms. In fact, even though all patients of the study were acutely depressed, 39% showed no cognitive impairment. These findings also help to explain the small-to moderate effects -depending on the domain- of cognitive dysfunction in previous studies that compare patients with MDD with healthy controls, considering the apriorism of cognitive homogeneity among MDD patients may have led to such disperse results. The present study, which is data-driven, demonstrates the relevant role of cognitive functioning in major depression, pointing at the existence of potential cognitive dysfunction in a high percentage of patients who will require more tailored treatments.

Socio-demographic variables have a low relative importance in the cluster formation (Figure 1). However, years of schooling and IQ significantly differ among clusters, where the most impaired patients –cluster 3– had on average two years less of schooling and almost one standard deviation less of IQ than the cognitively preserved group. Differences in IQ could be tautological as positive associations have been described between IQ and cognitive performance. However, in clinical practice it is usually observed that patients with normal or intact premorbid IQ show relevant cognitive impairment, and the other way around (patients with limited IQ who do not show any cognitive deficits). Although globally impaired patients had the lowest IQ in this study, their intellectual ability fell within normality, and their cognitive performance was below normality (1.5SD below, on average). All the above-mentioned variables, which are normally used as proxies for cognitive reserve, showed a significant importance in previous studies of cluster analysis (Pu et al., 2018; Vicent-Gil et al., 2018). And cognitive reserve itself has specifically shown to moderate the relationship between mood and

cognition (Opdebeeck et al., 2017). Thus, cognitive reserve should not be neglected when assessing MDD patients.

By considering both cognitive and other illness related variables, the three clusters may reflect variations of the disorder due to differences in underlying pathophysiology, in response to treatment or in illness trajectories, and not merely in cognitive subdivisions on a linear continuum (Carruthers et al., 2019). Consequently, the clinical implication of the present results refers to the necessity of considering cognitive functioning in clinical settings in all patients diagnosed with major depression. Firstly, clinicians should seriously contemplate addressing cognitive symptoms when a given patient begins to show resistance to treatment, as cognitive difficulties may be related with worse treatment outcomes. Therefore, the intervention should be directed not only to clinical symptoms, but also to cognitive dysfunction. Secondly, 42% of patients who respond adequately to antidepressants may also present a global cognitive dysfunction. In clinical practice, some patients with good response to antidepressant treatment complain about a lack of complete recovery and of difficulties to perform daily activities, partly due to their perceived cognitive problems. Detecting such unidentified cognitive difficulties is of great importance as they are associated with worse psychosocial functioning (Cambridge et al., 2018; Knight & Baune, 2018) and with the low rates of recovery (Groves et al., 2018). Hence, treating cognitive dysfunction together with clinical symptomatology in an active episode of depression could probably result in a better response to treatment. Different pharmacological strategies (e.g., vortioxetine, duloxetine, modafinil or erythropoietin), non-pharmacological approaches (cognitive remediation or aerobic exercise) and neurostimulation interventions have been shown to be effective in the treatment of cognitive dysfunction while improving psychosocial functioning and quality of life (Salagre et al., 2017; Zuckerman et al., 2018).

The present study was subject to some limitations. First, due to cross-sectional design it was not possible to assess the long-term stability of the cognitive profiles. Second, the sample included outpatients treated in a specialized clinical setting, and may not comprise worldwide clinical practice as mild outpatients may be underrepresented. Third, the mean age of the sample was older than other studies, which could have facilitated the inclusion of patients with cognitive deficits caused by other conditions (such as neurodegenerative processes). In any case, the presence of a neurological condition was an exclusion criterion which was strictly evaluated. Fourth, although two-step clustering analysis is one of the most robust techniques to classify individuals (as it combines k-means and hierarchical approaches), the generalizability of the findings is one of the main drawbacks as the results are very sample-specific. The lack of external replication with an independent dataset represents a limitation of these results. In any case, our findings are fairly similar to the scarce literature. Fifth, individual scores were corrected with demographic-adjusted norms from a similar population, which might affect the interpretation of the present findings; therefore, future research should consider the cognitive heterogeneity within the norm samples. To overcome this limitation, composite scores for cognitive

performance were used as a more objective patient's cognitive performance outcome compared to the use of single tests (Miskowiak et al., 2017). Sixth, the variety of impaired cognitive domains within the "selectively impaired cluster", when compared to other studies, reflects another kind of heterogeneity that cannot be resolved with cluster analysis, as the solution depends on the samples used in each study. However, by using a two-step clustering, we detected two clear and extreme subgroups (i.e, preserved and globally impaired) together with a subgroup of selective impairment, in which other factors, beyond cognition, help to better characterize them. Finally, concomitant medication could be a possible confounder because of its side effects on cognition. But due to clinical reasons and ethical concerns, it was not adequate to discontinue the medication.

In conclusion, the present study shows the existence of distinguishable subgroups in a sample of acute depressed patients, in which treatment resistance and cognitive performance are relevant factors to take into account. The current design provides evidence of the heterogeneity of cognitive dysfunction in MDD. Therefore, future clinical research should consider the existence of potential cognitive dysfunction in all MDD patients, in order to tailor new strategies to achieve a full clinical and functional recovery and to prevent new relapses.

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CONFLICTS OF INTEREST

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ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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5.3. Testing the efficacy of INtegral Cognitive REMediation (INCREM) in Major Depressive Disorder: Study protocol for a randomized clinical trial.

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ABSTRACT

Background

Given the limitation of pharmacological treatments to treat cognitive symptoms in patients with Major Depressive Disorder (MDD), cognitive remediation programs has been proposed as a possible procognitive intervention but findings are not conclusive. This study investigates the efficacy of an INtegral Cognitive REMediation (INCREM) that includes a combination of a Functional Remediation (FR) strategy plus a Computerized Cognitive Training (CCT) in order to improve not only cognitive performance but also the psychosocial functioning and the quality of life.

Methods

A single blind randomized controlled clinical trial in 81 patients with a diagnosis of MDD in clinical remission or in partial remission. Participants will be randomized to one of three conditions: INCREM (FR+CCT), Psychoeducation plus online games and Treatment As Usual (TAU). Intervention will consist in 12 group sessions, of approximately 110 minutes once a week. The primary outcome measure will be % of change in psychosocial functioning after treatment measured by the Functional Assessment Short Test (FAST); additionally, number of sick leaves and daily activities will also be recorded as pragmatic outcomes.

Discussion

To our knowledge, this is the first randomized controlled clinical trial using a combination of two different approaches (FR + CCT) to treat the present cognitive deficits and to promote their improvements into a better psychosocial functioning.

KEYWORDS

Cognitive remediation; depression; functional remediation; computerized cognitive training; clinical trial

BACKGROUND

Cognitive dysfunction is considered a new treatment target to improve psychosocial functioning and enhance the quality of life in patients with Major Depressive Disorder (MDD) (Chakrabarty et al., 2016; McIntyre et al., 2013). Previous research suggests that cognitive symptoms explain the low rates of global recovery and functional disability (Baune et al., 2010; Buist-Bouwman et al., 2009; Jaeger et al., 2006). In fact, current pharmacological treatments for MDD have not been considered useful for the improvement of cognitive dysfunction probably because they are focused on improving mood (Salagre et al., 2017). The only antidepressants that seem to have a potential procognitive impact are duloxetine and vortioxetine (Al-Sukhni et al., 2016; Frampton, 2016; Greer et al., 2014), but further studies are needed to clarify these findings.

Regarding non-pharmacological treatments, Cognitive Remediation (CR) is a psychotherapeutic approach that has shown improvement in cognition in other neuropsychiatric disorders (Penadés et al., 2012; Wykes et al., 2011). However, only few studies have been conducted in MDD patients (Bowie et al., 2013; Elgamal et al., 2007; Naismith et al., 2010; Trapp et al., 2016). The design features of the interventions differ from one another, making it difficult to demonstrate their efficacy. Moreover, samples included in CR studies were very heterogeneous with different disease burden, which would have impeded conclusions about the specific effect of CR for MDD. Analyses were also limited by the fact that not all patients show the same profile of cognitive impairment. It is estimated that 50% of depressed patients (Conradi et al., 2011; Vicent-Gil et al., 2018) present enduring cognitive deficits, which would significantly interfere in workplace and in psychosocial functioning, while another large percentage of patients do not suffer from cognitive dysfunction.

Apart from that, most of CR programs have been based on neurological models designed to reverse cognitive deficits acquired after or associated with neurological conditions (Choi & Twamley, 2013; Cicerone et al., 2011), while the focus of CR programs in psychiatric diseases should be more directed in improving everyday functioning rather than merely recovering cognitive losses. Computerized Cognitive Training (CCT), which is based on cognitive exercises and games, appears to be, by contrast, an optimal method to improve cognitive functioning in affective disorders due to the flexibility given to adjust the tasks to the needs of each patient. In addition, and according to a recent meta-analysis (Motter et al., 2016), CCT improved depressive symptomatology and everyday functioning in patients with MDD, though producing inconsistent effects on cognition.

The scarce evidence on the efficacy of cognitive interventions may have prevented a broad implementation of such programs in the clinical setting. Moreover, research should define how cognitive remediation programs are to be administered (e.g., number of sessions), what cognitive domains are to be trained, and how this intervention can impact on psychosocial functioning. Therefore,

there is a strong need of randomized clinical trials so as to demonstrate the efficacy of such interventions (Bowie et al., 2013; Trapp et al., 2016).

Recently, one new 'ecological' intervention named Functional Remediation (FR) has been designed with the aim of transferring cognitive improvements to the daily functioning, by using neurocognitive techniques and training but also through psychoeducation on cognition and problem-solving. The FR program includes modeling techniques, role-playing, verbal instructions, self-instructions, positive reinforcement and meta-cognitive cues using real-life problems (Martínez-Arán et al., 2011). FR in bipolar disorder has shown significant enhancement of functional outcomes as well as subsyndromal symptomatology (Bonnín et al., 2016; Solé et al., 2015; Torrent et al., 2013).This is a group intervention and, thus, it is difficult to tailor the tasks to the specific needs of each individual.

Considering the above, the evidence accumulated indicates that the most adequate intervention to treat cognitive symptoms in MDD would be a combination of a group FR plus a personalized CCT. The inclusion of both aspects will allow the intervention to focus on the present deficits through the formation of new strategies with compensatory techniques and promoting their use into everyday life.

Aims of the study

This study aims to show the efficacy of an INtegral Cognitive REMediation (INCREM) program specifically-designed for MDD patients so as to improve psychosocial functioning through the treatment of cognitive symptoms.

Primary research aims:

- To develop and to prove the efficacy of INCREM; this includes a FR program and a CCT.
- To improve psychosocial functioning in MDD patients.
- To decrease the rate of patients with enduring cognitive symptoms, and to reduce the risk of further relapses.

Secondary research aims:

- To establish cognitive profiles in MDD patients, to tailor the Integral Cognitive Remediation therapy so as to achieve full remission.
- To increase the effect size of the intervention by combining traditional group sessions plus computerized individual sessions.
- To study the specific elements (cognitive and psychosocial aspects) that mediate clinical and functional improvement, which can be ascertain through well-being and decrements in cognitive complaints.

METHODS AND DESIGN

This is a single blind, randomized controlled clinical trial approved by the Research Ethics Board of the Hospital de la Santa Creu i Sant Pau. All participants will receive extended information about the study and must give their written informed consent prior to the inclusion. The study will be carried out in accordance with the ethical principles of the declaration of Helsinki and Good Clinical Practices, complying with data protection laws with the anonymization of all the information collected (Data Protection Act 2018).

Participants

Patients aged between 18 to 60 years with a diagnosis of MDD (DSM-5 criteria) will be recruited from the psychiatry department of the Hospital de la Santa Creu i Sant Pau in Barcelona (Catalonia, Spain) to participate in the present study. This center covers a population of 400.000 inhabitants, and therefore, the recruitment will be achieved. All patients will have to be in clinical remission or in partial remission, defined by scores below 14 in the HDRS-17. To be allocated in one of the treatment arms, patients will have to display objective cognitive deficits (measured with the Screening for Cognitive Impairment in Psychiatry – SCIP, defined by a score below 80) (Guilera et al., 2009; Pino et al., 2008) together with psychosocial dysfunction, defined by a score from 12 to 20 (mildly impaired) in the FAST (Bonnín et al., 2018). All patients will continue with their usual pharmacological treatment. Exclusion criteria are: i) an intelligence quotient (IQ) below 85, ii) any medical condition that may affect neuropsychological performance, iii) presence of any comorbid psychiatric condition including non-nicotine substance use disorders on the previous three months, iv) having received electroconvulsive therapy on the previous year or psychological intervention in the previous 6 months.

Study design

Figure 1 provides a schedule of the study. Detailed oral and written information about the study will be provided to all potential candidates to participate in the study. If they are interested in participate, informed consent will be signed and demographic, clinical, neuropsychological and functional assessments will be performed by an experienced clinical neuropsychologist. After the fulfillment of the inclusion criteria, patients will be randomized to one of the three possible treatment options: INCREM program which includes both a FR program adapted to depression, and a CCT; Psychoeducation plus online mental skill games; and Treatment as Usual (TAU). A more detailed explanation of the two active treatment arms is provided below. An independent statistician from the Department of Epidemiology (Hospital de la Santa Creu i Sant Pau) will carry out the randomization by means of computer-generated random numbers. In order to ensure balanced sample sizes across groups over time, a block randomization method will be used. The block size will be set to 27, so as to have 9 patients per treatment arm, in 3 consecutive blocks. Blocks will then be randomly chosen to determine patients' final assignment. Another experienced clinical researcher will assign participants to the corresponding intervention. The psychologists conducting treatment interventions will be different from the clinical

neuropsychologist who will carry out the assessments and who will be blind to the treatment assignment. The intervention will be discontinued in case of request by the participant. Any other concomitant psychological treatment will not be permitted during the trial. Finally, to ensure adherence to intervention, after one unjustified absence rated by the psychologist, a phone call will be done prior to the next session.

After 3 months of treatment (12 sessions) efficacy measures will be collected: Functioning Assessment Short Test (FAST; Rosa et al., 2007), Perceived Deficit Questionnaire (PDQ-20; Lam et al., 2013; Strober et al., 2016), Hamilton Depression Rating Scale (HDRS-17; Bobes et al., 2003; Hamilton, 1960), Remission from Depression Questionnaire (RDQ; Zimmerman et al., 2013) and 36-Item Short Form Health Survey, Version 2 (SF-36-V2; Ware, 2000). Then, 6 months after the intervention, a complete demographic, clinical, neuropsychological and functional assessment will be performed in order to evaluate the eventual long term effects. To promote retention and interest in the study by the participants, a detailed report about their evolution will be provided to them.

Estimation of sample size was set at 27 participants in each treatment arm, assuming a minimum difference on 6 points on the FAST (primary outcome), and considering a bilateral significance level of 5% and a statistical power of 80%, adjusted by a 20% rate of dropouts.

	STUDY PERIOD				
	Enrolment	**Allocation**	**Intervention**	**Post-Intervention**	**End point**
TIMEPOINT	***-t1***	**t0**	***t1***	***t2***	***t3***
ENROLMENT:					
Eligibility screen	X				
Explanation of the study	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS*:					
INCREM (FR plus CCT)			X		
Psychoeducation plus online games			X		
TAU			X		
ASSESSMENTS:**					
Demographic Assessment	X				X
Clinical Assessment	X			X	X
Neuropsychological Assessment	X				X
Outcome measures	X			X	X

Figure 1. Schedule of enrolment, interventions, and assessments.
Footnote: INCREM: INtegral Cognitive REMediation; FR: Functional Remediation; CCT: Computerized Cognitive Training; TAU: Treatment As Usual.
*Interventions will consist in 12 sessions, once a week.
**Demographic, clinical, Neuropsychological assessments and outcome measure are explained in detail in Methods and Design section.

Demographic and clinical assessment

A semi-structured interview will be used to assess demographic and clinical variables at baseline. Demographic assessment will include gender, age, years of education, age at which schooling was completed, work situation, work adjustment, marital status, cohabiting characteristics, and the number of children if any.

The Cognitive Reserve Assessment Scale in Health (CRASH; in press) will be included so as to estimate the cognitive reserve. It is a semi-structured interview-based scale that evaluates three domains considered fundamental in the construct of cognitive reserve: education, occupation and intellectual and leisure activities.

The clinical evaluation will cover age at illness onset, number of previous episodes, age of first psychiatric hospitalization, number of hospitalizations, period of clinical stability, seasonal pattern, presence of rapid cycling depression, presence of melancholy, atypical depression and psychotic symptomatology during depression, comorbidities in axis I, II and III, life history of suicidal ideation, life history of suicide attempts, number of attempts, method and medical severity used, and family history

of psychiatric disorders and suicide. The HDRS-17 will be used to evaluate current depressive symptoms and assess clinical changes. In addition, the RDQ will be used to evaluate the patient-perceived remission that includes subscales for symptoms of depression, other symptoms such as anxiety and irritability, coping ability, positive mental health, functioning, life satisfaction and a general sense of well-being. These two scales will be analyzed as secondary clinical outcomes to evaluate the possible lasting effects.

Neuropsychological assessment

Following the clinical assessment, a neuropsychological battery of tests will be administered by experienced neuropsychologists at the beginning of the study and at 12 months after intervention. It comprises standardized tests to assess attention, working memory, verbal and visual memory, processing speed and executive function. Premorbid Intelligence will be estimated with Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale version-IV (WAIS-IV; Wechsler, 2008). Attention and verbal working memory performance will be evaluated with Digit forward and backward (WAIS-IV). The Conners Continuous Performance Test 3rd Edition (CPT-III; Conners, 2014) be used to assess sustained attention. Verbal learning memory will be measured by the California Verbal Learning Test (CVLT; Delis et al., 1987). Copy and recall of the Rey-Osterrieth Complex Figure (ROCF; Rey, 1941) will be used to evaluate visuoconstructive abilities and visual memory. Processing speed will be measured by the Digit Symbol Substitution Test (DSST; WAIS-IV) and the Trail Making Test Part A (TMT-A; Tombaugh, 2004). Finally, executive functioning will be measured with the Trail Making Test Part B (TMT-B; Tombaugh, 2004), the Stroop Color and Word Test (STROOP; Golden, 1978), the Wisconsin Card Sorting Test (WCST; Heaton, 1981), the Tower of London (TOL; Portella et al., 2003) and the Category Fluency and PMR (adapted for Spanish speaking population; Casals-Coll et al., 2013; Peña-Casanova et al., 2009). TMT-B is used to evaluate set-shifting abilities, STROOP interference is used to evaluate difficulties with response inhibition, WCST assess abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies, TOL is used to detect deficits in planning and problem-solving and Category Fluency and PMR are used to measure semantic and phonemic verbal fluency, respectively.

Intervention

Selected patients are going to be randomized to three possible intervention arms: INCREM; PSYCHOEDUCATION + online games; and Treatment as Usual (TAU).

INCREM will consist of 12 sessions, of approximately 110 minutes once a week, involving a FR and a CCT. FR program was originally developed for bipolar patients (Vieta et al., 2014) and it will be adapted for depressed patients creating a more intensive program focused on executive functions, memory and attention. The sessions aim at improving daily functioning based on ecological tasks where they need to use compensatory techniques. The specific explanation of the sessions is developed in Table 1. CCT will be applied right after FR group sessions in individual computer sessions during 20 minutes. The modules

of training will be facilitated by the licensed game-like software CogniFit (www.cognifit.com). This neurocognitive stimulation program consists of a battery of tasks that allows depressed patients to improve their cognitive skills depending on their individual performance throughout different activities.

Table 1. Content of the 12-week Functional Rehabilitation Program

Session	Topics Covered
1. What is attention? (I)	Strategies of concentration
2. What is attention? (II)	Strategies to improve attention
3. Reading	Recovering the habit of reading
4. What is memory? (I)	Mnemonic strategies
5. What is memory? (II)	The use of diaries and external aids
6. What are executive functions? (I)	Self-instructions
7. What are executive functions? (II)	Programing activities, prioritization and time management
8. What are executive functions? (III)	Problem solving strategies
9. What are executive functions? (IV)	Working memory strategies
10. Stress	Stress and neurocognition
11. Communication	Communication skills and assertiveness
12. Autonomy	Independence and autonomy

PSYCHOEDUCATION will consist of 12 sessions, 90 minutes once a week involving psychoeducation sessions plus 20 minutes online non-directed game playing. This treatment arm has been designed as the control intervention arm due to its beneficial effects for depression. The material for the psychoeducation intervention has been specifically designed for the study and is based on validated treatment protocols (Aragonès et al., 2013; Casañas et al., 2012; Lewinsohn et al., 1984). Information about the disease is provided during the sessions so as to gain knowledge and strategies to cope with their own difficulties and to improve their quality of life. Therefore, the intervention will be divided in two modules: the first module (sessions 1 to 4) will consist in providing information about the disease and its treatment, and the second one (sessions 5 to 12) will consist of introducing different cognitive-behavioral techniques that have proven to be effective for depression. The specific explanation of the sessions is developed in Table 2. The online game will be applied right after the psychoeducation sessions during 20 minutes. The games will be facilitated by a free mini-game online website (www.frivplus.com). No records will be gathered on this last part, as it is only used to make comparable the two active treatment arms.

Table 2. Content of the 12-week Psychoeducational Program

Session	Topics Covered
1. What is depression? (I)	Concept of depression
2. What is depression? (II)	Definition, symptoms, prevalence and course
3. Etiology of depression	Biopsychosocial model, psychobiology and psychological theories
4. Treatment of depression	Pharmacological, psychological and other treatment options
5. Behavioral Activation (I)	Introduction to Behavioral Activation
6. Behavioral Activation (II)	Exposition to positive activities
7. Cognitive Distortions	Cognitive distortions, automatic negative thoughts and cognitive restructuring technique
8. Anxiety	Anxiety management strategies
9. Social Skills (I)	Social skills deficits and communicational styles
10. Social Skills (II)	Social skills training
11. Problem-Solving Technique	Problem-Solving training
12. Relapse Prevention	Summary of the sessions and relapse prevention

TAU will consist in giving the usual treatment to patients according to accepted standards for depression (except psychotherapy which will not be allowed 6 months before the study nor during it).

Outcome measures

The primary outcome measure of the study will be the change in psychosocial functioning after treatment, which will be measured by means of the FAST. The FAST is a scale created to assess disability in functioning in mental health which contains 24 items evaluating autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The scores range from 0 to 72, with higher scores indicating a greater disability. A sum of ≥ 12 represents a mildly to severe functional impairment in patients with bipolar disorder (Bonnín et al., 2018). Given the complexity of the possible effects of the intervention, changes in pragmatic variables of psychosocial functioning will also be evaluated: number of sick leaves and number of daily activities.

Different secondary outcome measures will be analyzed: i) the change in cognitive performance across cognitive domains (through composite scores of the different cognitive domains and a global composite cognitive score); ii) change in subjective appraisal of cognitive functioning evaluated with the PDQ-20 which is a self-reported questionnaire that measures the patients' perception of their cognitive functioning. It consists of 20 items assessing attention, retrospective memory, prospective memory, and planning and organization; iii) change in depressive symptoms with the HDRS-17); iv) change in patients' perspective of clinical remission with the RDQ; and v) change in quality of life assessed with the SF-36-V2. It evaluates the patients' health-related quality of life gauging eight sections: vitality, psychical

functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

Statistical analysis plan

Data will be collected in three different moments: baseline, post-intervention and follow-up through a logbook data collection. Then, an online application called Clinapsis will be used for data collection, which ensures anonymisation of data (through encoding system). This system will grant public access to the full protocol and dataset at participant-level for further analysis beyond this proposal.

The data will be analyzed using the Statistical Package of Social Sciences (SPSS, IL, Chicago, version 20) and R Package (version 3.1.2). First, baseline differences between groups will be investigated using chi-square tests and ANOVAs depending on the nature of the variables. Secondly, mixed-models will be carried out to assess the impact of the three different treatment options on the psychosocial functioning scores assessed with the FAST scale (primary outcome measure). Effect sizes of interventions will be calculated. Secondary variables will also be analyzed with the same statistical approach. Mixed repeated measures ANOVAs will be carried out to investigate the long-term effects of interventions on secondary outcomes. Finally, in order to investigate predictors of treatment response, a study of mediators and moderators will be conducted. For the main statistical analysis, the Last Observation Carried Forward method will be used to minimize the effect of dropout rates at 6 months of follow-up after intervention.

DISCUSSION

Cognitive impairment is nowadays considered a core symptom of MDD and a critical determinant of psychosocial and workplace outcomes, as well as health outcomes such as the health-related quality of life. CR has been used to treat these cognitive deficits suggesting significant improvements in cognition but with small effect sizes for psychosocial functioning. This study aims to improve psychosocial functioning through the improvement in cognitive performance. To our knowledge, this is the first randomized clinical trial using an INtegral Cognitive REMediation (INCREM) composed by 12 sessions of a FR program and a CCT.

The major strength of this study is the combination of two different approaches at the same time: a group format therapy together with a computerized program that allows a personalized delivery of the intervention. This synergistic approach may represent the path to optimize treatment response and ensure better functional outcomes in patients with MDD. The presence of an active control group beyond treatment as usual (TAU) is another relevant strength of the study. A large battery of primary and secondary outcome measures will be used to evaluate the efficacy of the intervention. Patients will be approached six months after finishing the intervention to assess the maintenance of possible changes. Furthermore, this study will take into account the specific cognitive deficits of each patient by adapting CCT to individual performance.

A potential limitation of the present study is inherent to any clinical trial, given that participation and follow-up of the interventions could be more complicated. A 20 % of dropouts are calculated throughout the intervention and/or follow-up has been estimated, but this percentage could be higher, which would limit the power of the analysis. Patients should be in remission or in partial remission with cognitive deficits and difficulties in daily life, so that recruitment and inclusion might be more complicated. Concomitant medication might also represent a possible limitation because of side effects or even procognitive effects of newer drugs. In any case, medication regimes will be recorded during the different phases of the study and then will be taken into account in the analyses. In any case, in the clinical practice, polymedicated patients are the rule rather than the exception. Hence, it might limit internal validity but it is strength for the generalization of the results.

Conclusion

The presence of residual cognitive symptoms, observed in the clinical settings, may impede the achievement of full remission in patients with depression. Therefore, effective cognitive treatments are an unmet need. If the results of this study are conclusive, the INCREM could be added to the therapeutic arsenal for depression. This non-pharmacological treatment may seem expensive as it consists in 12 sessions, but if one considers the direct and indirect social and healthcare costs of depression (Sobocki et al., 2006), then targeting cognitive symptoms with a cognitive program will likely be cost-effective.

TRIAL REGISTRATION

Clinical Trials NCT03624621. Date registered 10th of August 2018 and last updated 24th August 2018.

ABBREVIATIONS

CCT: Computerized Cognitive Training; CPT-III: Conners Continuous Performance Test 3rd Edition; CR: Cognitive Remediation; CRASH: Cognitive Reserve Assessment Scale in Health; CVLT: California Verbal Learning Test; DSST: Digit Symbol Substitution Test; FAST: Functioning Assessment Short Test; FR: Functional Remediation; HDRS-17: Hamilton Depression Rating Scale; INCREM: INtegral Cognitive REMediation; IQ: Intelligence Quotient; MDD: Major Depressive Disorder; PDQ: Perceived Deficit Questionnaire; RDQ: Remission from Depression Questionnaire; ROCF: Rey-Osterrieth Complex Figure; SCIP: Screening for Cognitive Impairment in Psychiatry; SF- 36-V2: 36-Item Short Form Health Survey, Version 2; STROOP: Stroop Color and Word Test; TAU: Treatment As Usual; TMT-A: Trail Making Test Part A; TMT-B: Trail Making Test Part B; TOL: Tower of London; WAIS-IV: Wechsler Adult Intelligence Scale version-IV; WCST: Wisconsin Card Sorting Test

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AVAILABILITY OF DATA AND MATERIALS

This is an ongoing study and the investigators are currently collecting data. Therefore, any publication containing the results of this study has not been published. All the investigators collaborating in this study will have access to the final trial dataset. All writings and presentations will be performed by the members of the research team following the standard guidelines of dissemination policy.

AUTHORS' CONTRIBUTIONS

MVG drafted the manuscript which was critically reviewed by MJP. MJP designed the study with the collaboration of BR, EMM, AMA, MSB and NC. SGS, CMB, JT, JPB, JDA, DP were involved in the set-up of the study, providing information upon the availability of facilities and clinical settings. MVG, EMM, AMA, CMB, MSB and MJP reviewed the theoretical rationale for manuscript preparation. JT, JDA, DP and MJP defined the study design and the statistical approach for the manuscript. BR, EMM, SGS, AMA, CMB, JT, JPB, JDA, DP, MSB, NC read and approved the final version manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is approved by the Ethical Committee for Clinical Research (in Spanish, Comité Ético de Investigación Clínica) from the Hospital de la Santa Creu i Sant Pau, project number IIBSP-RID-2017-107. Protocol version 1, 14th February 2018. Central Clinical Research and Clinical Trials Unit (CCRCTU), Research Institute of the Hospital de Sant Pau, will monitor through periodic visits the correct progression of the project, alerting from protocol deviations. They will be constantly aware of every single step of the project. All participants will receive extended information about the study and must give their written informed consent prior to participate in the study. This study does not pose any risk to the participants.

CONSENT FOR PUBLICATION

Written informed consent from participants will be obtained prior to the inclusion to the study.

COMPETING INTERESTS

MJP has received honoraria as academic from Lundbeck. JDA has received consulting and/or lecture honoraria from Lundbeck, Pfizer and Qualigen. NC declares that he has received honoraria as consultant, advisor or CME speaker from Janssen, Lundbeck, Pfizer, Exeltis and MSD. The rest of the authors declare that they have no competing interests.

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5.4. Randomized clinical trial of INtegral Cognitive REMediation (INCREM) program for major depression.

By Vicent-Gil et al. (*under revision*)

ABSTRACT

Background

Despite achieving clinical remission, patients with major depressive disorder (MDD) encounter difficulties to return to their premorbid psychosocial functioning. Cognitive dysfunction has been proposed to be a primary mediator of functional impairment in MDD. Therefore, the new non-pharmacological procognitive strategy INtegral Cognitive REMediation for Depression (INCREM) has been developed with the aim of targeting cognitive and psychosocial functioning, as symptomatic remission may be an insufficient goal of treatment for MDD.

Methods

This is a single-blind randomized controlled clinical trial with 3 treatment arms. Fifty-two depressed patients in full or partial remission, with psychosocial difficulties and cognitive impairment, were randomly assigned to receive 12-session INCREM intervention, 12-session Psychoeducation programme, or psychopharmacological treatment as usual (TAU). Patients were assessed before and after the study period, and six months after. The primary outcome was the change of patients' psychosocial functioning measured with the Functioning Assessment Short Test (FAST). The change in cognitive performance across cognitive domains was also analysed.

Results

The analysis of the RCT showed a significant improvement in psychosocial functioning in the INCREM group, especially six months after the intervention, compared to patients who received the psychoeducation programme. An improvement in cognitive performance was also observed in the INCREM group.

Conclusions

These results provide preliminary evidence on the feasibility and potential efficacy of the INCREM program to improve not only cognitive performance but also psychosocial functioning in clinically remitted depressed patients, and such improvement is maintained six months after. It can be speculated that the maintenance is mediated by the cognitive enhancement achieved with INCREM.

KEYWORDS

Cognitive remediation; depression; functional remediation; computerized cognitive training

INTRODUCTION

Conventional standards of depression treatment suggest that reducing patients' depressive symptomatology should be viewed as the primary goal. However, there has been increasing evidence highlighting the importance of not only achieving clinical remission, but also restoring patients' premorbid psychosocial functioning while improving their quality of life (IsHak et al., 2016; Kan et al., 2020). Residual depressive symptomatology and cognitive deficits seem to be related to this lack of recovery of daily functioning in the clinical remission phases of depression (Lam et al., 2014; Xiao et al., 2018). In fact, persistent impairments in attention, memory and executive function predict low functional outcomes (De Nooij et al., 2020; Knight et al., 2018), and are also associated with an increased risk of relapse (Hammar & Ardal, 2009; Joormann & Gotlib, 2010) as well as with a heightened risk of treatment resistance along the illness (López-Solà et al., 2020; Vicent-Gil et al., 2020). Therefore, addressing cognitive symptoms appears to be a core treatment target for remitted depressed patients (Kim et al., 2018).

Cognitive Remediation (CR) is a non-pharmacological procognitive intervention that has been drawing considerable interest in the last decades. This strategy aims to improve cognitive functioning while transferring these improvements into the patients' daily lives (Kim et al., 2018). To corroborate its efficacy, different studies have been carried out following two different approaches: restoration and compensation. Restorative interventions are based on the basic principle of neural plasticity, with the assumption that the repetition of exercises (drill and practice) leads to an improvement in cognitive performance whereas compensatory interventions use behavioural strategies and environmental modifications to compensate for cognitive deficits (Kim et al., 2018). Moreover, there are some variations between CR programs in depression, in terms of the applied software, the techniques, the duration, the frequency, the targeted cognitive domain/s or the outcome measures used. Despite all these differences, research shows a significant improvement in impaired cognitive functioning. A recent meta-analysis of computerized cognitive training in depression showed significant improvements in attention, working memory and overall cognitive functioning after CR interventions (Motter et al., 2016). Unfortunately, due to the lack of studies assessing additional effects beyond cognition, it was not possible to explore the transfer of cognitive improvements to the patients' daily functioning. In the same line of this previous meta-analysis, Trapp, Engel, Goeran, Lautenbacher & Gallhofer (2016) examined the effects of a CR group using the game-like cognitive training software X-Cog in a sample of depressed inpatients (Trapp et al., 2016). The treatment group showed significant improvements in verbal and nonverbal memory, working memory and executive function, yet there was no measure of psychosocial functioning. Another similar study developed by Hammar et al. (2020) showed an improvement in working memory functions using the 'Cogmed Working Memory Training' over a 5-week period. Once again, the transfer of cognitive improvements to the patients' daily functioning was not assessed (Hammar et al., 2020).

To date, only three studies have included psychosocial functioning as a measure of efficacy of CR interventions, all of them showing significant improvements. Lee et al. observed memory and functional improvements after a CR programme (NEAR program plus a psychoeducation component regarding cognitive deficits) in the first episode of either major depression or psychosis (Lee et al., 2013). Likewise, Listunova et al. implemented a computer-based training plus compensatory-transfer sessions in a sample of remitted depressed patients. The main finding was the improvement in attention performance with a positive effect to psychosocial functioning in both CR interventions (individualized or generalized training group) (Listunova et al., 2020). Along the same line, Hagen et al. randomized 63 participants with current or pervious mild or moderate depression to receive 9 sessions of metacognitive intervention called 'Goal Management Training' or to Computerized Cognitive Training (CCT) using the platform BrainHQ. The results revealed significant improvements in executive functioning (performance-based measures) and in everyday executive functioning (measured with the Behaviour Rating Inventory of Executive Function-Adult version, BRIEF-A). The authors also found a decrease in depressive symptomatology following both treatment options (Hagen et al., 2020). To summarize, these CR studies in depression seem to be promising interventions for treating cognitive symptoms while improving functioning. However, further studies are needed to enhance the methodology used and to optimize interventions in order to achieve a full recovery from depression, also taking into account the attainment of a positive mental health.

Bearing in mind not only enhancing cognition, but also improving the bipolar patients' daily functioning, a CR intervention called Functional Remediation (FR) was designed (Martínez-Arán et al., 2011). FR is focused on compensating cognitive deficits in the daily life, and it comprises psychoeducation on cognition, neurocognitive techniques, positive reinforcement, and metacognitive cues, always using real-life situations. The cognitive domains targeted by this strategy include attention, memory and executive functions. Recent research points to FR as a promising tool in improving the daily functioning in bipolar patients (Bonnín et al., 2016; Solé et al., 2015; Torrent et al., 2013). Nevertheless, there are no studies showing its efficacy in other mental disorders, which also experience cognitive and psychosocial impairments, such as major depression.

Taking all these data into account, the current randomized clinical trial is the first to investigate whether a new CR intervention referred as INCREM (INtegral Cognitive REMediation for Depression) might improve psychosocial functioning and the quality of life by the enhancement of cognitive performance. In contrast to previous studies and also to optimize treatment outcomes, the INCREM intervention uses a combination of Functional Remediation (FR) program plus an individualized CCT. This new integral intervention is a synergy of compensation and restoration strategies, i.e., on the one hand, cognitive strategies are trained to be used in daily life to improve their functioning and, on the other hand, gamification of computerized cognitive training is carried out after group sessions, which is adapted to individualised cognitive performance. CCT is a widely used CR intervention in depression.

Aims of the Study

The primary aim of the present study is to examine the efficacy of INCREM on improvement of cognitive performance and daily psychosocial functioning in a sample of partial remitted depressed patients, compared to an active control group and to a non-active treatment-as-usual (TAU) group. Therefore, the primary hypothesis is that INCREM participants are expected to achieve a greater improvement in cognitive and psychosocial functioning compared to the other two groups.

METHODS

The present study was approved by the Research Ethics Board of the Hospital de la Santa Creu i Sant Pau. All participants provided written informed consent for participating after a comprehensive explanation. The study adhered to the ethical principles of the Declaration of Helsinki and to the principles of Good Clinical Practice, and complied with the current data protection law. A detailed description of the study protocol was published in a previous paper (Vicent-Gil et al., 2019), and the project is registered at clinical.trials.gov (NCT03624621).

Participants

Remitted depressed patients with subjective cognitive deficits were recruited from the Department of Psychiatry of the Hospital de la Santa Creu i Sant Pau by their psychiatrists. Of 100 screened participants, 52 participants fulfilled all the inclusion criteria: (i) age between 18 and 60, (ii) a history of Major Depression Disorder (DSM-5 criteria), (iii) currently in clinical remission or in partial remission (Hamilton Depression Rating Scale (HDRS) <14) (Bobes et al., 2003; Hamilton et al., 1960), presenting objective cognitive deficits (Screening for Cognitive Impairment in Psychiatry (SCIP) <80) (Strober et al., 2016) and displaying psychosocial dysfunction (Functioning Assessment Short Test (FAST) ≥12) (Rosa et al., 2007). None of them had previously participated in any procognitive intervention previously. Exclusion criteria were: an estimated intelligence quotient (IQ) lower than 85, any medical condition associated with neuropsychological impairments, a comorbid psychiatric condition including non-nicotine substance use disorders in the previous three months, having received electroconvulsive therapy in the previous year or any psychological intervention in the previous six months.

Study design

The study is a single blind randomized clinical trial with three treatment arms. After recruitment, an experienced clinical neuropsychologist conducted a baseline assessment (T0) that included demographic, clinical, neuropsychological and functioning variables. Subsequently, patients were randomly assigned to one of the three options of intervention: INCREM program, PSYCHOEDUCATION program and Treatment as Usual (TAU). A brief summary of each arm is provided in the "Intervention" section. Treatment allocation was based on a block randomization method, where each treatment arm had nine patients in the different blocks. All enrolled participants were reassessed (T1) after the intervention period (12 sessions, three months approximately) using the outcome measures (except the

neuropsychological battery). Six months after the post-intervention assessment, another follow-up evaluation (T2) was carried out using the same measures of baseline assessment. Based on the per-protocol principles (i.e., the non-availability of measurements of the primary endpoint and non-sufficient exposure to study treatment) patients had to attend at least 8 sessions to be included in the analyses.

Measures

At baseline, demographic and clinical variables were obtained through a semi-structured interview. Estimated intelligence quotient (IQ) was assessed with the Vocabulary subtest of the Wechsler Adult Intelligence Scale version-IV (WAIS-IV).

The primary outcome variable of the clinical trial was the Functioning Assessment Short Test (FAST; Rosa et al., 2007), which assesses functioning impairment through different facets: autonomy, occupational functioning, cognitive performance, financial issues, interpersonal relationships and leisure time. The FAST scale is an interviewer-administered instrument that is widely used for psychiatric patients. Its scoring ranges from 0 to 72, and scores of 12 or higher indicate a moderate disability in psychosocial functioning (Bonnín et al., 2018).

The change in cognitive performance was a secondary outcome in this study. For this purpose, the Screening for Cognitive Impairment in Psychiatry (SCIP) scale and a comprehensive neuropsychological battery were used. First, the SCIP is a brief neuropsychological instrument (15 minutes) that includes five subtests evaluating immediate and verbal learning and memory, working memory, verbal fluency and processing speed. Scores below the cut-off point of 80 indicate the presence of objective cognitive deficits (Strober et al., 2016). This test was not exclusively used as an inclusion criterion, but also was administered throughout the two study periods (post-intervention and follow-up) to analyse global cognitive changes. Second, the neuropsychological battery included the following standardized tests: Digit forward and backward (WAIS-IV); the California Verbal Learning Test (CVLT); the Rey-Osterrieth Complex Figure (ROCF); the Digit Symbol Substitution Test (DSST; WAIS-IV); the Trail Making Test Part A (TMT-A); the Trail Making Test Part B (TMT-B); the Stroop Color and Word Test (STROOP); the Wisconsin Card Sorting Test (WCST); the Tower of London (TOL); the Category Fluency and PMR (adapted for Spanish speaking population). This extensive neuropsychological evaluation was performed at baseline and six months after the intervention to avoid learning effects.

The rest of outcomes were used as additional measures of efficacy, and were carried out in all assessments (T0, T1, T2): i) patients' appraisal of their cognitive functioning (Perceived Deficit Questionnaire − PDQ-20) (Lam et al., 2013); ii) depressive symptomatology (Hamilton Depression Rating Scale − HDRS-17) (Bobes et al., 2003; Hamilton et al., 1960); iii) patients' perception of clinical remission

(Remission from Depression Questionnaire – RDQ) (Zimmerman et al., 2013); iv) and patients' quality of life (36-Item Short Form Health Survey, Version 2 − SF-36-V2) (Ware, 1976).

Intervention

The **INCREM** intervention involved 12 weekly sessions lasting 110 minutes. Each session included a Functional Remediation (FR) strategy and a Computerized Cognitive Training (CCT). FR is an ecological program created to improve daily functioning by improving cognitive deficits. The FR sessions are designed to learn compensatory strategies and neurocognitive techniques that can be used in day-to-day activities or in common situations where patients encounter a greater number of difficulties. It also includes psychoeducation on cognition focusing on attention, memory and executive functions. At the end of each session, patients received a document with a summary of the session's content. The detailed explanation of the different sessions is described elsewhere (Vicent-Gil et al., 2019). The CCT was applied right after the FR group sessions, and it consisted of individual cognitive training sessions using the game-like software CogniFit for 20 minutes. This tool was used before the commencement of INCREM sessions to get a baseline cognitive profile to adjust the computerized tasks to each individual. The battery of tasks was individualized for each patient depending on their basal performance and their subsequent performance throughout the sessions.

The **PSYCHOEDUCATION** treatment arm was also a 12-week program consisting of 90 minutes of a psychoeducation intervention plus 20 minutes playing with an online non-directed tile-matching game with increased difficulty. The psychoeducation sessions offered information to patients about major depression and about strategies to improve their mental health and quality of life. The paper and audio-visual materials of the different sessions are available in Spanish (Portella et al., 2020). After the group intervention, each participant played individually with a game facilitated by a free mini-game online website (www.frivplus.com).

Finally, **TAU** patients received their usual medical treatment without adding any psychotherapeutic intervention.

Statistical analyses

Statistical analyses of the clinical trial were carried out using the Statistical Package for Social Sciences (SPSS, IL, Chicago, version 20) and R statistics software (R Core Team, 2020). For cognitive performance, raw scores were transformed into T-scores using normative data. With the aim of reducing the number of neuropsychological variables, five cognitive domains were defined: i) Attention/Working Memory (Digit forward and backward); ii) Verbal Memory (CVLT immediate recall and delayed recall); iii) Visual Memory (ROCF copy and delayed recall); iv) Processing Speed (DSST and TMT-A); and v) Executive Function (TMT-B, Stroop Interference, PMR phonemic verbal fluency and WCST perseverative errors). To test the baseline differences between groups, ANOVAs and chi-squares were conducted depending on the nature of demographic, clinical, neuropsychological and functioning variables. Effect-sizes were also

reported between the three treatment options. Normality distribution for the outcome measures was tested by Kolmogorov-Smirnov test.

A repeated measures ANOVA was carried out to assess changes on the psychosocial functioning (FAST scale, primary outcome measure) among the three treatment arms (the between-subject factor) with time (baseline, post-intervention and follow-up assessments) as the within-subject factor. Percentages of change on FAST scores from baseline were also calculated for treatment arms. Additionally, rates of recovery on FAST scores at post-intervention assessment were calculated. In order to evaluate whether INCREM would be useful across different ages (Wykes et al., 2009), an interaction analysis was performed with mean FAST scores, treatment arm and age (in three categories: young adults, middle age adults and older adults). Similarly, repeated measures ANOVAs of cognitive functioning were performed. In this case, time factor had two points of assessment (baseline and long-term).

Additional repeated measures ANOVAs were performed with the rest of the outcome measures. Finally, descriptive analyses (mean group comparisons) of these outcome measures were carried out. P-values of significance were set below 0.05.

RESULTS

Descriptive analysis and baseline results

Figure 1 shows the flow diagram outlining the enrolment. Fifty-two participants entered the study with a mean age of 51 (SD = 7.14; range 37 – 60) and with a larger percentage of females (71.2%). All patients were diagnosed with MDD and, at the time of participating in the study, they were in partial (34.6%) or full remission (65.4%) with a mean HDRS score of 6.62 (SD=3.62). The mean age at illness onset was 33.54 (SD =9.79) and the mean of total number of depressive episodes was 3.12 (SD=1.78). All participants displayed objective cognitive deficits (SCIP: mean=68.94; SD=9.52) and showed psychosocial dysfunction (FAST: mean=24.46; SD=7.06).

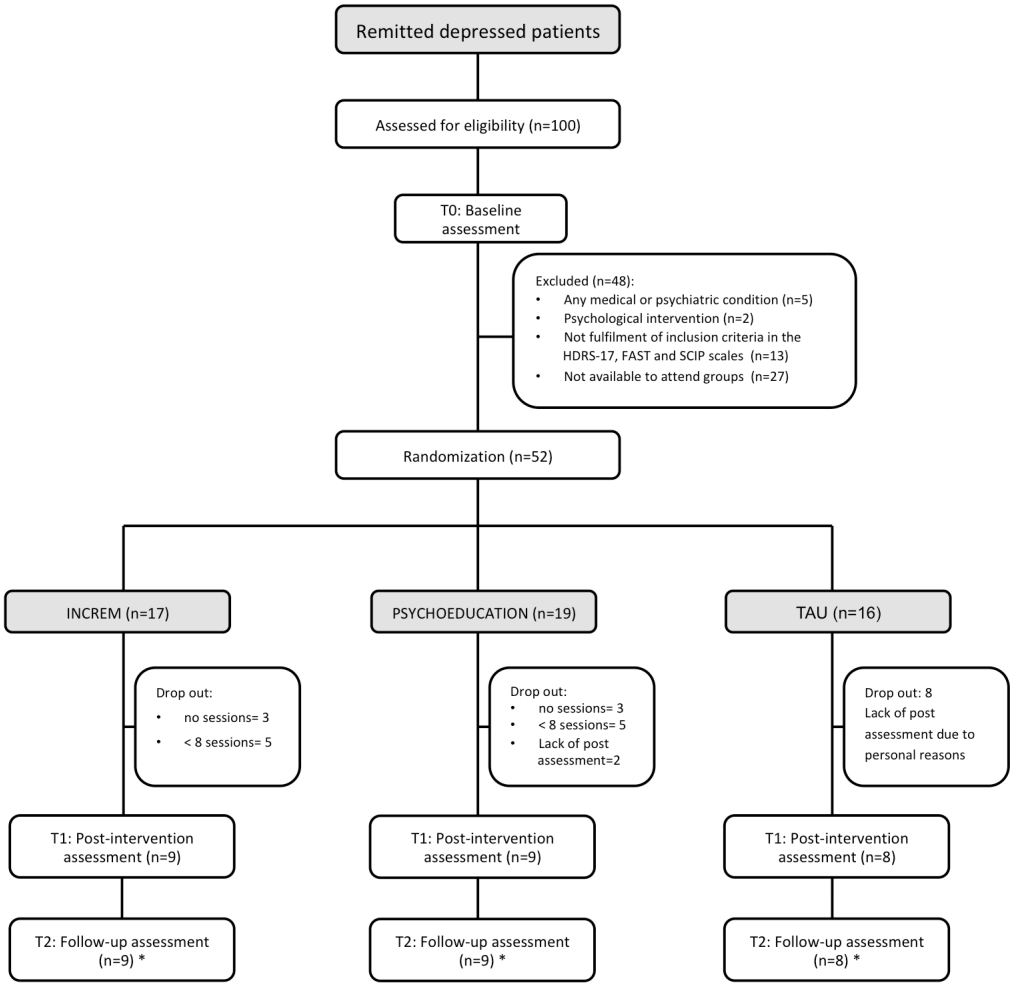


Figure 1. Flowchart outlining participant enrolment.

Nota. *The pilot study analyses were conducted only with those participants who had completed all the assessments.

From the fifty-two participants recruited, twenty-six completed the intervention fulfilling the post-intervention and follow-up assessments, i.e., eight patients in TAU, nine in INCREM program, and nine in psychoeducation. There were no differences between the analysed pilot sample and the group of patients who did not meet the minimum number of sessions and were excluded from the final analyses (data not shown). This high rate of dropouts was above expected rates, especially in the first series of intervention. Therefore, the strategy to allocate patients was changed in successive blocks of intervention. In brief, in the first set of group intervention the patients had been allocated in the day of baseline assessment. In the next series of interventions, the patients were assigned when the calendar for group sessions was already established so the patients could be sure to attend to. This change in the allocation strategy improved treatment adherence by decreasing the number of dropouts drastically (on average the first groups had a 70% of dropouts, the second groups a 50% of dropouts, and the last groups a 29% of dropouts).

Table 1 displays baseline demographic, clinical, neuropsychological and functional characteristics among allocated subjects in the three treatment options. There were no significant differences among groups, with the exception of the estimated IQ (Vocabulary Subtest of the WAIS-IV) ($p=0.04$) and sex distribution ($p=0.05$). Post-hoc comparisons of estimated IQ among groups showed no significant effect sizes. Therefore, this covariable was not finally included in the repeated measures ANOVA. Similarly, sex was also excluded from the final model due to the low frequency of males in the TAU group (n=1) and in the INCREM group (n=1).

Table 1. Final sample baseline characteristics and between-group comparisons.

	Treatment arm			Statistics		Post-hoc		
	INCREM (n=9)	Psychoeducation (n=9)	TAU (n=8)	*F* or $\chi 2$	*p*	INCREM vs TAU	Psychoeducation vs TAU	INCREM vs Psychoeducation
Age, *years*	50.56 (6.88)	51.22 (6.63)	53.75 (5.83)	0.56	0.58	0.96	1.00	1.00
Sex, *female* (n, %)	8 (88.9)	4 (44.4)	7 (87.5)	4.01	0.05	0.93	0.07	0.05
Years of schooling, *n*	13.22 (4.35)	15.11 (3.02)	11.5 (3.21)	2.15	0.14	1.00	0.15	0.83
Estimated IQ	112.33 (15.5)	113.67 (10.97)	98.75 (9.47)	3.71	0.04	0.10	0.06	1.00
Age at illness onset, *years*	33.78 (7.36)	31.89 (6.83)	37.25 (10.96)	0.87	0.43	1.00	0.62	1.00
Number of episodes	3 (1.87)	3.11 (1.17)	2.75 (2.38)	0.08	0.92	1.00	1.00	1.00
Clinical stability, *weeks*	106.89 (86.29)	114.89 (92.4)	115.5 (85.86)	0.03	0.97	1.00	1.00	1.00
Patients on treatment* *(n, %)*	6 (66.7)	9 (100)	7 (87.5)	0.58	0.45	0.33	0.29	0.07
FAST, *total score*	21.22 (4.12)	28.78 (8.84)	24.5 (6.09)	2.91	0.08	0.97	0.60	0.07
SCIP, *total score*	66.78 (10.34)	74 (3.67)	64.5 (9.02)	3.2	0.06	1.00	0.08	0.22
Attention / Working Memory	47 (3.45)	48.06 (5.29)	49.31 (8.65)	0.31	0.74	1.00	1.00	1.00
Verbal Memory	41.67 (9.01)	46.67 (6.61)	47.5 (11.02)	1.08	0.36	0.58	1.00	0.75
Visual Memory	40.56 (9.65)	44.67 (7.21)	38.69 (9.94)	1.00	0.38	1.00	0.55	1.00
Processing Speed	51.11 (8.76)	48.94 (6.84)	50.44 (7.16)	0.19	0.83	1.00	1.00	1.00
Executive Function	45.39 (5.64)	48.89 (2.93)	44.31 (6.55)	1.83	0.18	1.00	0.25	0.50
PDQ-20, *total score*	31.89 (14.34)	36.33 (14.09)	25.5 (14.28)	1.23	0.31	1.00	3.93	1.00
HDRS-17, *total score*	6.22 (3.83)	8 (3.39)	6 (3.02)	0.89	0.43	1.00	0.74	0.86
RDQ, *total score*	24 (17.15)	33 (12.33)	20.38 (17.65)	1.46	0.25	1.00	0.34	0.72
SF-36,-V2 *total score*	123.56 (25.13)	113.44 (18.88)	109.5 (26.41)	.817	0.45	0.70	1.00	1.00

INCREM, INtegral Cognitive REMediation for Depression; TAU, Treatment As Usual; FAST, The Functioning Assessment Short Test; SCIP, Screening for Cognitive Impairment in Psychiatry; PDQ-20, Perceived Deficit Questionnaire; HDRS-17, Hamilton Depression Rating Scale; RDQ, Remission from Depression Questionnaire; SF-36-V2, 36-Item Short Form Health Survey. *Antidepressant treatment following clinical guidelines. Values in treatment arm represent mean scores (standard deviation). Cognitive domains performance is displayed as T-scores.

Primary outcome: effects of treatment arm on FAST scores

The repeated measures ANOVA concerning psychosocial functioning showed no significance in the time × group interaction (Pillai's trace F=0.90; df=4, 46; p=0.47) but a significant time effect (Pillai's trace F=6.34; df=2, 22; p=0.01) and a univariate treatment effect (F=4.57; df=2, 23; p=0.02). Post hoc comparisons showed that INCREM program decreased FAST scores compared to psychoeducation, especially in the 6-month post-intervention assessment (p=.041). More in detail, the improvement in functioning occurred in all three-treatment options in the post-intervention session (T1). But a long-term functioning improvement was only observed in INCREM intervention group (Baseline FAST mean score=22; Post-intervention FAST mean score=15; Follow-up FAST mean score=9). **Figure 2 (A)** displays changes on the psychosocial functioning measure between groups over time.

Percentages of change in FAST score from baseline among groups over time are shown in **Figure 2 (B)** as well. Although the psychoeducation group had higher baseline scores on the FAST (non-significant difference), the percentage of change revealed that this initial difference was negligible.

Indeed, the INCREM group showed a percentage of change of 55%, significantly larger than the other intervention groups (Psychoeducation=20%, TAU=3%).

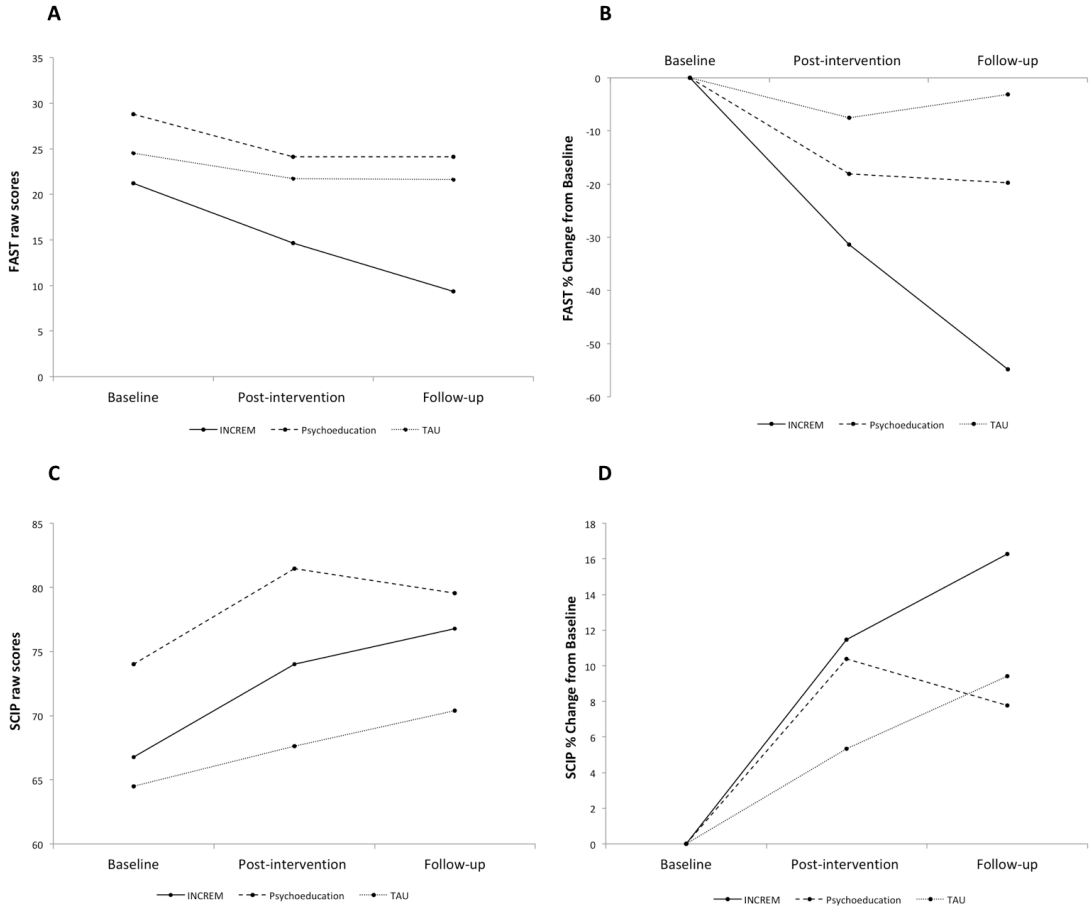
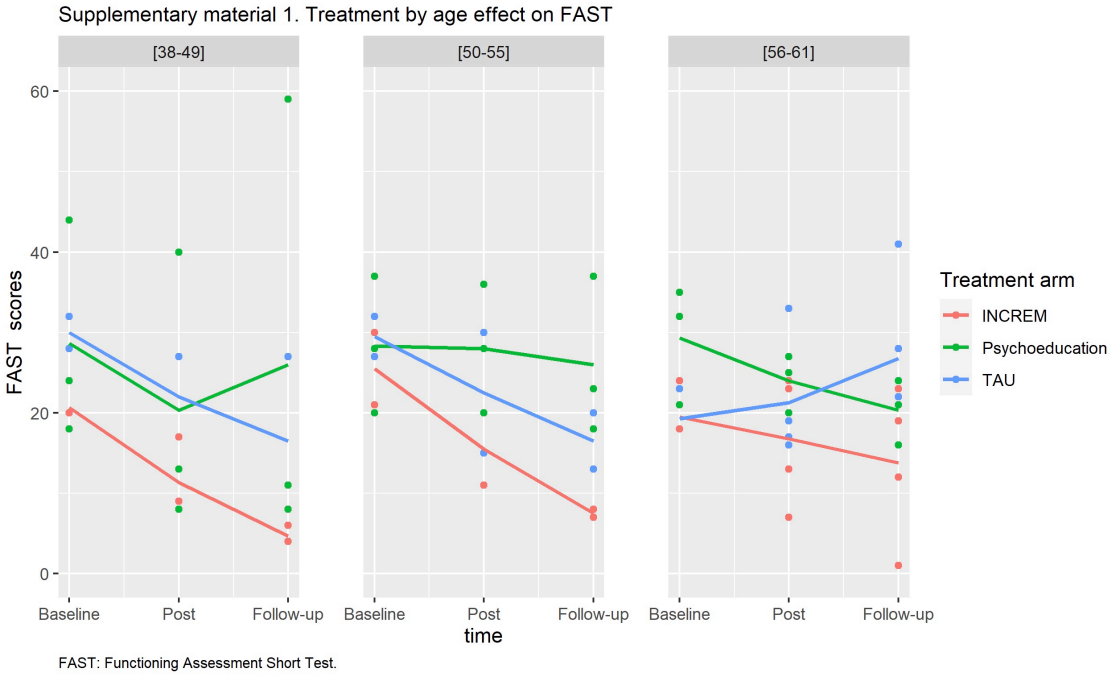


Figure 2. Changes on the psychosocial functioning measure between groups over time (A), the percentage of FAST score change from baseline among groups over time (B), changes on the cognitive functioning measure between groups over time (C) and the percentage of SCIP score change from baseline among groups over time (D).

Additionally, rates of recovery on FAST scores (Bonnín et al., 2018) at post-intervention assessment were of 44.5% in the INCREM group, 0% in the TAU group and 11.2% in the psychoeducation group, while at follow-up the figures were 66.7%, 12.5% and 22.3%, respectively.

Furthermore, the interaction analysis of FAST × treatment arm × age did not reach significance (see **Supplementary Material 1**) and the findings showed the progressive improvement of psychosocial functioning across all age categories included in the analysis for those patients who underwent INCREM program.



Secondary outcome: effects of treatment arm on cognitive performance

No statistically significant time x group interaction on the SCIP was revealed (Pillai's trace F=0.82; df=4, 46; p=5.17). However, a significant effect of time (Pillai's trace F=11.72; df=2, 22; p=<0.001) and a significant univariate treatment effect (F=3.97; df=2, 23; p=0.03) were found in general cognitive performance. Certainly, there was a cognitive improvement in all treatment groups across time. In addition, the SCIP total score was increased substantially at the follow-up assessment from post intervention in the INCREM group compared to the other groups, suggesting a long-term general cognitive improvement. **Figure 2 (C)** displays changes on the cognitive functioning measure between groups over time, and **Figure 2 (D)**, shows percentages of change in SCIP score from baseline among

groups over time. **Table 2** displays baseline, post-intervention and follow-up performance of groups on SCIP.

Table 2. Baseline, post-intervention and follow-up performance of groups on outcome measures.

	INCREM (n=9)			**Psychoeducation** (n=9)			**TAU** (n=8)		
	Baseline	Post intervention	Follow-up	Baseline	Post intervention	Follow-up	Baseline	Post intervention	Follow-up
FAST	21.22 (4.12)	14.67 (6.54)	9.33 (7.35)	28.78 (8.84)	24.11 (10.22)	24.11 (15.53)	24.5 (6.09)	21.75 (7.11)	21.63 (10.68)
SCIP	66.78 (10.34)	74 (12.17)	76.78 (9.38)	74 (3.67)	81.44 (7.97)	79.56 (7.80)	64.5 (9.02)	67.63 (9.02)	70.38 (11.41)
PDQ-20	31.89 (14.34)	26.67 (10.82)	25.22 (13.65)	36.33 (14.09)	31 (13.78)	29.67 (12.80)	25.5 (14.28)	26.5 (12.32)	25.75 (13.44)
HDRS-17	6.22 (3.83)	6.56 (5.08)	3.67 (4.44)	8 (3.39)	8.44 (3.28)	10.22 (7.19)	6 (3.02)	4.75 (3.81)	6.75 (4.43)
RDQ	24 (17.15)	23.89 (20.19)	17.22 (18.97)	33 (12.33)	35.33 (15.23)	32.22 (17.34)	20.38 (17.65)	20.38 (11.55)	25.75 (21.57)
SF-36	123.56 (25.13)	121.56 (24.95)	122.33 (25.18)	113.44 (18.88)	108.89 (17.27)	112.56 (20.93)	109.5 (26.41)	116.75 (19.73)	116.38 (15.96)

INCREM, INtegral Cognitive REMediation for Depression; TAU, Treatment As Usual; FAST, The Functioning Assessment Short Test; SCIP, Screening for Cognitive Impairment in Psychiatry; PDQ-20, Perceived Deficit Questionnaire; HDRS-17, Hamilton Depression Rating Scale; RDQ, Remission from Depression Questionnaire; SF-36-V2, 36-Item Short Form Health Survey. Values represent mean scores (standard deviation).

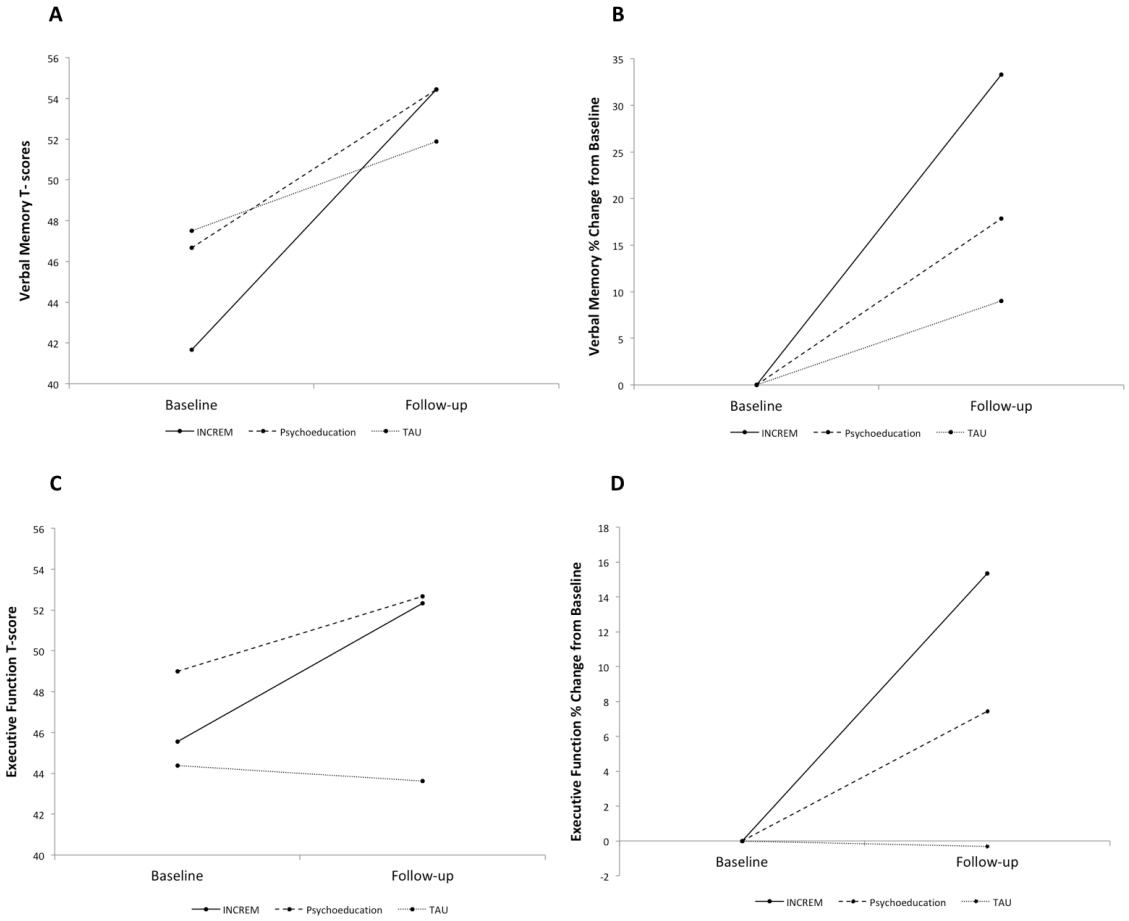
Regarding cognitive performance across cognitive domains, the repeated measures ANOVA of Attention/Working Memory showed no significant effect of group × time interaction (Pillai's trace F=0.56; df=2, 23; p=0.58), neither significant effect of time (Pillai's trace F=0.77; df=1, 23; p=0.39) nor a univariate effect of treatment (F=0.74; df=2, 23; p=0.49). In respect of Verbal Memory, the repeated measures ANOVA revealed significant time × group interaction (Pillai's trace F=4.21; df=2, 23; p=0.03) with a significant time effect (Pillai's trace F=49.42; df=1, 23; p=<0.001) but non-significant univariate treatment effect (F=0.19; df=2, 23; p=0.83). Concerning Visual Memory, the repeated measures revealed no significant interaction between group x time (Pillai's trace F=0.09; df=2, 23; p=0.92), nor a univariate treatment effect (F=1.35; df=2, 23; p=0.28). However, a main effect for time was observed (Pillai's trace F=5.29; df=1, 23; p=0.03). Similarly, Processing Speed showed no significant effect of group × time interaction (Pillai's trace F=2.97; df=2, 23; p=0.07) and no significant effect of treatment (Pillai's trace F=0.56; df=2, 23; p=0.58). But, revealed a main effect for time (Pillai's trace F=6.46; df=1, 23; p=0.02). With regard to executive function, the repeated measures ANOVA showed a significant time × group interaction (Pillai's trace F=5.11; df=2, 23; p=0.02), a significant time effect (Pillai's trace F=10.96; df=1, 23; p=0.003) and a significant univariate treatment effect (F=5.11; df=2, 23; p=0.15). **Table 3** displays baseline and follow-up cognitive performance across cognitive domains.

Table 3. Baseline and follow-up cognitive performance of groups across cognitive domains.

	INCREM (n=9)		**Psychoeducation** (n=9)		**TAU** (n=8)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Attention / Working Memory	47 (3.45)	46.44 (6.21)	48.06 (5.29)	49.22 (9.25)	49.31 (8.65)	51.75 (8.25)
Verbal Memory	41.67 (9.01)	54.44 (7.27)	46.67 (6.61)	54.44 (5.27)	47.5 (11.02)	51.88 (13.87)
Visual Memory	40.56 (9.65)	45.06 (5.48)	44.67 (7.21)	48.11 (10.46)	38.69 (9.94)	41.63 (9.41)
Processing Speed	51.11 (8.76)	55.94 (8.49)	48.94 (6.84)	55.83 (7.64)	50.44 (7.16)	49.25 (9.36)
Executive Function	45.39 (5.64)	52.19 (6.35)	48.89 (2.93)	52.56 (4.36)	44.31 (6.55)	43.47 (4.04)

INCREM, INtegral Cognitive REMediation for Depression; TAU, Treatment As Usual. Values represent mean T-scores (standard deviation).

Also, percentages of change in Verbal Memory and Executive Function are also shown in **Supplementary Material 2.** Despite the fact that INCREM and psychoeducation had similar follow-up scores on Verbal Memory and Executive Function, the INCREM group showed the largest percentages of change (33% in Verbal Memory and 15% in Executive Function).



Supplementary material 2. Changes on the Verbal Memory performance between groups over time (A), the percentage of Verbal Memory score change from baseline among groups over time (B), changes on the Executive Function performance between groups over time (C) and the percentage of Executive Function score change from baseline among groups over time (D).

Additional outcome measures

Regarding patients' appraisal of their own cognitive functioning, repeated measures revealed no significant interaction between group × time (Pillai's trace F=1.24; df=4, 46; p=0.31), nor a univariate treatment effect (F=0.59; df=2, 23; p=0.56). Nevertheless, a substantial main effect for time was observed when analysing the PDQ (Pillai's trace F=4.79; df=2, 22; p=0.02). Indeed, significant reductions in self-reported cognitive deficits were observed between baseline (T0) and follow-up (T2) for both intervention groups.

In respect of residual depressive symptomatology, the repeated measures ANOVA revealed no significant time × treatment group interaction (Pillai's trace F=2.31; df=4, 46; p=0.07), no significant time effect (Pillai's trace F=0.76; df=2, 22; p=0.93), and no significant univariate treatment group effect (F=2.09; df=2, 23; p=0.15). Finally, repeated measures on patients' perception of clinical remission revealed no significant group × time interaction (Pillai's trace F=1.12; df=4, 46; p=0.36), no significant

time effect (Pillai's trace F=0.23; df= 2, 22; p=0.8), and no significant univariate treatment group effect (F=1.73; df=2, 23; p=0.2).

Similarly, patients' quality of life showed no significant effect of group × time interaction (Pillai's trace F=0.98; df=4, 46; p=0.43), neither significant effect of time (Pillai's trace F=0.25; df=2, 22; p=0.78) nor a univariate effect of treatment (F=0.68; df=2, 23; p=0.52). Table 2 displays baseline, post-intervention and follow-up performance of groups on all the outcome measures.

DISCUSSION

The present analysis of this clinical trial provides preliminary evidence on the efficacy of the INCREM program in improving psychosocial functioning in remitted depressed patients with cognitive residual symptoms and regardless their age. A greater improvement in everyday functioning is observed for the INCREM group, and notably in long-term outcomes, compared to those patients receiving the psychoeducation-based intervention. Decrement of 55% on average between baseline and follow-up FAST scores indicates a significant improvement in everyday functioning after attending INCREM. Moreover, there is also an enhancement of general cognition, with improved scores on the SCIP scale over time. By contrast, depressive symptoms or other secondary variables did not show relevant improvements after the intervention.

In clinical practice, it is very common to observe patients who have a good clinical response referred to depressive symptomatology, but who do not see the return of their psychosocial functioning or cognitive ability prior to the depressive episode. Unfortunately, there are few studies that attempt to improve both clinical symptoms and psychosocial functioning, and most of them show the need to treat cognitive symptoms in order to improve the functioning of individuals. In the present study, both active treatment arms (Psychoeducation and INCREM) showed an improvement in psychosocial functioning at the end of the intervention. Yet unlike the other groups, functional improvements also increased over time in the INCREM intervention. A possible explanation is that INCREM seeks the long-term improvement of the cognitive resources to cope with functioning requirements of daily living by teaching patients to use their skills in ecological activities together with some training (drill and practice strategies), while providing information through an extensive psychoeducation program about what is major depression and what strategies can be useful may not be sufficient to consolidate alternatives to deal with usual problems in everyday life. Indeed, after six months of the INCREM program, more than 65% of patients reached functional recovery values (scores below 12), presenting good functioning in their lives, whereas the other two groups (Psychoeducation and TAU) showed lower percentages of functionally recovered patients (22.3% and 12.5%, respectively). Therefore, the study suggests that the combination of compensatory strategies based on a Functional Remediation (FR) in conjunction with Computerized Cognitive Training (CCT) leads to a maintained amelioration of daily functioning difficulties in depressive patients.

In secondary analyses, all participants showed a significant enhancement in general cognitive performance (SCIP) along the study period. With respect to the effect of treatment arm, the psychoeducation group also improved after the intervention even though cognitive performance worsened in the long term. By contrast, patients in the INCREM group continued to show improvements in the long-term assessment. Indeed, taking into account performance in the different cognitive domains, the results showed a greater improvement in verbal memory and executive function in the INCREM intervention group. These results are in line with previous research on depression showing that CR is effective in improving cognitive function (Hagen et al., 2020; Listunova et al., 2020), and it could be interpreted that this improvement mediates the return to premorbid psychosocial functioning (McIntyre et al., 2013). INCREM is based on the premise that in order to improve cognition, patients should understand what cognitive functions are, and how deficits in cognition lead to many of the difficulties they encounter in their everyday lives. The ultimate purpose of this intervention is to promote changes in the patients' daily lives by applying neurocognitive techniques in order to achieve their goals and by promoting continuous cognitive training. This habit can be fostered during the intervention, but it shall be assimilated by patients in the different facets of their lives in the following months. For this reason, cognitive and functional improvements can be seen months after treatment.

With respect to the depressive symptoms, no significant changes were observed in either treatment group. This is not surprising, given that the intervention is not primarily aimed at reducing residual depressive symptoms. Furthermore, the patients included in the study were already in clinical remission (65.4% of the patients) or in partial remission, leaving little room for improvement. Even so, patients in the CR group improved three points on the HDRS-17 in the last assessment of the study. One plausible explanation for this slight improvement is that INCREM intervention uses different techniques focused on coping with day-to-day difficulties. Being able to respond to them with greater competence may lead to greater satisfaction with life and a general sense of well-being, which could be translated into a decrease in residual depressive symptomatology, something highly prevalent in remitted depressed patients (Veeh et al., 2017). However, this is a mere speculation provided that the sample was too limited to explore the impact of the intervention on specific items that assess well-being, satisfaction or positive mental health from RDQ or SF-36.

These findings should be taken with caution due to the small sample size, but future studies are warranted to replicate them. The present study had to face some limitations, for example the end of the clinical trial had to be anticipated because of the COVID-19 pandemic and lockdown. Consequently, with less information available, the likelihood of reaching statistical significance in favour of the new treatment was more limited. Also, the power of the analysis might have been affected by the high dropout rate of participants, mostly due to personal or working reasons, because in the first series of intervention, allocation of subjects was done just after evaluation and not just before intervention commencement. This was amended in the next series of groups, and the dropout percentages

diminished drastically. It is worth mentioning that the high dropout rates could also be due to presenteeism at work of those active patients (more than 53% were in clinical remission) or at least with greater responsibilities due to work (less flexible schedules to attend to group-therapy). An additional observation to take into account is that the inclusion of a TAU group, which was not comparable with the two other types of interventions, allowed us to determine whether the mere fact of being part of a group therapy led to improvements in functioning. The results of the present study showed a clear difference in the main outcome measure between the two active intervention groups, with greater functional and cognitive change observed in the patients who were allocated in the INCREM intervention group. Finally, the effect of concomitant medication could not be controlled. However, as it is expectable that a high percentage, if not the majority, of patients who may benefit from this integral remediation strategy receive prescribed medication, it might not be entirely important to try to isolate its effect in the present or future research.

The results of the study have shown that INCREM is a well-accepted intervention, leading not only to functional improvement, but also to cognitive enhancement. Therefore, INCREM program proves to be a promising intervention strategy for partial or full clinically remitted depressed patients, who still experience cognitive and functioning difficulties in their day-to-day lives. These results provide a rationale for considering the use of this group-based strategy in naturalistic clinical settings in the future, thereby decreasing health care costs for those patients who do not achieve a full recovery (i.e., psychosocial remission and clinical remission).

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DECLARATION OF INTEREST

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ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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6. Discussió

Durant les últimes dues dècades, són molts els estudis que han intentat determinar la magnitud de la simptomatologia cognitiva en la depressió, no només amb l'objectiu de definir quines són les habilitats cognitives afectades, sinó també el grau d'afectació d'aquests dèficits. Les discrepàncies observades entre els diferents estudis han afavorit una insuficient comprensió d'aquests dèficits, fet que ha comportat que aquests símptomes cognitius no s'avaluïn sistemàticament en l'àmbit clínic i que la millora cognitiva quedi al marge dels objectius del tractament antidepressiu. Una possible hipòtesi que explica les inconsistències en la interpretació dels dèficits cognitius en la depressió és l'existència de diferents perfils cognitius entre els pacients, és a dir, que no necessàriament totes les persones que pateixen depressió haurien de presentar dificultats cognitives ni tampoc el mateix grau d'afectació al llarg de la malaltia. En aquest sentit, la present tesi explora el rendiment cognitiu de pacients depressius en les diferents etapes de la malaltia i mostra la presència de diferents perfils cognitius, tant en un primer episodi depressiu com en la fase activa de la depressió.

Més específicament, davant d'un primer episodi depressiu, els resultats mostren la presència de dos perfils cognitius diferents; un subgrup de pacients preservats a nivell cognitiu i un altre subgrup que mostra dificultats cognitives rellevants (Vicent-Gil et al., 2018). Així doncs, es confirma l'existència d'heterogeneïtat cognitiva ja en etapes inicials de la malaltia, explicant així la falta d'acord que existeix sobre quins són els dèficits cognitius específics en un primer episodi depressiu. A la vegada, emfatitza el concepte que la disfunció cognitiva no ha d'estar necessàriament lligada a la presència de símptomes depressius, ja que s'observen diferents perfils de rendiment cognitiu en una mostra de pacients amb un mateix curs de la malaltia i amb una gravetat de la simptomatologia depressiva similar.

De forma paral·lela, la recerca ha girat al voltant d'entendre què és el que passava amb les dificultats cognitives després d'un episodi depressiu. Alguns estudis defensaven la idea que la millora de la simptomatologia depressiva anava lligada a una millora cognitiva, mentre d'altres, recolzaven la persistència de dèficits cognitius després d'un episodi depressiu, inclús en períodes de remissió clínica. En aquest context, diversos autors, com per exemple Hammar & Ardal, ja havien suggerit que un sol perfil de rendiment cognitiu que caracteritzés a tots els pacients depressius era molt poc probable, i que a més, no tots els pacients havien de tenir el mateix grau d'afectació cognitiva (Hammar & Ardal, 2009). Seguint en aquesta línia d'investigació al voltant de la possible heterogeneïtat cognitiva, es va publicar un estudi amb una mostra de pacients depressius en remissió clínica on es va observar la presència de tres subgrups de pacients amb diferents perfils de rendiment cognitiu amb diferent grau d'afectació (Pu et al., 2018). La presència d'heterogeneïtat cognitiva durant un primer episodi depressiu i en etapes de major estabilitat clínica, fa pensar, de forma conseqüent, en la presència de diferents perfils cognitius al llarg de la malaltia incloent també les fases actives. No obstant, fins el moment de realitzar aquesta tesi, no existien estudis que demostressin la presència de diferents perfils cognitius durant un episodi actiu.

Sobre aquesta qüestió, tant en l'estudi anterior de primers episodis depressius (Vicent-Gil et al., 2018) com en l'estudi en remissió clínica (Pu et al., 2018), es van realitzar comparacions entre els diferents subgrups de pacients obtinguts, i es van observar diferències significatives en característiques clíniques i sociodemogràfiques (edat inici de la malaltia i/o capacitat intel·lectual). Aquests resultats van donar lloc a la reflexió sobre si aquest tipus de variables podien tenir un paper rellevant en la formació dels diferents clústers. Per aquest motiu, en la mostra de pacients en fase activa, es van incloure variables sociodemogràfiques i clíniques en l'anàlisi de clústers per tal d'observar el seu grau de relació amb els diferents perfils cognitius. Els resultats van mostrar la presència de tres perfils cognitius diferents: preservat, afectat selectivament i afectat globalment. A més, es va observar com l'existència d'aquests grups de pacients amb un mateix perfil cognitiu, no només depenia de la cognició, sinó també de variables clíniques, tal i com la literatura prèvia havia suggerit. La resistència al tractament sembla ser una variable important en la diferenciació d'aquests perfils cognitius. Per una banda, s'observa una relació entre la resistència al tractament i el fet de presentar majors dificultats en memòria verbal i funcions executives, en línia amb estudis recents que mostraven una afectació en l'hipocamp i en el còrtex prefrontal en pacients resistents al tractament (Ge et al., 2019). D'altra banda, existeix un perfil de rendiment cognitiu totalment afectat amb puntuacions molt per sota la normalitat en totes les proves neuropsicològiques utilitzades. Però aquest subgrup inclou tant pacients resistents al tractament com pacients que no ho són. De manera que tot i la premissa de relacionar la resistència al tractament amb una simptomatologia clínica més greu i amb una major probabilitat de patir disfunció cognitiva, no serà així en tots els casos, ja que hi hauran pacients no resistents que també mostraran un patró de disfunció cognitiva greu. Doncs, aquest perfil d'afectació cognitiva global sembla tenir com a característica principal la cognició i les dificultats en el funcionament psicosocial, i no sembla estar lligat a la resistència al tractament, funcionant així com un fenotip diferent.

Un raonament que s'extreu d'aquesta primera part de la tesi és la presència objectiva de diferents perfils cognitius ja des de l'inici i en les diferents etapes de la malaltia. Aquesta heterogeneïtat cognitiva ja ha estat descrita en altres trastorns afectius, específicament en el trastorn bipolar (Burdick et al, 2014; Cotrena et al., 2017; Lima et al., 2019; Solé et al., 2016), recolzant les troballes mostrades en depressió. Tenint en compte aquesta heterogeneïtat, la forma en la què s'ha investigat sobre cognició i depressió fins el moment no ha estat del tot eficaç, ja que el fet de combinar tots els pacients i tenir-los en compte en un conjunt, ha desvirtuat els resultats observant-se una afectació cognitiva menys severa del que possiblement podria arribar a ser. Convé ressaltar que el fet d'observar diferents perfils cognitius al llarg de la malaltia permet realitzar un pas més en l'enteniment de les dificultats cognitives en la depressió. És a dir, patir un primer episodi depressiu dóna lloc a un gran ventall de possibilitats quant a possibles cursos de la cognició, donada aquesta gran heterogeneïtat cognitiva en les diferents etapes de la malaltia (**Figura 5**). En altres paraules, existeixen nombroses possibles trajectòries de la malaltia des d'un primer episodi depressiu, d'aquí la importància en realitzar un seguiment individualitzat des de l'inici de la depressió. Això ens permetrà determinar si hi han dèficits cognitius en

les diferents etapes de la malaltia, si aquests dèficits estan causant dificultats funcionals psicosocials i si tot plegat està donant lloc a un curs més tòrpid de la depressió, dificultant així la recuperació completa dels pacients. A més, tal i com s'ha observat en aquesta tesi, el rendiment neuropsicològic a l'inici de la malaltia ja ens pot ajudar a predir la seva possible trajectòria clínica.

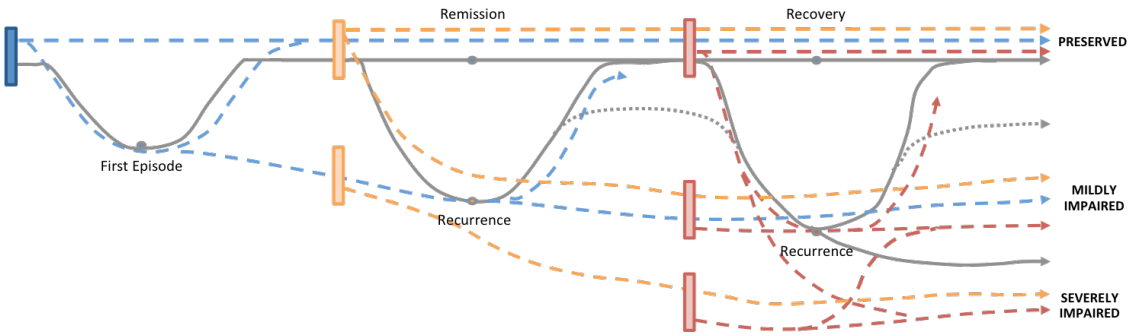

Figura 5. Representació esquemàtica de les diferents trajectòries de la malaltia durant el curs de la depressió.
Extret de "Determining the cognitive performance in the first episode of depresssion", per Vicent-Gil & Portella, 2021. In In Martin, C. R., Hunter, L-A., Patel, V. B., Preedy, V. R., Rajendram, R., *The neuroscience of depression: genetics, cell biology, neurology, behaviour and diet* (Annex).

En resum, els resultats de la present tesi posen de rellevància la necessitat de considerar el funcionament cognitiu de forma rutinària en els entorns clínics ja des de l'inici de la malaltia, i tant en aquells pacients depressius que presentin una major resistència al tractament com en aquells que estiguin responent adequadament al tractament antidepressiu ja que també poden presentar greus dificultats cognitives. De fet, molts dels pacients que milloren a nivell de simptomatologia depressiva, no tenen sensació de recuperació funcional ja que continuen percebent dificultats en les activitats de la vida diària. I moltes d'aquestes dificultats funcionals poden anar lligades a dèficits cognitius que no han estat identificats, i per conseqüència no tractats. Per tant, és important poder detectar aquells pacients amb majors dificultats cognitives i així poder establir tractaments més adequats per tal d'aconseguir una recuperació clínica i funcional dels pacients, i prevenir la possibilitat de patir noves recaigudes. Fins el moment, la majoria de les intervencions procognitives han estat dirigides majoritàriament a pacients en períodes de remissió clínica, que no havien retornat al nivell de funcionament previ al primer episodi depressiu, sense objectivar si presentaven dèficits cognitius. Poder identificar els pacients amb dificultats cognitives en les diferents etapes de la malaltia, permetrà portar a terme tractaments dirigits a no només a disminuir la simptomatologia depressiva sinó també la cognitiva, sense haver d'esperar a que es doni una millora clínica de la depressió. De fet, poder començar intervencions procognitives ja en fases inicials de la malaltia, podria donar lloc a una major probabilitat de presentar un curs menys tòrpid de la malalta (**Figura 6**).

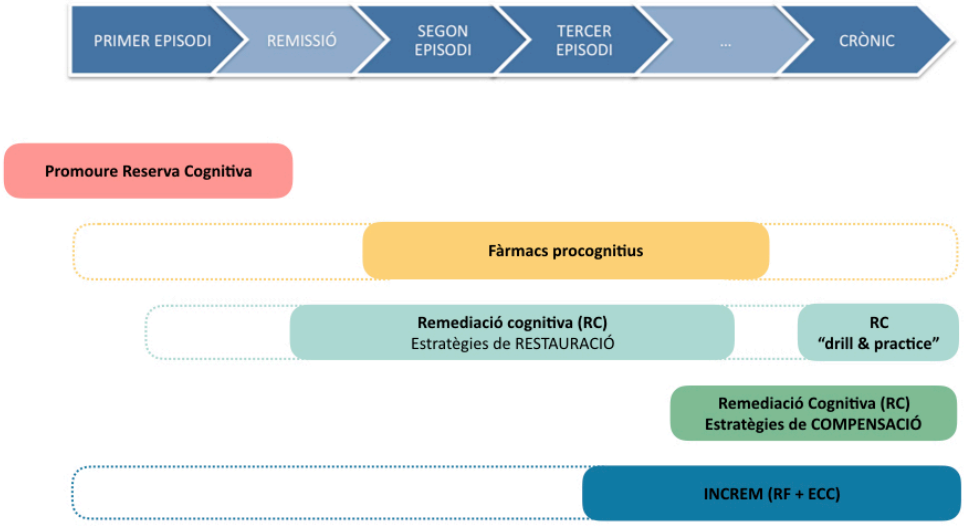

Figura 6. Proposta de tractament per als símptomes cognitius en línia temporal a la malaltia.
Nota. Tractaments per als símptomes cognitius habituals al llarg de la malaltia (color fosc) i proposta d'inici de tractaments (punts en color). RF: Rehabilitació Funcional, ECC: Entrenament Cognitiu Computeritzat.

Les intervencions dirigides a millorar la cognició en depressió no són tractaments del tot usuals en els entorns clínics en salut mental, tot i l'evidència d'estudis que mostren millores en atenció, memòria de treball, memòria verbal i no verbal, funció executiva i el funcionament cognitiu en general (Motter et al., 2016; Trapp et al., 2016; Hammar et al., 2020). Sembla ser que les estratègies de remediació cognitiva no només milloren la cognició sinó que també podrien millorar el funcionament psicosocial dels pacients (Lee et al., 2013; Listunova et al., 2020; Hagen et al., 2020). Tanmateix, la majoria d'aquests estudis no tenen en compte si aquests pacients presenten símptomes cognitius objectius, és a dir, no es realitzen exploracions neuropsicològiques ni escales de cribatge cognitiu que permetin identificar els pacients amb dèficits cognitius i incloure'ls en els estudis. Aquest fet podria haver esbiaixat els resultats observats en els estudis anteriors, disminuint la mida de l'efecte de les millores observades. La mida petita de les mostres d'estudi i les diferències metodològiques entre estudis, també podrien haver afectat a la transferència d'aquest coneixement a la pràctica clínica.

L'estratègia d'intervenció neurocognitiva INCREM permet realitzar un pas més en comparació als estudis previs. Per una banda, s'utilitza una escala de cribatge cognitiu, que permet portar a terme la intervenció en només aquells pacients que pateixen una disfunció cognitiva objectiva i unes dificultats funcionals rellevants que els impedeixen disposar d'una bona qualitat de vida. Per altra banda, s'uneixen dues estratègies de remediació cognitiva amb enfocs molts diferents: un programa de rehabilitació funcional (estratègia de compensació) i un entrenament cognitiu computeritzat (estratègia de restauració). Les dues estratègies per separat semblen donar lloc a millores cognitives, però la unió entre aquestes dues té com a objectiu el trasllat d'aquestes millores cognitives al funcionament diari dels pacients, que en definitiva, no deixa de ser l'objectiu final de qualsevol intervenció neurocognitiva.

Per tal de promoure canvis en el dia a dia dels pacients, INCREM treballa amb exemples de la vida diària dels propis pacients, és a dir, es treballen les dificultats funcionals personals i s'examinen quines facetes vitals s'estan veient afectades. És necessari poder identificar metes i valors personals per tal de promoure canvis en els seus hàbits, perquè trobin un sentit a la intervenció i perquè ho apliquin de forma rutinària a la seva vida. Els resultats de la implementació d'aquesta nova estratègia han suposat millores funcionals, millores en el rendiment cognitiu global i millores en els dominis cognitius de memòria verbal i funció executiva, sobretot en el seguiment a llarg termini, mostrant una evidència clara quant a l'eficàcia d'aquesta nova estratègia.

Així doncs, INCREM es basa en què els pacients comprenguin què són les funcions cognitives i que entenguin com els dèficits cognitius porten a les dificultats en la vida quotidiana tant a nivell personal, social com laboral. Aleshores, a través de l'ús de tècniques neurocognitives, de l'entrenament de certes habilitats mitjançant tasques ecològiques i del fet de portar a terme un entrenament cognitiu computeritzat, es comencen a produir canvis en el dia a dia dels pacients, aconseguint així objectius personals i fomentant un entrenament cognitiu continu. Segurament la intervenció és l'incentiu per promoure un hàbit, però el trasllat d'aquest aprenentatge a la vida dels pacients no succeeix fins el següents mesos, on comencen a aplicar tot allò après durant la intervenció en les diferents facetes de la seva vida. Potser, aquest podria ser el motiu per el qual les millores cognitives i funcionals s'observen mesos després d'haver realitzat el tractament. Entendre que els dèficits cognitius són un símptoma més de la malaltia, normalitzar que aquests poden estar presents en etapes de major estabilitat clínica, que hi han eines que poden ajudar a millorar la cognició, i que aquestes millores es traslladen a la nostra vida quotidiana si existeix un entrenament cognitiu continu, és possiblement clau per a la millora de la qualitat de vida dels pacients i pel manteniment d'una salut mental positiva en els pacients depressius.

LIMITACIONS

No obstant, qualsevol tesi no està exempta de limitacions. En primer lloc, el seguiment neuropsicològic dels perfils cognitius en la mostra de primers episodis depressius ens permetria entendre millor com és la heterogeneïtat cognitiva al llarg de la malaltia, i quin paper juga la cognició en la trajectòria de la depressió. En segon lloc, s'ha de tenir en compte la mida petita de la mostra en l'estudi de primers episodis depressius. Tanmateix, els resultats són força prometedors ja que aporten nova evidència respecte la cognició a l'inici de la malaltia. En tercer lloc, degut al disseny transversal de l'estudi dels pacients depressius en fase activa és impossible valorar l'estabilitat dels perfils cognitius. En quart lloc, el perfil cognitiu afectat selectivament divergeix força en els dominis cognitius respecte els estudis previs en trastorns afectius. Possiblement, existeix un altre tipus d'heterogeneïtat en aquest perfil en concret, la qual no s'ha pogut desentrellar mitjançant una anàlisi de clúster. En últim lloc, les limitacions principals en l'estudi d'eficàcia de la intervenció neurocognitiva INCREM són la quantitat d'abandonaments a l'inici de l'estudi donat una equívoca estratègia d'assignació (millorada en els següents grups d'estudi) i a la finalització precipitada de l'estudi donada la pandèmia mundial per

COVID-19. Amb tot, els resultats són totalment esperançadors ja que tot i la mida petita de l'estudi, es mostra l'eficàcia del tractament tant a nivell de cognició com en el funcionament psicosocial.

7. Conclusions

En la present tesi es discuteix la presència d'heterogeneïtat en el rendiment cognitiu dels pacients, tant en fases inicials de la malaltia com en fases més avançades. A més, s'aplica una nova estratègia de remediació cognitiva específica per aquells perfils cognitius amb disfunció cognitiva i se'n discuteix la seva eficàcia en un estudi preliminar.

A continuació, es presenta un llistat de les conclusions que es poden extreure dels diferents treballs que aquí s'integren:

1. Existeixen diferents dos perfils cognitius ja en l'inici de la malalta: preservat i afectat. Així doncs, no tots els pacients presentaran dificultats cognitives durant un primer episodi depressiu.

2. El rendiment cognitiu dels pacients a l'inici de la malaltia permet predir la simptomatologia depressiva a nivell basal i com serà l'evolució clínica d'aquests pacients.

3. En una mostra de pacients en fase aguda existeixen tres perfils cognitius (preservat, selectivament afectat i globalment afectat) considerant no només el rendiment cognitiu, sinó també variables sociodemogràfiques i clíniques, com ara la resistència al tractament antidepressiu.

4. Els pacients amb un perfil d'afectació cognitiva global presenten majors dificultats en el funcionament psicosocial.

5. La resistència al tractament no va sempre lligada a la presència de majors dificultats cognitives. És a dir, tots els pacients són susceptibles a presentar dèficits cognitius, no només aquells amb un curs més tòrpid de la malaltia.

6. INCREM es mostra com una nova estratègia d'intervenció procognitiva eficaç en el tractament dels dèficits cognitius i funcionals de pacients depressius en remissió clínica.

8. Línies de futur

Al llarg d'aquesta tesi s'ha discutit sobre el concepte de dèficit cognitiu en la depressió i en com poder millorar les dificultats cognitives i funcionals dels pacients amb l'aplicació d'una nova estratègia d'intervenció procognitiva.

A conseqüència, els resultats i conclusions d'aquesta tesi, han donat lloc a una nova línia de treball actual centrada en: demostrar l'eficàcia del tractament d'intervenció INCREM, respecte a una intervenció de psicoeducació, a través d'un assaig clínic aleatoritzat multicèntric.

Així mateix, els resultats de la tesi han plantejat noves qüestions no resoltes en què seria interessant continuar treballant:

1. Seguir l'evolució dels diferents perfils neuropsicològics a partir d'una mostra de primers episodis depressius. D'aquesta manera, es podria corroborar fins a quin punt el rendiment neuropsicològic a l'inici de la malaltia pot ajudar a determinar quina serà l'evolució clínica dels pacients, i quin serà el millor tractament per reduir la possibilitat d'una evolució més tòrpida de la malaltia.

2. Provar l'eficàcia de la intervenció INCREM en una mostra de pacients amb un primer episodi depressiu o en fase activa de la malaltia, per així observar si utilitzar aquest tipus d'intervenció, sense haver d'esperar a una millora de la simptomatologia depressiva, podria millorar el curs de la malaltia.

3. Incloure mesures de benestar i salut mental positiva, per tal d'observar si l'estratègia INCREM pot afavorir la consecució d'una recuperació completa (no només funcional) després d'un episodi depressiu.

4. Seguint la línia de tractaments procognitius, valorar si l'ús de fàrmacs antidepressius dissenyats per a la millora de la cognició conjuntament amb un seguiment terapèutic basat en INCREM podria portar a una major millora de la cognició i del funcionament psicosocial.

9. Resum tesi

PERFILS COGNITIUS EN LA DEPRESSIÓ I DESENVOLUPAMENT D'UNA ESTRATÈGIA D'INTERVENCIÓ NEUROCOGNITIVA

Introducció

Existeix suficient evidència científica que mostra la presència de dificultats d'atenció, de memòria, de velocitat de processament i de funcionament executiu en les fases actives de la depressió, fins i tot en períodes de major estabilitat clínica. Tanmateix, hi ha pacients que no presenten mai cap dèficit cognitiu al llarg de la malaltia o que milloren aquesta simptomatologia amb el pas del temps, és a dir, no tots els pacients disposen d'un mateix grau d'afectació cognitiva. Així doncs, existeix una clara heterogeneïtat cognitiva en la pràctica clínica, però no hi han estudis que recolzin la presència de diferents perfils cognitius en la depressió. A més, aquesta disfunció cognitiva ha estat relacionada amb un pitjor funcionament psicosocial i laboral, amb una pitjor qualitat de vida, amb una major probabilitat de patir noves recaigudes i amb una baixa taxa de recuperació completa. Però, els tractaments farmacològics i de psicoteràpia actuals, tot i millorar els símptomes depressius, no semblen ser suficients per a una recuperació completa dels pacients. De manera que es fa necessari la implementació d'intervencions neurocognitives, que no només millorin la cognició, sinó també, la funcionalitat i la qualitat de vida dels pacients depressius.

Objectius

El primer objectiu principal d'aquesta tesi és l'estudi de l'heterogeneïtat en el rendiment cognitiu dels pacients en depressió, tant en la primera fase de la malaltia com en fases més avançades. De forma lligada, s'estudia la relació entre la disfunció cognitiva i variables sociodemogràfiques, clíniques i de funcionament psicosocial.

El segon objectiu principal és el desenvolupament d'una estratègia d'intervenció neurocognitiva dirigida a pacients amb dèficits cognitius i funcionals, i la seva posterior aplicació en una mostra de pacients depressius en remissió clínica total o parcial.

Metodologia

Per tal d'acomplir el primer objectiu principal, es van portar a terme dos estudis dissenyats per a estudiar els possibles perfils cognitius en els pacients depressius. En el primer estudi, es va explorar la presència d'heterogeneïtat cognitiva en una mostra de pacients amb un primer episodi depressiu a través d'una anàlisi de clúster jeràrquic. A més es va estudiar el paper del rendiment cognitiu en la manifestació clínica de la malaltia, tant a nivell basal com a llarg termini. En el segon estudi, donat que existeixen variables sociodemogràfiques i clíniques que han estat relacionades amb la disfunció

cognitiva i que podrien estar afectant al perfil cognitiu al llarg de la malaltia, es va portar a terme una anàlisi de clúster "two-step" en una mostra de pacients en fase activa de la malaltia.

De forma paral·lela i per tal de dur a terme el segon objectiu principal d'aquesta tesi, es va desenvolupar una nova estratègia d'intervenció cognitiva integral anomenada INtegral Cognitive REMediation (INCREM), amb l'objectiu de millorar el funcionament psicosocial a través de la millora del rendiment cognitiu. Aquesta està formada per un programa de rehabilitació funcional (RF) i un programa d'entrenament cognitiu computeritzat (ECC), en la qual s'utilitzen estratègies de compensació i restauració per tal d'aconseguir una millor recuperació funcional dels pacients depressius. Per tal de valorar-ne l'eficàcia, es va dissenyar un assaig clínic aleatoritzat per a pacients depressius en remissió clínica total o parcial. Els pacients s'aleatoritzen a una de les tres branques de tractament (INCREM, Psicoeducació o tractament habitual) i s'avaluen en tres moments temporals diferents (basal, post-intervenció i longitudinalment). Finalment, l'últim estudi de la tesi, va ser la implementació de l'assaig clínic en una mostra de pacients depressius en remissió clínica total o parcial (avaluat a través de l'escala HDRS-17). A més, els pacients havien de mostrar dèficits cognitius objectius (valorat amb l'escala SCIP) i dificultats funcionals (valorat a través de l'escala FAST).

Resultats

Els resultats del primer estudi van mostrar la presència de dos perfils cognitius diferents en pacients amb un primer episodi depressiu: preservat i afectat. El perfil cognitiu afectat mostrava una alteració subtil en la funció executiva i una alteració significativa en atenció/working memory i memòria verbal. A més, una major simptomatologia depressiva basal es va relacionar amb una major disfunció en memòria verbal. Per últim, es va mostrar com les millores simptomàtiques als 12 mesos es relacionaven amb la presència d'un millor rendiment executiu i lingüístic basal. El segon estudi mostrava l'existència de diferents perfils cognitius en pacients depressius en fase activa, tenint en compte no només la cognició, sinó també variables sociodemogràfiques i clíniques. La resistència al tractament va ser la variable amb més importància en la separació dels clústers, seguit pel rendiment cognitiu (habilitat verbal, funció executiva, atenció/memòria de treball i memòria verbal). Es van determinar tres subgrups de pacients: clúster 1 (preservat) caracteritzat per pacients no resistents al tractament amb un rendiment cognitiu preservat, clúster 2 (afectat selectivament) format per pacients resistents amb dèficits en memòria verbal i funció executiva, i el Clúster 3 (afectat globalment) amb pacients resistents i no resistents al tractament amb una afectació cognitiva global. Tal i com s'esperava, el grup amb dèficits cognitius globals presentaven majors dificultats funcionals envers la resta de clústers.

El tercer estudi de la tesi va donar lloc a la creació de la nova estratègia d'intervenció procognitiva INCREM. A continuació, es va dissenyar un assaig clínic aleatoritzat per tal de demostrar l'eficàcia d'INCREM i es va publicar el protocol de l'estudi. En últim lloc, es va portar a terme l'estudi i es va observar una millora significativa del funcionament psicosocial en una mostra de pacients depressius en

remissió clínica. Més concretament, el grup INCREM va mostrar una millora del funcionament a llarg termini, un percentatge de canvi en la funcionalitat molt superior a la resta de branques de tractament, i una taxa de recuperació funcional del gairebé 70%. A més, el grup d'intervenció INCREM també va mostrar una millora en el rendiment cognitiu global dels pacients al llarg del temps, així com una millora en els dominis cognitius de memòria verbal i funció executiva. Així doncs, els resultats va mostrar evidència preliminar quant a l'eficàcia d'aquesta nova estratègia.

Conclusions

La present tesi explora l'heterogeneïtat cognitiva dels pacients depressius en diferents etapes de la malaltia i mostra la presència de diferents perfils cognitius, tant en un primer episodi depressiu com en la fase activa de la depressió. El fet d'observar diferents perfils cognitius ja des de l'inici i en les diferents etapes de la malaltia, obre una gran ventall de possibilitats quant a possibles trajectòries dels símptomes cognitius, i conseqüentment, possibles cursos de la malaltia. Considerar el rendiment cognitiu dels pacients depressius en els entorns clínics de forma rutinària podria ajudar a detectar aquells pacients amb majors dificultats cognitives i funcionals, i portar a terme estratègies d'intervenció més adequades per tal d'aconseguir un curs menys tòrpid de la malaltia. La remediació cognitiva (RC) és un estratègia d'intervenció procognitiva que ha mostrat resultats positius en la millora de la cognició, i en cert punt del funcionament, però fins el moment les diferències metodològiques entre estudis han fet difícil la seva transferència a la pràctica clínica. Mitjançant aquesta tesi, s'ha desenvolupat i aplicat una intervenció cognitiva integral anomenada INCREM, la qual unifica dos enfocs de RC (restauració i compensació) que donen lloc a no només una millora en el rendiment cognitiu, sinó sobretot, una millora del funcionament psicosocial dels pacients depressius a llarg termini. El fet d'entendre la disfunció cognitiva i aprendre eines que poden ajudar a millorar la cognició en el nostre dia a dia, conjuntament amb un entrenament cognitiu continuat, permet millorar la qualitat de vida i mantenir una salut mental positiva en els pacients depressius.

COGNITIVE PROFILES IN DEPRESSION AND DEVELOPMENT OF A NEUROCOGNITIVE INTERVENTION STRATEGY

Introduction

There is sufficient scientific evidence showing the presence of difficulties in attention, memory, processing speed and executive functioning in the active phases of depression, even in periods of greater clinical stability. However, there are patients who do not show any cognitive deficit throughout the course of the illness or who improve this symptomatology over time, i.e. not all patients have the same degree of cognitive impairment. Therefore, there is clear cognitive heterogeneity in clinical practice, but there are no stduies supporting the presence of different cognitive profiles in depression. Moreover, this cognitive dysfunction has been associated with poorer psychosocial and occupational functioning, poorer quality of life, a higher likelihood of relapse and a low rate of full recovery. However, current pharmacological and psychotherapeutic treatments, despite improving depressive symptoms, do not seem to be sufficient for a full recovery of patients. Hence, it is necessary to implement neurocognitive interventions that not only improve cognition, but also the functionality and quality of life of depressive patients.

Aims

The first aim of this thesis is to study the heterogeneity in the cognitive performance of depressed patients, both in the first phase of the disease and in more advanced phases. Linked to this, the relationship between cognitive dysfunction and sociodemographic, clinical and psychosocial functioning variables is also studied.

The second main purpose is the development of a neurocognitive intervention strategy designed for patients with cognitive and functional deficits, and its subsequent application in a sample of depressive patients in total or partial clinical remission.

Methods

In order to fulfill the first main objective, two studies designed to study possible cognitive profiles in depressive patients were carried out. In the first study, the presence of cognitive heterogeneity in a sample of patients with a first depressive episode was explored through a hierarchical cluster analysis. In addition, the role of cognitive performance in the clinical manifestation of the illness, both at baseline and in the long term, was studied. In the second study, given that there are sociodemographic and clinical variables that have been related to cognitive dysfunction and that could be affecting the cognitive profile throughout the course of the disease, a two-step cluster analysis was conducted in a sample of patients in the active phase of the disease.

In parallel, and in order to carry out the second main objective of this thesis, a new comprehensive cognitive intervention strategy called INCREM (Integral Cognitive Remediation) was developed, with the aim of improving psychosocial functioning by improving cognitive performance. This consists of a Functional Rehabilitation (FR) programme and a Computerised Cognitive Training (CCT) programme, in which compensation and restoration strategies are used in order to achieve better functional recovery of depressive patients. In order to assess its efficacy, a randomised clinical trial was designed for depressive patients in total or partial clinical remission. Patients are randomised to one of the three treatment arms (INCREM, Psychoeducation or treatment as usual) and are assessed at three different time points (baseline, post-intervention and longitudinally). Finally, the last study of the thesis was the implementation of the clinical trial in a sample of depressive patients in total or partial clinical remission (assessed through the HDRS-17 scale). In addition, patients had to show objective cognitive deficits (assessed by the SCIP scale) and functional difficulties (assessed by the FAST scale).

Results

The results of the first study showed the presence of two different cognitive profiles in patients with a first depressive episode: preserved and impaired. The impaired cognitive profile showed a subtle impairment in executive function and a significant impairment in attention/working memory and verbal memory. In addition, greater baseline depressive symptomatology was related to greater dysfunction in verbal memory. Finally, it was shown that symptomatic improvements at 12 months were related to the presence of better baseline executive and linguistic performance. The second study showed the existence of different cognitive profiles in depressive patients in the active phase, taking into account not only cognition, but also socio-demographic and clinical variables. Treatment resistance was the most important variable in terms of cluster separation, followed by cognitive performance (verbal ability, executive function, attention/working memory and verbal memory). Three subgroups of patients were determined: cluster 1 (preserved) characterised by non-treatment-resistant patients with preserved cognitive performance, cluster 2 (selectively affected) consisting of resistant patients with deficits in verbal memory and executive function, and cluster 3 (globally affected) with treatment-resistant and non-treatment-resistant patients with global cognitive impairment. As expected, the group with global cognitive deficits presented greater functional difficulties for the other clusters.

The third study of the thesis led to the development of the new procognitive intervention strategy INCREM. Next, a randomised clinical trial was designed to demonstrate the efficacy of INCREM and the study protocol was published. Finally, the above study was conducted, and a significant improvement in psychosocial functioning was observed in a sample of depressive patients in clinical remission. More specifically, the INCREM group showed an improvement in long-term functioning, a much higher rate of change in functioning than the other treatment arms, and a functional recovery rate of almost 70%. In addition, the INCREM intervention group also showed an improvement in patients' overall cognitive

performance over time, as well as an improvement in the cognitive domains of verbal memory and executive function. Thus, the results showed preliminary evidence for the efficacy of this new strategy.

Conclusions

The present thesis explores the cognitive heterogeneity of depressive patients at different stages of the illness and shows the presence of different cognitive profiles, both in a first depressive episode and in the active phase of depression. The fact that different cognitive profiles are observed already at the onset and at different stages of the illness opens up a wide range of possibilities regarding possible trajectories of cognitive symptoms and, consequently, possible courses of the illness. Considering the cognitive performance of depressive patients in clinical settings on a routine basis could help to detect those patients with greater cognitive and functional difficulties, and to implement more appropriate intervention strategies to achieve a less torpid course of the illness. Cognitive remediation (CR) is a procognitive intervention strategy that has shown positive results in terms of improving cognition, and to some extent functioning, but to date methodological differences among studies have made difficult the transfer to clinical practice. Through this thesis, a comprehensive cognitive intervention called INCREM has been developed and applied, which combines two CR approaches (restoration and compensation) that result not only in improved cognitive performance, but above all, in improved psychosocial functioning in long-term depressive patients. Understanding cognitive dysfunction and learning tools that can help improve cognition in our daily lives, in conjunction with ongoing cognitive training, can improve quality of life and maintain positive mental health in depressive patients.

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11. Annex

Determining the cognitive performance in the first episode of depression

(Vicent-Gil & Portella, 2021. In Martin, C. R., Hunter, L-A., Patel, V. B., Preedy, V. R., Rajendram, R., *The neuroscience of depression: genetics, cell biology, neurology, behaviour and diet.*

ABSTRACT

The most recent evidence suggests that cognitive dysfunction is a nuclear symptom of major depressive disorder (MDD), which in turn mediates the psychosocial functioning of depressed patients. However, few studies have determined whether cognitive disturbances are observable in the first stages of the disorder as some authors have described worse cognitive performance in both first episode and recurrent depressed patients, others have reported small impairments across most cognitive domains. Such disparity may be accounted by a great heterogeneity of cognitive profiles among patients that has not been taken much into account. The chapter goes on to briefly review the history of cognitive performance in MDD and to discuss the necessity of determining the cognitive dysfunction in the early stages of the disorder. The chapter concludes with the consideration of cognitive impairment alongside core depressive symptoms to direct efforts towards full recovery of patients from the very beginning of MDD.

KEYWORDS

Cognitive dysfunction, cognitive impairment, neuropsychology, psychosocial functioning, major depressive disorder, first-episode of depression, full recovery.

INTRODUCTION

Although diminished ability to think or to concentrate or to make decisions were some of the items for the diagnostic criteria of major depressive episode in the previous versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), and are still included in the latest version DSM-5 and ICD-11, cognitive dysfunction has not received enough attention to be considered a treatment target. There is sufficient scientific evidence that proves the existence of cognitive impairment not only in the acute phase of the disorder, but even in periods of remission of the so-called clinical symptoms (Rock et al., 2014). However, there is not a consensus on the specificity or the degree of such impairment: most of the studies report alterations in attention, processing speed, memory and executive functioning, but disparate findings cast doubt on the importance of assessing and treating cognitive dysfunction in MDD.

Although cognitive dysfunction is now starting to be considered a central characteristic of Major Depressive Disorder (MDD; Bortolato et al., 2015), this occurs mainly in the academic/research community. Cognitive symptoms are not assessed nor treated routinely in many clinical settings across countries, although difficulties in neuropsychological functioning have been correlated with poorer occupational and psychosocial function as well as with an increased risk of recurrences (Evans et al., 2014; Hammar & Ardal, 2009), impeding in most cases the full recovery of patients after clinical symptoms resolution.

Several factors have been associated with the small impact of such evidence on mental health care. The main one is the small-to-moderate effect sizes reported in the majority of studies, which has led to consider cognitive deficits as secondary to the disorder itself or a negligible aspect to be sorted out after relief of the rest of depressive symptoms (Bortolato et al., 2016). The mixture of patients often included in these studies could explain the difficulty to detect differences in cognitive performance when compared to healthy controls. As nicely described by Hammar and Ardal (2009), cognitive deficits may depend on the stage of the illness and on the specific illness trajectory of each patient, making it difficult to ascertain whether cognitive symptoms arise jointly with the rest of depressive symptoms (Hammar & Ardal, 2009). Therefore, the most recent studies are now investigating cognitive functioning in depressed sample with more homogeneous characteristics in terms of illness burden (i.e., comparing acute versus remitted; using staging methods; controlling for medications effects,…).

In the last ten years few studies have been published including patients with a first episode of depression (FED), with the aim to determining the cognitive performance in the early stages of MDD. Although the literature is still scarce, the findings suggest that cognitive impairment is already observable at the beginning of the disorder in a non-negligible percentage of patients. Therefore, in this chapter, a narrative description of the current literature on cognitive dysfunction is offered to the readers.

Cognitive Dysfunction in MDD

Depression is among the most common psychiatric disorders, and has become a leading cause of disability world-wide (Mayberg, 2013, pp. 365-526). Although great advances in the neurobiological description of MDD, the disorder continues to be diagnosed through clinical definitions based on patient self-report of a list of criteria delivered by a psychiatrist or a psychologist. Even treatments are generally prescribed without consideration of etiology or pathophysiological models provided by an enormous amount of scientific studies and the considerable progress in the understanding of the disorder.

The current diagnostic systems for MDD (DSM and the International Classification of Disease –ICD–) rely on the presence of one or more core stem criteria, and the addition of any combination of a defined number of associated criteria. Depressed mood and/or anhedonia are the nuclear criteria in both nosologic systems for major depressive episode. Cognitive disturbances appear as an associated criterion, similarly to weight loss/gain or appetite increase/decrease; psychomotor retardation or agitation; feeling of worthlessness or inappropriate guilt; etc. Cognitive impairment is defined as diminished ability to think or concentrate, or indecisiveness. However, cognitive disturbances in MDD go beyond these nonspecific difficulties and if patients, when interviewed by their psychiatrists or psychologists, do not refer these particular problems, this criterion might not be attended. In addition, standard depression scales such as Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI) or Patient Health Questionnaire (PHQ) do not assess all the cognitive domains either.

Brief history of cognitive dysfunction in MDD

In late 90's, evidence on the cognitive impairments in MDD increased exponentially, with findings showing alterations across multiple domains including executive functioning (Dunkin, 2000; Merriam, 1999; Paradiso, 1997; Schatzberg, 2000; Trichard, 1995); attention (Landro, 2001; Schatzberg, 2000); verbal and non-verbal memory (Basso, 1999; Purcell, 1997) and psychomotor functioning (Borkowska, 2001; Landro, 2001; Swann, 1999). Such difficulties were considered secondary to the disorder or even a consequence of some antidepressant treatments.

The number of published articles kept increasing up to date, and in many cases the theoretical model evolved together with neuroimaging studies, which provided a neurobiological base for cognitive dysfunction in MDD. These joint efforts leaded to some consensus in accepting a common neurobiological basis for cognitive dysfunction and depression (Pizzagalli, 2014). In particular, it was demonstrated that monoamines (including serotonin), glutamate and GABA are involved in depression and in cognition, as well as depression and disrupted cognition would affect the same pathways within a common neurocircuitry dysfunction (McIntyre, 2013; Seminowicz, 2004).

Meta-analyses of neuropsychological studies in MDD conducted during the first decade of 2000 showed that the magnitude of dysfunction in attention, executive function and memory provide effect sizes that range from approximately 0.3 to 0.5 Cohen's *d* (Baune, 2014; Lee, 2012; McDermott, 2009). This might be a strong reason why some researchers suggested that individuals with MDD were less cognitively impaired than people with schizophrenia or bipolar disorder. Consequently, cognitive dysfunction received little attention being considered a poor weight associated criterion in most of the current diagnostic systems. The relatively small magnitude of this dysfunction was also obvious when compared to the magnitude of cognitive dysfunction in some other conditions such as Alzheimer's disease or chronic schizophrenia, leading to consider that amelioration of cognitive dysfunction was not an important target for pharmacological or psychological interventions (Maruff & Jaeger, 2016, pp. 15-29)

Impact of Cognitive Dysfunction in MDD

During this last decade research on cognitive functioning in MDD has shifted its focus on the effects of neuropsychological dysfunction to achieve full recovery (i.e, going beyond clinical remission and achieving an optimal general daily functioning). This change has been possible because recent evidence suggest that cognitive dysfunction in MDD, despite its presumably small magnitude, impacts negatively on the psychosocial functioning of individuals. Up to 90% of individuals experiencing an acute episode of depression report impaired psychosocial function and 60% continue to experiencing such difficulties after antidepressant treatment (IsHak et al., 2016), which suggest that the resolution of stem depressive symptoms does not lead to improvements of psychosocial adaptation (McIntyre et al., 2015). Cognitive impairment appears to be associated with disturbances in a number of psychosocial domains such as workplace productivity and social relationships both during an acute episode (Iverson & Lam, 2013) and in clinically remitted patients (Knight, Air & Baune, 2018). Specifically, executive functioning has been considered the strongest independent predictor of functioning in remitted MDD patients (Knight et al., 2018). Some other studies have suggested a mediating effect of cognitive dysfunction in psychosocial disturbances (Zuckerman et al., 2018), in line with the findings on the relation between depressive symptoms and work functioning published by Lam and colleagues (2012), in which up to 52% of depressed patients reported that cognitive difficulties severely interfered with their occupational functioning.

Another aspect that may have undermined the importance of cognitive dysfunction in MDD, leading to small effect sizes reported until last decade, is the mixture of patients included in previous studies. Indeed more recent studies have shown that cognitive dysfunction in MDD can vary across stages of the illness (Rock, 2014; Robinson, 2007), has been associated with severity and number of recurrences (Semkovska et al., 2019), may be interfered by response to antidepressant treatment (Murrough, 2015; Pimontel, 2016; Serra-Blasco, 2015), and depends on the premorbid functioning of each individual (Venezia et al., 2018). In particular, the presence of psychotic or melancholic symptoms was associated with more severe cognitive impairments (Schatzberg, 2000; Withall, 2010). In addition, the magnitude

and scope of cognitive impairment is typically more severe in treatment-resistant depression than in patients who are responsive to treatment (Bowie, 2013; Harvey, 2007; López-Solá, submitted). A recent meta-analysis (Semkovska et al., 2019) has suggested that cognitive performance worsens after each depressive episode. Other sociodemographic variables, such as years of schooling, intellectual abilities and age have also been associated with lower cognitive functioning in patients with MDD. The synergistic effects of all these factors are far from being understood but may determine some sort of differential degrees of cognitive impairment in MDD. In other words, the neuropsychological dysfunction is extremely heterogenic and studies should establish different cognitive profiles to avoid regression to mean effect, which may hinder those patients with severe cognitive disturbances or patients without relevant cognitive symptoms.

Therefore, the heterogeneity of cognitive dysfunction in MDD needs to be taken into account both in clinical practice and in research studies. Particularly, in clinical settings, it would be highly recommended to use cognitive screening tests in all patients, not only in those who complain about their cognition, and research in the cognitive performance of MDD, heterogeneity can be dealt with the consideration of subgroups or clusters of patients defined by the degree of cognitive alterations. Clustering or cluster analysis encompasses a number of different algorithms and statistical methods that allow a classification of sets of objects or points (e.g. neuropsychological tests scoring) based on their similarity. This statistical technique has been used in studies of cognitive functioning in bipolar disorders (Burdick, 2014; Lima, 2019; Solé, 2016), and it is starting to be applied in MDD.

In this regard, a recent study has determined discrete neurocognitive subgroups in a sample of MDD patients with current affective stability (Pu et al., 2018). Noteworthy, while patients were clinically remitted, some of them were classified as globally impaired in terms of cognitive performance, showing moderate to severe cognitive deficits (>0.8 Cohen's *d*). Some unpublished findings also demonstrate three distinguishable clusters upon cognitive functioning in a sample of acutely depressed individuals. Interestingly, treatment resistance was the most important variable for clustering, in which non-resistant patients were cognitively preserved; resistant patients were selectively preserved; and a mixture of treatment resistant and non-resistant patients were globally and severely impaired (Vicent-Gil et al., submitted). Hammar & Ardal (2009) described different scenarios with regard to cognitive and depressive symptoms along the course of MDD (Hammar & Ardal, 2009). These authors stated that no single cognitive functioning could characterize all the patients with a diagnosis of MDD, and that not all patients would manifest the same cognitive disturbances nor at the same degree along the course of the illness (see **Figure 1**).

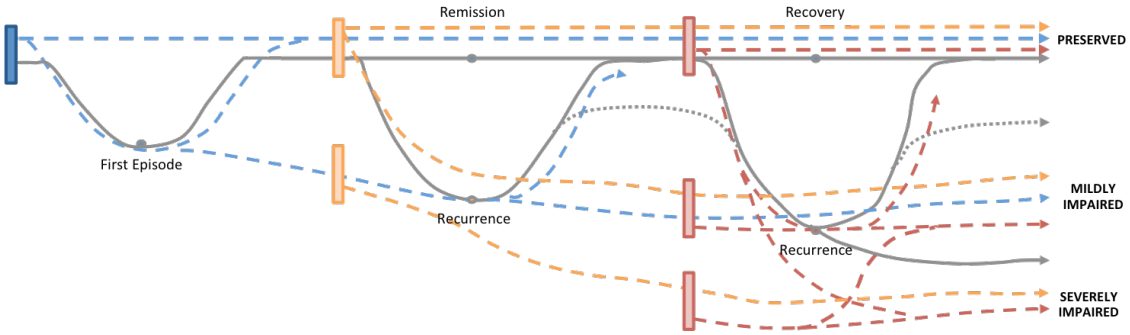

Figure 1. Schematic representation of different illness trajectories during the course of MDD.
Grey full line represents oscillating depressive symptoms which define episodes. According to Eaton and colleagues (2008), in the natural history of MDD one can expect that 50% of patients suffer a single episode with no future recurrences; 35% have recurrences and may present interepisodic residual symptoms (dotted grey line); and up to 15% of patients become chronic. Colored dotted lines represent different trajectories of cognitive symptoms along the course of MDD that evolve independently of MDD state. Colored boxes indicate episode start points, where cognitive symptoms may already be present (blue for first episode; yellow for second episode, red for recurrent episodes). The variability of cognitive functioning describes two subgroups of patients in the first episode (with mild cognitive symptoms or preserved cognition; Vicent-Gil et al., 2018), and three different clusters of cognitive performance from the second episode onwards (preserved, mildly impaired and severely impaired individuals).

COGNITIVE DYSFUNCTION IN THE FIRST EPISODE OF MDD

Previous research

As mentioned before, the majority of research studies focused on determining whether cognitive deficits were independent or a consequence of the clinical manifestation of MDD (Hammar & Ardal, 2009). The episodic nature of MDD also guided some reports, which showed that cognitive deficits worsened with repeated depressive episodes (Gorwood, 2008; Semkovska, 2019) and persisted during interepisodic clinical remission (Hasselbalch et al., 2011). However, such cognitive symptoms have been neglected for many years in the clinical management of depressed patients (Fiorillo et al., 2018), and in particular, in the first stages of MDD.

Because of that, cognitive functioning in patients suffering from their first episode of depression (FED) received little attention for many years, and few studies have been published in the last decade. Kaymak et al. (2010), in 20 drug-free female FED patients, found that those patients had significantly lower scores on attention, working memory, verbal memory, visual memory, psychomotor speed and executive functions than healthy females. This subgroup of FED patients also showed smaller hippocampus already at the onset of the illness. The work by Schmid and Hammar (2013a) studied cognitive functioning in a sample of 30 FED patients and 30 healthy controls. They found significant differences in inhibition and semantic verbal fluency, without differences between other measures of executive functioning. Subsequently, these authors (Schmid and Hammar (2013b) followed the previous patient group in a longitudinal perspective so as to study the possible relationship between cognitive functioning and the existences of relapses of depressive symptoms, 28 patients took part in the follow-up testing. Most patients were in clinical remission and showed a sustained impairment in inhibition and semantic fluency. Whereas patients with a relapse performed significantly worse in inhibition than patients that did not relapse. The narrative review by Trivedi and Greer (2014), described cognitive deficits in memory and decision making early in the course of the illness together with structural abnormalities in the hippocampus and prefrontal cortex. In line with the hippocampus involvement in the pathophysiology of MDD, Hansson, Murison, Lund and Hammar (2015) studied the relationship between cortisol levels before and after the Dexamethasone Suppression Test (DST) and cognitive functioning in 21 FED patients. However, no significant associations were found between cortisol and verbal memory and executive function.

On the other hand, other studies have investigated the cognitive performance of FED patients by comparing them with recurrent patients. In the work by Roca et al. (2015) such comparison was carried out before and after six months of treatment. At baseline, there were no differences between FED and recurrent patients in any cognitive domain. After treatment, remitted patients scored better in psychomotor speed, set-shifting ability, semantic verbal fluency, and planning and problem-solving, regardless of the stage of the illness. Another work comparing FED and chronic patients (Serra-Blasco et al. 2015) after one year of their prescribed treatment, showed an improvement in verbal memory in the

two groups. Chen et al. (2018) measured cognitive functioning in first episode drug-naïve patients compared to a group of medicated MDD patients and a healthy control group. This study provided evidence of an impairment in FED patients in visual, working and verbal memory. In light of these previous works, scarce longitudinal studies have been performed. Gu and colleagues (2016) studied a sample of 100 patients for two years after their first-episode of depression to identify predictors of cognitive impairment. Performance in processing speed, executive function and attention showed differences between impaired and unimpaired MDD patients.

Overall, the findings suggest that FED patients manifest cognitive deficits when compared to healthy controls, as it has been summarized in two meta-analyses by Lee and co-workers (2012) and Ahern & Semkovska (2016). The first one, including 13 studies and 644 FED patients, identified small to moderate significant cognitive deficits for psychomotor speed, attention, visual learning and memory, and executive functioning as verbal fluency, cognitive flexibility and attention switching (Lee et al., 2012). Similarly, the second one, using 31 studies with 994 patients, identified small to large impairments across most cognitive domains during a FED as well as, impairment in verbal learning and memory, and working memory (Ahern & Semkovska, 2016). Despite the presumably converging evidence from these two meta-analyses, the authors agree with the great heterogeneity of the cognitive variables included, and the large variation in the characteristics of the patients assessed.

Therefore, similar factors as the ones described previously in this chapter could be associated with the heterogeneity of cognitive performance in FED. Lee et al. (2012) found that some clinical characteristics such as depression severity and inpatient status were associated with lower cognitive performance in psychomotor speed, working memory and verbal and visual memory. The study also noted antidepressant medication correlated with worse verbal memory but with better cognitive flexibility. Besides, demographic factors as educational attainment or age have been found to influence the extent of cognitive impairment. In fact, older patients performed worse on tests assessing psychomotor speed, visual memory and executive functioning. And the less educated patients demonstrated worse verbal and visual memory, and attention switching as well. Ahern and Semkovska (2016) concluded that it is difficult to analyze the effects of these factors on cognitive function due to the scarce information provided in the studies (and thus, probably not taken into account).

Recent approach

One plausible explanation for such inconsistencies in the interpretation of neuropsychological performance in FED patients is the fact that, as in recurrent depressed patients, not all of them may show the same cognitive profile. So far, and as pointed out above, most of the previous studies on cognition were based on the average neurocognitive performance across all patients in the same sample. Therefore, using subgroups of patients taking into account their cognitive characteristics would also be more adequate to study cognitive performance in FED.

In this regard, one study explored cognitive performance in FED patients considering the presence of different cognitive profiles (Vicent-Gil et al., 2018). Using a hierarchical cluster analysis, FED patients were classified in two different subgroups within patients' performance: the preserved and the impaired cluster. FED patients displaying significant cognitive deficits, showed impairment in attention/working memory and verbal memory, and subtle impairment in executive functioning (See **Figure 2**). These results highlighted the importance of considering the heterogeneity in patients' cognitive performance, which might have hindered the interpretation of neuropsychological findings observed in previous literature.

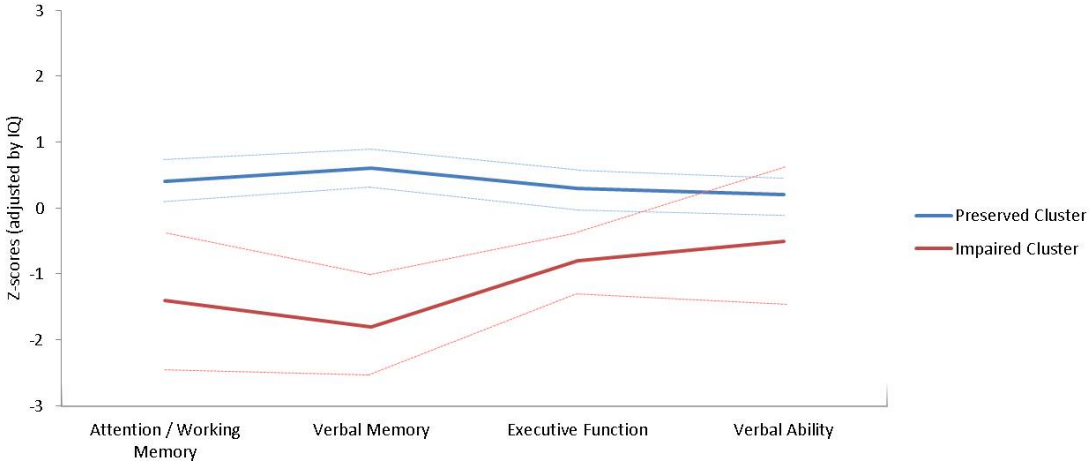

Figure 2. Neuropsychological profiles of z-scores for each cognitive component (four-dimension solution in principal component analysis).
The blue line represents preserved patients, and the red line represents impaired patients. Dash lines represent standard deviation of means. (Adapted from Vicent-Gil et al., 2018, no permissions required).

According to these findings, neuropsychological performance at the beginning of the disorder appears to be a relevant predictor of depressive symptoms at baseline and 12 months after the first-episode. In particular, depressive symptoms might be more predicted by verbal memory whereas executive function and verbal abilities might be more relevant indicators of depressive symptoms at long-term, i.e., associated in psychosocial engagement of patients. Given that cognitive performance seems to be related to clinical manifestation along the course of the illness, it is important to bear in mind the need of early detection at illness onset.

CONCLUSIONS

Compelling recent evidence has identified several types of disrupted cognition in MDD from high-level psychological constructs (attributional style or negative schemata) to basic cognitive processes (such as memory, executive functioning or processing speed), driving to the current cognitive and neuropsychological model of depression (Portella, 2019). However, to date, therapeutic interventions in clinical settings have been focused to the former, while theoretical accounts of depression propose that basic cognitive processes play a causal role in the development of both high-level psychological

constructs and symptoms (Harmer et al., 2009), which may even account for the modest effects of antidepressant treatments. Fortunately, since late 2000's, the growing body of literature started to examine cognitive symptoms as core characteristics of depression, in which for example rumination (as a psychological construct) is inherently associated with deficits in working memory and executive functioning (as cognitive processes).

Considering the above, it is important to identify those patients with cognitive impairment, and try to cope with these deficits using procognitive agents or remediation programs at very early stages of the illness. This early intervention could be the key to achieve a better functional outcome (Clark, 2016; Evans, 2014), and also to reduce the relapse rate in those patients (Hammar & Ardal, 2009). Cognitive remediation interventions are designed to improve psychosocial functioning through the treatment of cognitive impairment taking into account the heterogeneity in cognitive performance in MDD patients (Vicent-Gil et al., 2019).

KEY FACTS OF COGNITIVE DYSFUNCTION IN THE FIRST EPISODE OF MDD

- Cognitive dysfunction is a core symptom of MDD.
- Cognitive dysfunction is present in the first episode of MDD
- Cognitive impairment in the first episode of MDD affects attention, executive functioning, learning and memory, and psychomotor speed.
- There are different subgroups of cognitive dysfunction among patients with a first episode of MDD, from cognitively preserved patients, selectively/moderately affected patients.
- Cognitive dysfunction in the first episode can predict the short-term prognosis of MDD.
- Cognitive dysfunction is a mediating factor of poor psychosocial functioning in first episode of MDD.

SUMMARY POINTS

- This chapter focuses on the cognitive dysfunction in the first episode of major depressive disorder
- There is wide evidence of cognitive dysfunction in major depressive disorder, but it is mostly neglected by psychiatrists and psychologists in routine mental health care.
- Cognitive impairment has also been associated with poorer occupational and psychosocial functioning, as well as, with higher rate of recurrence of depressive episodes.
- Several factors have been proposed to explain why there are no or few treatments to ameliorate cognitive symptoms together with clinical symptoms: lack of consistent assessment of cognition, lack of specificity due to the variability within cognitive performance among patients, and heterogeneity of patients included in the studies would underlie quasi-negligible effect sizes reported so far.
- The potential existence of different cognitive profiles among depressed patients may explain inconsistent findings due to such heterogeneity.
- However, few clustering studies have been carried out in MDD, which have included clinically stable patients.
- Recently, studies are taking into account demographic and clinical characteristics to establish the cognitive dysfunction in MDD.
- Patients in their first episode of MDD offer a good opportunity to determine the extent of cognitive impairment in more homogeneous samples, in which treatment exposure is also better controlled.
- Cluster analysis of cognitive performance in patients with a first episode of depression can detect those individuals with greater cognitive disturbances, who will be susceptible to received more specific treatments to improve cognition in the early stages of the illness.

LIST OF ABBREVIATIONS

Abbreviations

MDD	Major Depressive Disorder
FED	First Episode of Depression
DSM	Diagnostic and Statistical Manual
ICD	International Classification of Disease
HAM-D	Hamilton Depression Rating Scale
MADRS	Montgomery-Åsberg Depression Rating Scale
BDI	Beck Depression Inventory
PHQ	Patient Health Questionnaire
d	differential (in Cohen's *d*)

MINI-DICTIONARY OF TERMS

***Cluster Analysis*.** It is a statistical analysis technique in which objects or subjects or points with similar characteristics are classified into separate categories (i.e. clusters) through a number of different algorithms.

Cognitive Dysfunction in MDD. Alterations of attention, executive functioning, psychomotor speed and memory as part of the symptomatology of MDD.

Cognitive Performance. It refers to the mental functioning of an individual, when evaluated through cognitive tests that cover several cognitive abilities such as learning, remembering, thinking, reasoning, problem-solving, decision-making, attention, etc.

First Episode of Depression. It is a cluster of depressive symptoms occurring together for the first time, fulfilling DSM or ICD criteria for a major depressive episode.

***Full Recovery*.** In mental health, it refers not only getting better from a clinical perspective, but achieving a full and satisfying life after an acute episode. Improving cognitive symptoms in MDD may help patients to feel themselves more fully recovered.

Major Depressive Disorder (MDD). It is an episodic and chronic mental disorder characterized by persistent feelings of sadness or incapacity, or lack of interest in outside stimuli most of the time for at least two weeks, normally accompanied by other symptoms affecting most of the body systems.

***Psychosocial Functioning*.** A compendium of abilities required to adapt to life in the context of a combination of psychological factors and social characteristics of the near environment.

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