Universitat Autònoma de Barcelona

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Al Joan i l'Helena. A la mare i la Nau.

I un home tot sol no sempre se basta.

Clint Eastwood, Antònia Font

Agraïments

Dec moltes coses a molta gent, i no tot ho podré tornar. Malgrat aquesta sensació d'incompliment, com a mínim m'agradaria poder agrair tota l'ajuda que he rebut. En primer lloc, voldria donar les gràcies al Miquel Àngel Fullana per obrir-me, literalment, les portes de casa seva, per compartir el seu bagatge i el seu temps, i portar-me a roda fins a *Les Champs-Élysées*. A la Bárbara Arias li agriria també moltes coses, però especialment la calidesa i els ànims quan la fatiga es feia perceptible. L'Albert Bonillo i el Carlos García Forero m'han transmès la bellesa de determinats conceptes estadístics, i amb ells també he compartit precioses estones sobre el món de la recerca, de les publicacions, de les universitats, de la sanitat pública i de la Humanitat en general. Al Natxo Garrido, la disponibilitat i l'alegria. A la Roser Guillamat i al Vicenç Vallès, les infinites facilitats i haver confiat en aquest projecte. I, *last but not least*, als companys del CST. Teniu una paciència de percentil 98. Moltíssimes gràcies a tots.

Índex

Abreviacions

ADIS-IV	Anxiety Disorders Interview Schedule for DSM-IV
AIC	Akaike Information Criterion
APA	American Psychiatric Association
BDNF	Brain-derived neurotrophic factor
BIC	Bayesian Information Criterion
BLRT	Bootstrap Likelihood Ratio Test
CFA	Confirmatory Factor Analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders
EFA	Exploratory Factor Analysis
GBTM	Group-Based Trajectory Modeling
GMM	Growth Mixture Modeling
ISRS	Inhibidors selectius de la recaptació de la serotonina
MIA	Mobility Inventory for Agoraphobia
MET	Metionina
NICE	National Institute for Health and Care Excellence
PDSS	Panic Disorder Severity Scale
PDSS-SR	Panic Disorder Severity Scale - Self Report
SSBIC	Sample-Size Adjusted BIC
TP	Trastorn de pànic
TCC	Teràpia cognitivoconductual
TCCG	Teràpia cognitivoconductual grupal
TOC	Trastorn obsessivocompulsiu
TPEP	Trastorn per estrès posttraumàtic

VAL	Valina
YBOCS	Yale-Brown Obsessive Compulsive Scale

I. Introducció

1. El trastorn de pànic

Tal i com explica David M. Clark (reconegut professor de la Universitat d'Oxford i referent en trastorns d'ansietat) en un article publicat el 1986 (1), no va ser fins als anys 60 que els atacs de pànic van esdevenir *per se* un focus d'interès per la recerca. Tot i que prèviament ja s'acceptava que eren un fenomen freqüent en els trastorns d'ansietat, no és fins als treballs de Donald F. Klein que es va produir aquest canvi d'èmfasi. Klein (2) va observar que els trastorns d'ansietat caracteritzats per la presència d'atacs de pànic responien a un tractament amb imipramina, mentre que altres trastorns d'ansietat no responien a aquest tractament. Segons Clark, aquesta *dissociació farmacològica* va conduir a Klein a considerar els trastorns d'ansietat amb atacs de pànic qualitativament diferents de la resta. Finalment, amb la publicació el 1980 de la tercera edició del Manual Diagnòstic i Estadístic dels Trastorns Mentals (DSM-III) (3), es va establir el concepte global amb el que actualment es coneix el trastorn de pànic (TP) (1, 4), que no ha variat substancialment en les posteriors edicions del DSM.

Segons el DSM-5 (5), els atacs de pànic es defineixen per l'aparició brusca de por o malestar intens, s'assoleix la seva màxima expressió en minuts, i es requereix que es produeixin un mínim de quatre símptomes d'una llista de tretze (p.e., increment de la freqüència cardíaca, sudoració, tremolors, sensació d'ofec, inestabilitat o desrealització). Tanmateix, per establir el diagnòstic de TP també és necessari que es doni una preocupació elevada i

contínua sobre possibles atacs de pànic futurs i les seves conseqüències (p.e., patir un atac de cor o asfixiar-se) i/o un canvi significatiu a nivell funcional, de forma associada a la preocupació pels atacs. Bàsicament, per la presència de conductes o estratègies de seguretat orientades a prevenir o minimitzar les conseqüències dels atacs.

Entre un 35 i un 65% dels pacients amb TP també compleixen criteris diagnòstics d'agorafòbia (6), definida per la por a llocs o situacions on podria resultar difícil escapar o rebre ajuda. Entre les situacions típicament temudes s'hi inclouen allunyar-se de casa, els mitjans de transport, els grans magatzems, els cinemes o les discoteques. En el cas de patir agorafòbia, aquestes situacions s'eviten, es resisteixen amb una elevada ansietat, o es requereixen tot una sèrie de conductes i estratègies de seguretat per poder-les suportar.

Tot i que hi ha evidència que suggereix que el TP i l'agorafòbia són dues entitats diferents que poden concórrer (6, 7), es manté l'assumpció tàcita que hi ha una relació temporal entre els dos fenòmens, i que l'agorafòbia suposa una complicació evolutiva del TP (8). De fet, hi ha estudis que mostren que en la majoria dels pacients diagnosticats de TP amb agorafòbia les evitacions agorafòbiques apareixen després a l'inici del TP (8).

En tot cas, l'elevada prevalença del TP, l'impacte en la qualitat de vida dels pacients (9), i els colossals costos econòmics i socials que suposa, fan que aquest sigui un important problema de salut pública. Segons resultats de Kessler *et al.* (10), la prevalença-any del TP arriba al 2.8% i la prevalença-vida al 4.7%. A nivell econòmic, Olesen *et al.* (11) estimen que a Europa el TP implica un cost de 11.894 milions d'euros l'any (1505 euros per pacient/any).

Tanmateix, aquestes xifres poden variar substancialment en funció dels països i estudis escollits. En el cas d'Holanda, per exemple, s'estima que el cost arriba als 10269 euros per pacient/any (12). Sigui com sigui, el TP suposa un malestar i una limitació importants, tendeix a cronificar-se, i a presentar-se amb símptomes associats (p.e., depressius) o de forma comòrbida amb altres trastorns mentals (10, 13).

2. La *Panic Disorder Severity Scale – Self Report*

Pel que fa a l'avaluació del TP, arribats a aquest punt hem de retrocedir una mica en el temps. Als anys 90 ja existien entrevistes semiestructurades per establir el diagnòstic de TP, com per exemple l'*Anxiety Disorders Interview Schedule for DSM-IV* (ADIS-IV), i escales autoadministrades que avaluen característiques concretes del TP, com per exemple el *Mobility Inventory for Agoraphobia* (MIA). Tanmateix, segons Shear i col·laboradors (14), calia abordar la necessitat de disposar d'un instrument de mesura, simple i estandaritzat, que avalués la gravetat global del TP. D'aquesta necessitat, i seguint el model de la *Yale-Brown Obsessive Compulsive Scale (14-16)* va nèixer la *Panic Disorder Severity Scale* (PDSS): un escala breu, administrada pel clínic, i que avalua tant la gravetat global del trastorn, com els diferents fenòmens que el constitueixen. La PDSS consta de 7 ítems que es puntuen en una escala ordinal de 0 a 4 i que fan referència a la freqüència dels atacs de pànic, el malestar durant els atacs, l'ansietat anticipatòria, l'evitació agorafòbica, l'evitació interoceptiva i la limitació laboral i social associada. La puntuació total, per tant, va de 0 a 28.

Des que es va presentar, la PDSS ha tingut un èxit considerable. Ha estat àmpliament utilitzada tant en recerca com en clínica, i les propietats psicomètriques han estat avaluades en diversos entorns (14, 17-20). Tanmateix, el fet que hagi de ser administrada per clínics entrenats en limita el seu ús en alguns contextos. Per aquest motiu, Houck *et al.* (21) van desenvolupar la versió autoaplicada de la PDSS: la *Panic Disorder Severity Scale – Self Report* (PDSS-SR). La PDSS-SR avalua les mateixes àrees que la PDSS i té el mateix sistema de puntuació: 7 ítems de 0 a 4 i una puntuació total de 0 a 28. La principal modificació respecte la PDSS és el marc temporal, que passa de mensual a setmanal ("*Durante la última semana*..."). Aquest canvi es va fer amb una doble finalitat: reduir el possible biaix associat al record, i poder utilitzar l'instrument per monitoritzar els símptomes amb una freqüència setmanal (21).

Tanmateix, en el moment d'iniciar aquesta tesi doctoral, només tres estudis havien avaluat les propietats psicomètriques de la PDSS-SR, dos amb la versió anglesa (21, 22) i un altre amb una versió en coreà (23). Els resultats d'aquests estudis mostren que la PDSS-SR presenta una consistència interna i una fiabilitat test-retest excel·lents, una validesa convergent i divergent adequada, i una bona sensibilitat al canvi. Tot i així, la versió en castellà encara restava pendent de ser validada. Per aquest motiu, es va portar a terme un primer estudi per tal d'avaluar les propietats psicomètriques de la versió castellana de la PDSS-SR (estudi 1 de la present tesi doctoral). Posteriorment, l'any 2015 Sánchez-Arribas *et al.* (24) van aportar dades sobre una altra versió en castellà de la PDSS-SR, mostrant unes propietats psicomètriques similars a les obtingudes en els estudis previs.

Respecte l'estructura factorial de l'escala, es mantenen certes discrepàncies entre diferents estudis, tant amb la versió heteroaplicada (PDSS) com amb l'autoaplicada (PDSS-SR). Mentre alguns autors troben que un model d'un sol factor és el que millor s'ajusta a les dades (17, 19, 23), altres autors suggereixen una estructura bifactorial, amb un factor referent a la freqüència dels atacs de pànic i el malestar associat, i un segon factor relacionat amb els components cognitius i conductuals del trastorn (14, 18, 20). En aquest context, juntament amb les propietats psicomètriques, també es va avaluar l'estructura factorial de la versió castellana de la PDSS-SR.

3. Tractament del trastorn de pànic

3.1. La teràpia cognitivoconductual

Tal i com s'ha comentat anteriorment, el TP suposa un problema de salut de gran abast. Afortunadament, però, es disposa de tractaments que han demostrat ser eficaços pel TP, com per exemple els inhibidors selectius de la recaptació de la serotonina (ISRS) o la teràpia cognitivoconductual (TCC). Pel que fa a la TCC, la seva eficàcia està actualment ben consolidada a partir d'assajos clínics controlats i aleatoritzats (25-31), així com també la seva efectivitat en entorns més naturalístics i menys controlats, amb comorbiditats i altres variables de confusió que típicament es troben en la pràctica clínica *real* (32-34). A més, diversos estudis de seguiment han demostrat que els beneficis obtinguts amb la TCC tendeixen a mantenir-se al llarg del temps (29, 32, 35). En aquest context, tant la guia de pràctica clínica de la NICE -*National Institute*

for Clinical Excellence- (36) com la de l'APA -*American Psychiatric Association*- (37), estableixen la TCC com a tractament de primera línia i la situen, conjuntament amb determinats tractaments farmacològics, entre les intervencions que han demostrat una major evidència empírica.

Tot i que el volum de recerca és menor respecte l'aplicació de la TCC a nivell grupal (TCCG) (38), actualment ja es disposa d'estudis que conclouen que no hi ha diferències entre els formats individual i grupal (35, 39, 40), i d'estudis que han avaluat específicament l'eficàcia i l'efectivitat de la TCCG pel TP (a les taules 1 i 2 es mostren, respectivament, els estudis previs d'eficàcia i efectivitat). Això és important tenint en compte el *plus* que aporta la TCCG en termes de cost/benefici. Tanmateix, encara resta pendent analitzar per quins perfils de pacients és més indicada una modalitat o altra (35).

3.2. Trajectòries de resposta

Entre les diferents maneres d'avaluar la resposta a un tractament, cada cop hi ha més estudis que opten per aplicar anàlisis de trajectòries. Les anàlisis de trajectòries permeten no només avaluar la magnitud del canvi entre dos punts de mesura, sinó també quina "forma" té el canvi observat (41-43), i caracteritzar les trajectòries obtingudes a partir de paràmetres que descriuen la gravetat inicial i l'evolució al llarg del temps.

Les anàlisis de trajectòries formen part de la família de tècniques que estimen contstructes latents (és a dir, no observats directament) a partir de variables observades. Segurament, l'exemple més conegut d'aquest tipus d'abordatge és el de les anàlisis factorials, en les quals a partir de la covariació

Taula 1. Estudis d'eficàcia de la TCCG per al trastorn de pànic.

Estudi	País	N	Participants per grup de TCCG	Abandonaments	Número de sessions / duració de la TCCG	Comparació	Resultats
Marchand *et al.*, 2009 (35)	Canadà	TCC (N=33) TCCG (N=35) TCCB (N=32) Llista d'espera (N=27)	8	TCC: 9% TCCG: 14% TCCB: 25%	14 / 60 min	TCC = TCCG = TCCB > Llista d'espera	En els tres grups de tractament, reducció en la MIA, BSQ, ASI, BDI, ACQ, GASS i GFI. Els resultats es mantenen als seguiments a un i dos anys. Respecte el grup en llista d'espera, major reducció de la simptomatologia, major increment de la qualitat de vida, major manteniment dels guanys i menor taxa de recaigudes.
Rosenberg *et al.*, 2005 (44)	Dinamarca	TCCG (N=60) Llista d'espera (N=45)	6	11%	14 / 90 min	TCCG > Llista d'espera	Major reducció en el grup de tractament respecte el grup control en la SCL-Anxiety i SCL-Depression. Absència d'atacs de pànic en el 47.2% al post-tractament (12.5% en el grup control), i en el 66.7% al seguiment a 1'5/2 anys.
Dannon *et al.*, 2004 (45)	Israel	TCCG (N=24) Paroxetina (N=33)	8	TCCG: 4% Paroxetina: 18%	8 / ?	TCCG = Paroxetina	Reducció en la HRSA, CGI, PSQ i VAS. Absència d'atacs de pànic en el 100% dels pacients al post-tractament. Els resultats es mantenen al seguiment a 3 mesos.
Telch *et al.*, 1993 (46)	Estats Units	TCCG (N=34) Llista d'espera (N=33)	4-6	TCCG: 0%	12 / 90 min	TCCG > Llista d'espera	Reducció en l'SPRAS, FQ-A, ASI i BDI. Absència d'atacs de pànic en el 85% dels pacients al post-tractament. Remissió total en el 64%. Els resultats es mantenen al seguiment a 6 mesos.

TCC = Teràpia cognitivoconductual, TCCG = Teràpia cognitivoconductual grupal, TCCB = Teràpia cognitivoconductual breu, MIA = Mobility Inventory for Agoraphobia, BSQ = Body Sensations Questionnaire, ASI = Anxiety Sensivity Index, BDI = Beck Depression Inventory, ACQ = Agoraphobic Cognitions Questionnaire, GASS = Global Assessment of Severity Scale, GFI = Global Functioning Index, SCL-Anxiety = Symptom Checklist - 90 - Revised, Anxiety Subscale, SCL-Depression = Symptom Checklist - 90 - Revised, Depression Subscale, HRSA = Hamilton Rating Scale for Anxiety, CGI =Clinical Global Impression, PSQ = Panic Self Questionnaire, VAS = Visual Analog Scale, SPRAS = Sheehan Patient-Related Anxiety Scale, FQ-A = Fear Questionnaire - Agoraphobia

Taula 2. Estudis d'efectivitat de la TCCG per al trastorn de pànic.

Estudi	País	N	Participants per grup	Abandonaments	Número de sessions / duració	Resultat
Prats *et al.*, 2014 (38)	Espanya	56	4-8	7%	10 / 60 min	Reducció en la PAS, ASI-3, BDI-II, STAI-T i SDI. Els resultats es mantenen al seguiment a 3 mesos.
Garriga *et al*., 2009 (47)	Espanya	35	10-12	8%	12 / 90 min	Reducció en la STAI-T, STAI-S, FQ, BSQ, ACQ i BDI. El 62% redueix el tractament farmacològic.
Nakano *et al.,* 2008 (48)	Japó	70	3-4	20%	10 / 120 min	Reducció en la PDSS, FQ-A, MIA, ACQ, BSQ. Els resultats es mantenen al seguiment a un any.
Austin *et al.,* 2008 (49)	Dinamarca	18	?	0%	?	Reducció en la PDSS-SR, MIA, BAI i BDI. Els resultats es mantenen al seguiment a un any.
Galassi *et a*l., 2007 (50)	Itàlia	76	10-12	22%	14 / 120 min	Reducció en la STAI-S, STAI-T, BDI, MIA, DS-FR, DS-W, DS-SR. Absència d'atacs de pànic en el 54% dels pacients i reducció parcial en el 25%. Els resultats es mantenen al seguiment a 6 mesos.
Heldt *et al*., 2006 (51)	Brasil	71	7	7%	12 / ?	Reducció en la CGI, PI i HRSA. Reducció del 50% dels símptomes agorafòbics en el 78% dels pacients. Reducció del 50% de l' ansietat anticipatòria en el 62%. Absència d'atacs de pànic en el 81%. Remissió (no atacs de pànic i CGI<=2) en el 64%. Els resultats es mantenen al seguiment a un any.
García-Palacios *et al*., 2002 (52)	Espanya	25	5-6	0%	14 / 90 min	Reducció en el BCT, BAI, BDI, AAF, FQ-A, CIT, CIP, i en la freqüència i intensitat dels atacs de pànic.
Leveni *et al*., 1999 (53)	Itàlia	22	?	?	?	Reducció en la SF-36, PAAAS, MSPS, STAI-T i STAI-S.
Martinsen *et a*l., 1998 (54)	Noruega	83	6-10	14%	11 / 240 min	Reducció en la PARS, ACQ, ACS, MIA, BSQ i BDI. Els resultats es mantenen al seguiment un any.
Wade *et al*., 1998 (55)	Estats Units	110	?	26%	15 / 90 min	Millora en la freqüència d'atacs de pànic, ansietat anticipatòria, ansietat general, FQ-A, FQ-SP, FQ-BI, BDI, PANAS-PA, PANAS-NA. Augment del pacients sense atacs de pànic del 18 al 87%. Reducció de pacients que prenen tractament ansiolític del 60% al 23%, i reducció dels que prenen tractament antidepressiu del 20 al 16%.
Penava *et al*., 1998 (56)	Estats Units	39	?	5%	12 / 90 min	Reducció en la PDSS i l'ASI.

PAS = Panic and Agoraphobia Scale, ASI = Anxiety Sensitivity Index, ASI-3 = Anxiety Sensitivity Index-3, BDI = Beck Depression Inventory, BDI-II = Beck Depression Inventory-II, STAI-T = State-Trait Anxiety Inventory-Trait, STAI-S = State-Trait Anxiety Inventory-State, SDI = Sheehan Disability Index, FQ = Fear Questionnaire, FQ-A = Fear Questionnaire - Agoraphobia, FQ-SP = Fear Questionnaire - Social Phobia, FQ-BI = Fear Questionnaire - Blood/Injury, BSQ = Body Sensations Questionnaire, ACQ = Agoraphobic Cognitions Questionnaire, PDSS = Panic Disorder Severity Scale, PDSS-SR = Panic Disorder Severity Scale - Self Report, MIA = Mobility Inventory for Agoraphobia, BCT = Belief in Catastrophic Thoughts, BAI = Beck Anxiety Inventory, DS-FR = Disability Scale-Family Relationship, DS-W = Disability Scale-Work, DS-SR = Disability Scale-Social Relationship, CGI = Clinical Global Impression, PI = Panic Inventory, HRSA = Hamilton Rating Scale for Anxiety, AAF = Agoraphobic Avoidance and Fear Scale, CIT = Clinical Improvement assessed by the therapist, CIP = Clinical Improvement assessed by the patient, SF-36 = The Short Form (36) Health Survey, PAAAS = Panic Attack and Anticipatory Anxiety Scale, MSPS = Marks-Sheehan Phobia Scale, PARS = Phobic Avoidance Rating Scale, ACS = Agoraphobic Cognitions Scale, PANAS-PA = The Positive and Negative Affect Schedule - Positive Affect, PANAS-NA = The Positive and Negative Affect Schedule - Negative Affect

de les dades observades es poden identificar uns factors latents. De forma similar, és possible estimar trajectòries latents a partir de dades recollides longitudinalment.

Entre el conjunt de tècniques que formen part d'aquesta aproximació metodològica, hi ha les que permeten estimar la trajectòria d'un grup d'individus com un sol conjunt. Tanmateix, també hi ha tècniques -com el *group-based trajectory modeling* (GBTM) de Nagin *et al.* (57) o el *growth mixture modeling* (GMM) de Muthén (58)- que, a més a més, permeten identificar subgrups latents de pacients que segueixen trajectòries de canvi similars (*trajectory classes*) (59). És a dir, són mètodes que superen l'assumpció que un model de "talla única" s'ajusta a l'evolució de tots els pacients. Un altre tret distintiu del GBTM i GMM és que tenen caràcter exploratori. És a dir, no parteixen d'una teoria o taxonomia prèvia (amb un nombre de categories establert) que pugui condicionar els resultats (57). Aquesta és una diferència similar a la que hi ha entre el *Confirmatory Factor Analysis* (CFA) i l'*Exploratory Factor Analysis* (EFA). En el cas del GBTM i GMM, doncs, no es parteix d'un nombre de categories fixat a priori. Per posar alguns exemples, recentment s'ha utilitzat aquesta metodologia per identificar trajectòries de canvi en simptomatologia depressiva en adolescents (60), o patrons evolutius en el consum de substàncies, també en adolescents (61).

En aquest context, a l'estudi principal (estudi 2 de la present tesi doctoral) es va aplicar la tècnica GMM per identificar i descriure subgrups latents de pacients que segueixen trajectòries similars (*trajectory classes)* (62). Bàsicament, amb aquesta tècnica es posen a prova models amb diferent nombre i tipus de *trajectory classes*, i diversos índexs de bondat d'ajust

permeten escollir el model òptim. Inicialment es comença amb models d'una sola classe (assumint que tots els subjectes segueixen una mateixa trajectòria), i progressivament es va augmentant el nombre de *trajectory classes*. Anàlogament, primer es posen a prova models amb trajectòries lineals, i posteriorment models amb trajectòries curvilínies (quadràtiques i cúbiques). En el nostre cas, es van examinar els següents índex de bondat d'ajust: *Akaike Information Criterion* (AIC), *Bayesian Information Criterion* (BIC), *Sample-Size Adjusted* BIC (SSBIC), i *Bootstrap Likelihood Ratio Test* (BLRT), i es va escollir el model amb un SSBIC menor (63). El BLRT es va utilitzar per comparar models amb *k* i *k+1* classes, on una $p<0.05$ indica la conveniència d'afegir una classe més (64). A més, es va comprovar que el model escollit presentava un valor d'entropia per sobre del punt de tall recomanat (65). Finalment, amb aquesta tècnica també és possible obtenir la probabilitat de cada subjecte de pertànyer al subgrup assignat, i d'aquesta manera poder calibrar la precisió en la classificació dels individus (57). Les trajectòries obtingudes es van descriure a partir dels paràmetres *intercept* (gravetat inicial; en el nostre cas puntuació de la PDSS-SR a l'inici del tractament) i *slope* (evolució al llarg del temps; en el nostre cas augment o disminució de punts de la PDSS-SR per setmana).

En definitiva, d'aquesta manera es pot captar l'heterogeneïtat en la resposta als tractaments de forma més acurada que a partir de simples diferències pre-post. Potencialment, aquesta informació pot ser molt útil en el progrés cap a una medicina més "personalitzada", en la que els tractaments es poden ajustar de forma més precisa a determinats perfils de pacients.

3.3. Predictors de resposta i aspectes translacionals

Tot i la considerable potència de la TCC pel TP, encara hi ha un percentatge significatiu de pacients que no milloren amb aquest tractament (66). Segons dades de Barlow *et al.* (25), a l'entorn d'un 25% no compleixen criteris de resposta després de la TCC. Per aquesta raó, nombrosos investigadors han dirigit els seus esforços cap a la identificació dels factors implicats en la resposta terapèutica. Tanmateix, aquests estudis tradicionalment s'han focalitzat en variables clíniques i sociodemogràfiques, i en general s'han obtingut resultats inconsistents (66-68). Darrerament, però, i atenent a la crida per a una major integració entre la psicologia clínica i la neurobiologia (69), s'han començat a contemplar com a possibles factors de mal pronòstic variables genètiques o fenòmens provinents de la recerca bàsica, tant en animals com en humans. Un bon exemple d'aquesta recerca translacional ("del laboratori al llit del malalt") és l'estudi de Berry *et al.* (70) amb ansietat social, en el que es relaciona el model d'extinció de la por amb la resposta a un tractament per exposició. En la categoria de recerca translacional també s'hi podrien incloure els estudis de *therapygenetics,* neologisme encunyat per fer referència a la predicció de la resposta a tractaments psicològics a partir de marcadors genètics. En aquest context, alguns autors fins i tot han anat més enllà i han combinat factors genètics i processos d'aprenentatge associatiu (p.e., extinció condicionada) per explorar possibles predictors de resposta. Tal és el cas de la recerca amb el gen del *BDNF* (acrònim en anglès de *brain-derived neurotrophic factor*) i la resposta a la TCC.

El BDNF és el factor neurotròfic més abundant en el sistema nerviós central dels mamífers, i està implicat en la supervivència, creixement i diferenciació de neurones i sinapsis (71, 72), i en última instància en processos d'aprenentatge i memòria (73). Entre d'altres, el BDNF s'ha vist implicat en processos de condicionament paulovià (74, 75) i també en processos d'extinció de respostes prèviament condicionades (76). Per altra banda, el gen que codifica el BDNF presenta un polimorfisme al codó 66 (Val66Met), en el que una valina (Val) és substituïda per una metionina (Met). Segons s'ha pogut observar (77), aquest polimorfisme afecta la secreció i el tràfic intracel·lular del BDNF, mostrant-se uns nivells inferiors en els portadors de l'al·lel Met. Més recentment, i tant en ratolins com en humans, l'al·lel Met del *BDNF* s'ha relacionat amb alteracions en els aprenentatges d'extinció (78, 79). A més, en persones portadores de l'al·lel Met s'han observat diferències en els patrons d'activació de determinades àrees cerebrals (incloses l'amígdala i el còrtex prefrontal ventromedial), la qual cosa encaixa amb les alteracions en els processos d'extinció prèviament mencionades (71, 78). Considerant que l'aprenentatge d'extinció es un dels elements mes importants dels tractaments per exposició, té sentit preguntar-se si l'al·lel Met del *BDNF* s'associa a una pitjor resposta a la TCC en determinats trastorns d'ansietat. Actualment, aquesta relació ha estat observada amb pacients amb trastorn obsessivocompulsiu (TOC) (80) i amb trastorn per estrès posttraumàtic (TPEP) (81). Tanmateix, s'han obtingut resultats negatius quan s'ha estudiat amb ansietat social (82) i amb una mostra infantil que incloïa diversos trastorns d'ansietat (83). En el cas del TP, Kobayashi *et al.* (84) van trobar nivells inferiors de BDNF en sèrum en pacients que presentaven una pitjor resposta a

la TCC. Tot i així, en el TP la relació directa entre el polimorfisme Val66Met i la resposta a la TCC encara no havia estat posada a prova.

Pel que fa a factors ambientals, el maltractament infantil ha estat sense cap dubte un dels que ha generat més volum de recerca. Més enllà de la seva implicació com a factor de risc per a desenvolupar múltiples trastorns mentals (85, 86), també ha estat estudiat com a possible predictor de resposta a diversos tractaments. En depressió, per exemple, el maltractament infantil s'ha associat a un pitjor resposta tant al tractament farmacològic com al psicològic (87). Tanmateix, aquesta qüestió ha estat relativament poc estudiada en trastorns d'ansietat, i encara menys contemplant formes específiques de maltractament infantil, com ara la negligència o l'abús. De fet, en trastorns d'ansietat només es disposa de dos estudis previs que hagin avaluat el rol del maltractament infantil en la resposta a la TCC -ambdós en ansietat social- (88, 89). Mentre Alden *et al.* (88) troben que la presència d'abús parental augmenta el risc a presentar una pitjor resposta, Bruce *et al.* (89) no troben que les diferents formes de maltractament estudiades s'associïn a un pitjor resultat terapèutic. Anàlogament al que anteriorment s'ha comentat amb el BDNF, en el TP la relació entre diverses formes de maltractament infantil (abús i negligència infantil) i la resposta a la TCC encara restava pendent de ser avaluada.

A més, fins al moment actual només un treball previ havia combinat factors genètics, clínics i demogràfics en l'estudi dels predictors resposta a la TCC -en aquest cas amb una mostra infantil amb diversos trastorns d'ansietat- (68). Amb adults, l'efecte de la interacció entre factors genètics i ambientals (com el *BDNF* i el maltractament infantil) en la resposta a la TCC pel TP encara no s'havia explorat.

4. Objectius

L'objectiu de la present tesi doctoral era avaluar les propietats psicomètriques de la versió castellana de la PDSS-SR (estudi 1), i avaluar si el polimorfisme Val66Met del *BDNF* i/o el maltractament infantil s'associen a una pitjor resposta (mesurada aplicant anàlisis de trajectòries) a la TCC pel TP (estudi 2). Basant-nos en recerca prèvia, la nostra hipòtesi era que tant l'al·lel Met del gen del *BDNF* com el maltractament infantil s'associarien amb una trajectòria de resposta menys favorable.

II. Estudi 1: *Psychometric properties of the Spanish self-report version of the Panic Disorder Severity Scale*

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Psychometric properties of the Spanish self-report version of the Panic Disorder Severity Scale

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Abstract

Objective: The goal of the study was to assess the psychometric properties and the factor structure of the Spanish self-report version of the Panic Disorder Severity Scale (PDSS-SR).
Method: One hundred and twenty four patients meeting DSM-IV criteria for panic disorder were assessed with the Spanish PDSS-SR, the Anxiety Sensitivity Index-3 (ASI-3), the Sheehan Disability Inventory (SDI) and the Beck Depression Inventory-II (BDI-II). Cronbach's alpha was used to evaluate internal consistency. Pearson correlations were used to evaluate test-retest reliability, convergent and divergent validity. Sensitivity to change data was obtained for 91 patients that had completed a cognitive behavioural therapy. The factor structure was analysed using a confirmatory factor analysis (CFA).
Results: The Spanish PDSS-SR showed excellent internal consistency, good test-retest reliability and adequate convergent validity. Regarding divergent validity, the correlation with the BDI-II was larger than expected. The Spanish PDSS-SR was sensitive to change. Our CFA suggested a two-factor model for the scale.
Conclusions: The Spanish PDSS-SR has similar psychometric properties as the previous versions of the PDSS-SR and it can become a useful instrument to assess panic symptoms in clinical and research settings in Spanish-speaking countries.

1. Introduction

Panic disorder (PD) is a well-defined syndrome characterized by recurrent panic attacks and concern about future attacks and their implications. It leads to significant distress and functional limitation, tends to become chronic [1] and is often associated with psychiatric comorbidities [2]. Panic disorder is highly prevalent [2,3] and entails high economic costs to society [4].

Several instruments have been developed to assess PD and its associated features. The ideal instrument to assess PD would be an easy-to administer scale evaluating overall severity, the distinct phenomena that constitute the syndrome (panic attacks, anticipatory anxiety, and agoraphobic avoidance) [5], as well as the interference associated with the disorder in different life domains. The *Panic Disorder Severity Scale* (PDSS) [6] seems to fulfil most of such criteria.

The PDSS was initially developed as a clinician-administered interview with seven questions that refer to frequency of panic attacks, associated distress, anticipatory anxiety, agoraphobic avoidance, interoceptive avoidance, and social and work impairment. The PDSS has been widely used in research and clinical settings and its psychometric properties have been relatively well investigated [6–11]. There are, however, some discrepancies about the factor structure of the scale. While some studies [7,9] suggest a one-factor model, others [6,8,10,11] present data that fit a two-factor solution, with one factor related to panic frequency and associated distress

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and another factor related to behavioural/cognitive changes secondary to panic. This is important given that some neurobiological data support the existence of different neural systems involved in the different features of PD [5].

However, a limitation of the PDSS is that it has to be administered by a trained clinician. This motivated the development of a self-report version of the instrument (PDSS-SR) [12]. The PDSS-SR assesses the same contents as the PDSS and is also scored on a 5-point ordinal scale (0–4); the total score also ranges between 0 and 28. The main modification with respect to the PDSS is the time frame (from past month for the PDSS to past week for the PDSS-SR). This was made to reduce possible recall bias and to use the instrument to monitor symptoms on a weekly basis [12].

To the best of our knowledge, only two studies have investigated the psychometric properties of the original English version of the PDSS-SR [12,13], but one of them [13] used a modified version of the instrument that excluded the items assessing social and work interference. These studies have generally shown that the PDSS-SR has excellent internal consistency and test-retest reliability, adequate convergent and divergent validity, and good sensitivity to change [12,13].

Only one study has assessed a non-English version of the PDSS-SR. Lee et al. [14] reported on a Korean version of the instrument and found psychometric properties similar to those obtained for the original English PDSS-SR. The factor structure of the PDSS-SR has only been assed with this Korean version of the scale, and the results supported a unidimensional structure. Table 1 offers a summary of previous results on the psychometric properties and the factor structure of the PDSS-SR.

Taking into account that there is only one cross-cultural evaluation of the PDSS-SR, and considering that the factor structure of the scale (for both the clinician-administered and the self-report version) remains unclear, the aim of this study was to assess the psychometric properties and the factor structure of the Spanish version of the PDSS-SR.

2. Method

2.1. Sample

One hundred and twenty-four patients meeting DSM-IV criteria for PD [15] were included in the study (110 with agoraphobia and 14 without agoraphobia). Patients were referred for treatment at three different mental health centres from Barcelona, Spain. The sample included 40 men (32.3%), and the mean age was 37.1 years (range 18–69, *SD* = 10.14). The corresponding ethical committees approved the study and all participants provided voluntary and informed written consent. Diagnosis was established by experienced clinicians using the validated Spanish version [16] of the *Mini International Neuropsychiatric Interview* (MINI) [17]. Exclusion criteria consisted of the presence or history of any organic mental disorder, bipolar disorder or psychosis; substance abuse or dependence in the last 3 months; intellectual disability or language barriers. Other comorbid disorders were allowed as long as they were not a primary source of distress.

2.2. Measures

The MINI (Spanish version 5.0.0) is a brief and structured interview to evaluate the presence of Axis I disorders according to DSM-IV criteria [17], and it is a widely used instrument in clinical and research settings. The Spanish version of the MINI has shown to have sound psychometric properties [18].

Table 1
Summary of previous studies on the psychometric properties of the PDSS-SR.

Authors/year	Sample	Internal consistency (Cronbach's alpha)	Test-retest reliability	Convergent and divergent validity (Pearson correlations)	Sensitivity to change (*t*-test)	Exploratory factor analysis
Houck et al., 2002	N = 108 (psychiatric outpatients)	0.92	ICC = 0.83		Significant decrease on the total score between pre and post CBT (N = 27)	
Lee et al., 2009	N = 148 (panic disorder)	0.88	r_s = 0.94	ASI-R: 0.58 APPQ-agora: 0.54 APPQ-intero: 0.55 BAI: 0.67 STAI-T: 0.46 BDI: 0.52	Significant decrease on the total score between pre and post paroxetine treatment (N = 33)	One-factor model
Wuyek et al., 2011	N = 52 (panic disorder)	0.80		ACQ: 0.43 ASI: 0.29 IIRS: 0.34 MI-Alone: 0.29 MI-Acc: 0.27		

ICC = intraclass correlation coefficient, r_s = spearman correlation, CBT = cognitive behavioural therapy, ASI-R = Anxiety Sensitivity Index-Revised, APPQ-agora = agoraphobia factor of the Albany Panic and Phobia Questionnaire, APPQ-intero = interoceptive fear factor of the Albany Panic and Phobia Questionnaire, BAI = Beck Anxiety Inventory, STAI-T = Spielberg State-Trait Anxiety Inventory-Trait Version, BDI = Beck Depression Inventory, ACQ = Agoraphobic Cognitions Questionnaire, ASI = Anxiety Sensitivity Index, IIRS = Illness Intrusiveness Ratings Scale, MI-Alone = Mobility Inventory for Agoraphobia-Alone, MI-Acc = Mobility Inventory for Agoraphobia-Accompanied.

The *Anxiety Sensitivity Index-3* (ASI-3) is a18-item self-report measure that assesses fear of anxiety symptoms (i.e. anxiety sensitivity) [19]. The total score ranges from 0 to 72 and consists of three factors (physical, cognitive and social concerns, range 0–24 each). The Spanish version has shown excellent internal consistency, test-retest reliability and divergent validity, and adequate convergent validity [20]. Heightened anxiety sensitivity is a hallmark of PD. It predicts panic symptoms in response to biological challenge as well as the emergence of unexpected panic attacks and PD [21]. The *Anxiety Sensitivity Index* (and its revised versions) has often been used as part of the assessment protocol to test treatment-related changes in PD [22,23].

The *Beck Depression Inventory-II* (BDI-II) is a 21-item self-report scale designed to measure depressive symptoms [24]. The total score ranges from 0 to 63. The Spanish version of the BDI-II has shown excellent internal consistency and convergent validity, and adequate divergent validity [25].

The *Sheehan Disability Inventory* (SDI) is a 3-item self-report measure that evaluates functional impairment in three fields: work, social life and family [26]. Total scores range between 0 and 30. The Spanish version of the SDI has shown excellent test-retest reliability, and adequate internal consistency [27].

2.3. Procedure

The original version of the PDSS-SR was translated into Spanish by one of us (AB) and back-translated by a professional bilingual translator. The translated version was then reviewed by the authors in order to verify the accuracy of the translation. The Spanish PDSS-SR is available from the last author upon request.

Data were obtained in the context of a wider project on the effectiveness of cognitive behavioural group therapy (CBGT) for PD in a naturalistic setting. For the current study, data correspond to the pre-treatment assessment, except for the analyses regarding sensitivity to change, that were obtained from 91 patients after they had completed the CBGT protocol. All patients completed the assessment measures individually on paper during the first group session with the assistance, when needed, of the group therapist.

2.4. Data analyses

Internal consistency of the PDSS-SR was assessed using Cronbach's alpha. Test-retest reliability was examined using Pearson correlations between session one and session two scores (a week later; no formal treatment had already started) of the CBGT. Convergent and divergent validity were evaluated with Pearson correlations between the PDSS-SR (total and item scores) and the different measures administered (ASI-3, BDI-II and SDI). Cohen's criteria [28] were used to evaluate the size of the correlations. Correlations from 0.50 to 1 will be defined as "large", from 0.30 to 0.49 as "medium", and from 0.10 to 0.29 as "small". A test of dependent correlations was conducted to compare the correlations of the PDSS-SR with the ASI-3 and the BDI-II. To assess sensitivity to change, a paired samples *t*-test was used to compare pre and post-treatment PDSS-SR scores. Finally, the factor structure was analysed using a confirmatory factor analysis (CFA). Data were analysed with SPSS software for Windows, version 21, except for the CFA, that was conducted with Mplus version 6 [29].

3. Results

3.1. Internal consistency

Cronbach's alpha for the PDSS-SR was 0.85. See Table 2 for the resulting alpha by omitting items from the scale, correlations between items and corrected item-total correlations (i.e. correlations of each item with the sum of the remaining items). Results indicated a high internal consistency of the PDSS-SR, and that consistency would not increase with the omission of any item.

3.2. Test-retest reliability

A large correlation (0.77) was found between the PDSS-SR scores on day one and a week later.

3.3. Convergent and divergent validity

Table 3 shows the Pearson correlation coefficients between the PDSS-SR and the other self-report measures. The PDSS-SR total score was positively correlated with the other self-report measures (ASI-3, BDI-II and SDI). The largest correlation was with the SDI (0.77), but it also had a large positive correlation with the BDI-II (0.53). The test of dependent correlations comparing the correlations of the PDSS-SR total score with the ASI-3 total score and the BDI-II revealed no significant differences between both correlations ($z = -0.68$, $p = 0.248$). However, the correlation between the PDSS-SR and the BDI-II was not significant after controlling for the SDI score, i.e. overall disability ($r = 0.29$, $p = 0.753$).

3.4. Sensitivity to change

The pre-treatment PDSS-SR mean score was 12.57 ($SD = 5.33$), while the post-treatment PDSS-SR mean score was 7.98 ($SD = 5.22$), a statistically significant decrease according to a paired samples *t*-test ($N = 91$, $t = 8.25$, $p < 0.01$).

3.5. Confirmatory factor analysis

On the basis of previous research [6–11,14], we conducted a CFA to test a one and a two-factor model for the scale. As usual, each item was specified to load on only one symptom factor; factors were allowed to correlate with each other, and error covariances were constrained to zero. The model fit was assessed with "traditional" maximum-likelihood chi-square ($\chi 2$ ML), comparative fit index (CFI) [30] and root-mean-square error of approximation (RMSEA) [31]. The fit indices for our data are shown in Table 4. In the two-factor model, the first two items – that measure physical symptoms – loaded on one factor and the other five items

Table 2
Cronbach's alpha if item deleted, correlations of each item with the sum of the remaining items and correlations between items for the PDSS-SR.

	Cronbach's alpha if item deleted	Corrected item-total correlation	Correlations between items						
			Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7
Item 1	.847	.541	1						
Item 2	.850	.512	.641*	1					
Item 3	.848	.532	.384*	.336*	1				
Item 4	.813	.770	.448*	.413*	.474*	1			
Item 5	.831	.657	.322*	.324*	.378*	.601*	1		
Item 6	.829	.673	.407*	.391*	.391*	.656*	.566*	1	
Item 7	,830	.670	.323*	.289*	.439*	.679*	.633*	.523*	1

* $p < 0.01$.

loaded into another factor. The two factor model improved significantly the fit (nested $\chi 2 = 38.89$, df = 1, $p < .001$) and the fit indices reached optimal values, since CFA and TLI were closer to one and SRMR/RMSEA were lower than .05.

4. Discussion

The results indicate that the Spanish version of the PDSS-SR has excellent internal consistency and good test-retest reliability. The large correlation with the SDI and the medium correlation with the ASI-3 suggest that the Spanish PDSS-SR has adequate convergent validity. However, the correlation between the PDSS-SR and the physical concerns subscale of the ASI-3 was lower than expected (based on the alleged association between the fear of anxiety symptoms – i.e. anxiety sensitivity – and PD), a fact that may be interpreted as a need for some refinement in terms of convergent validity. No previous study on the PDSS-SR (or PDSS) reports on this specific correlation, and therefore, our data on this topic cannot be compared with previous research. Regarding divergent validity, a large correlation was found with the BDI-II. One possible explanation, as pointed out by Lee et al. [14], relates to the true overlap between depressive and panic symptoms more than a validity concern: there is a high comorbidity between PD and depressive symptoms [2,32,33]. The fact that our sample consisted mainly of clinical patients may have contributed to this large correlation with the BDI-II. On the other hand, the correlation between the PDSS-SR and the BDI-II was not significant when general disability (SDI) was controlled. Therefore, another possible explanation is that the large correlation between the PDSS-SR and the BDI-II may be attributed to disability resulting from both conditions (depression and panic). The Spanish PDSS-SR also showed good sensitivity to change. In summary, these results are similar to those found in previous research for both the original English version [12,13] and the Korean adaptation [14]. Furthermore, the psychometric properties of the Spanish PDSS-SR seem globally comparable to previous studies for both the clinician-administered and the self-report version of the instrument as well as for the several translations available.

Our CFA suggested a two-factor model for the scale, which is in disagreement with the only previous study conducted with the PDSS-SR [14]. Our results fit better with previous studies with the PDSS [6,8,10,11], which propose a two-factor structure: one factor including the first two items, and a second factor including the rest. This could be interpreted as if physical symptoms of PD would have a separate effect on the outcome of the PDSS-SR. The second factor would then be related to the behavioural and cognitive components (i.e., anticipatory anxiety, agoraphobic and interoceptive avoidance) of the disorder. This could have important implications for the conceptualization of PD. Whereas the DSM-IV diagnostic definition of PD presents panic as a coherent syndrome, previous research and our data suggest a partial independence of different symptom domains, which could be interpreted as a possible multidimensional structure of PD [6].

Table 3
Pearson correlation coefficients between the PDSS-SR items and other self-report measures.

	ASI-3 Total	ASI-3 Physical concerns	ASI-3 Psychological concerns	ASI-3 Social concerns	BDI-II	SDI
PDSS-SR Total	.467**	.281**	.383**	.426**	.533**	.773**
Item 1	.241**	.164	.177	.228*	.288**	.380**
Item 2	.119	.072	.051	.168	.215**	.370**
Item 3	.485**	.336**	.379**	.437**	.357**	.490**
Item 4	.379**	.191*	.306**	.380**	.395**	.689**
Item 5	.386**	.303**	.347**	.271**	.492**	.624**
Item 6	.369**	.257**	.310**	.288**	.414**	.657**
Item 7	.390**	.122	.341**	.411**	.520**	.692**

ASI-3 = Anxiety Sensitivity Index-3, BDI-II = Beck Depression Inventory-II, SDI = Sheehan Disability Inventory.
* $p < 0.05$.
** $p < 0.01$.

Table 4
Confirmatory factor analysis for the PDSS-SR.

MODEL	*Df*	$\chi 2$	CFI	TLI	SRMR	RMSEA
1 factor	21	53.37	.890	.835	.072	.151
2 factor	13	14.48	.996	.993	.035	.030

df = degree of freedom, $\chi 2$ = Maximum likelihood Chi-squared, CFI = Comparative Fit Index, TLI = Tucker Lewis Index or Non-normed Fit Index, SRMR = Standardized Root Mean Square Residual, RMSEA = Root Mean Square Error of Approximation.

Our study has several limitations. First, our sample was relatively small to conduct a CFA [34]. Second, our sample included only PD patients and this may have limited the range of PDSS-SR scores. Further studies on the PDSS-SR representing the entire spectrum of panic symptoms (e.g. with sub-clinical patients) are warranted. Third, no other measures of treatment response were included in the current study. Therefore, the PDSS-SR could not be compared to other instruments in terms of sensitivity to change. Moreover, we did not include the PDSS in the assessment and therefore the degree of agreement between the Spanish versions of the PDSS and the PDSS-SR remains to be established. Finally, we did not assess the diagnostic sensitivity or specificity of the PDSS-SR.

In the future, it would be important to develop a guideline to interpret changes in the PDSS-SR score in terms of worsening, improvement or remission, as Furukawa et al. [35] have done with the PDSS. Considering that the PDSS-SR was designed to monitor symptoms of PD [12], this seems to be an especially relevant objective for future research. Also, it is desirable to address in the future the small correlation found between the PDSS-SR and the physical concerns subscale of the ASI-3. It is also worth pointing out that a new instrument to assess PD severity has been developed [36] and comparing its performance with the PDSS-SR should be a goal for future research.

In conclusion, our data show that the Spanish PDSS-SR has similar psychometric properties as the previous versions of the PDSS-SR. Given that it is an easy-to-administer and efficient tool, it can become a very useful instrument to assess panic symptoms in clinical and research settings in Spanish-speaking countries.

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III. Estudi 2: *Predicting response trajectories during cognitive-behavioural therapy for panic disorder: no association with the BDNF gene or childhood maltreatment*

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PLOS ONE

RESEARCH ARTICLE

Predicting Response Trajectories during Cognitive-Behavioural Therapy for Panic Disorder: No Association with the *BDNF* Gene or Childhood Maltreatment

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Abstract

Background

Anxiety disorders are highly prevalent and result in low quality of life and a high social and economic cost. The efficacy of cognitive-behavioural therapy (CBT) for anxiety disorders is well established, but a substantial proportion of patients do not respond to this treatment. Understanding which genetic and environmental factors are responsible for this differential response to treatment is a key step towards "personalized medicine". Based on previous research, our objective was to test whether the *BDNF* Val66Met polymorphism and/or childhood maltreatment are associated with response trajectories during exposure-based CBT for panic disorder (PD).

Method

We used Growth Mixture Modeling to identify latent classes of change (response trajectories) in patients with PD (N = 97) who underwent group manualized exposure-based CBT. We conducted logistic regression to investigate the effect on these trajectories of the *BDNF* Val66Met polymorphism and two different types of childhood maltreatment, abuse and neglect.

Results

We identified two response trajectories ("high response" and "low response"), and found that they were not significantly associated with either the genetic (*BDNF* Val66Met

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polymorphism) or childhood trauma-related variables of interest, nor with an interaction between these variables.

Conclusions

We found no evidence to support an effect of the *BDNF* gene or childhood trauma-related variables on CBT outcome in PD. Future studies in this field may benefit from looking at other genotypes or using different (e.g. whole-genome) approaches.

Introduction

The high prevalence of the anxiety disorders is a major public health concern. Twelve-month prevalence rates have been estimated at 18.1% in the US [1] and 13.6% in Europe [2]. In addition, anxiety disorders have a marked impact on the quality of life of those affected [3], and cause a huge social and economic burden. At the European level, Olesen *et al.* [4] quantified the total annual cost of anxiety disorders as 74.4 billion euros.

The efficacy of cognitive-behavioural therapy (CBT) for anxiety disorders is well established from randomised controlled trials [5], and is recommended by current clinical guidelines [6, 7]. However, a substantial proportion of patients do not respond to this treatment [8], and identifying the factors underlying this differential treatment response is now a research priority. In this context, genetic and environmental predictors of outcome have gained attention [9, 10] and will make a key contribution towards "personalized medicine" [11]. However, it remains to be tested whether results of basic research can be translated into clinical practice.

The prediction of treatment response based on genetic background has a long history in pharmacotherapy, but is a relatively new development in the field of psychological treatment. The term "therapygenetics" was coined a few years ago to indicate the prediction of psychological treatment outcomes from genetic markers [10, 12, 13]. Most research in this area has focused on testing the effects of specific single nucleotide polymorphisms (SNP) on response to CBT in anxiety and depressive disorders. Although the field is in its infancy, initial evidence indicates that specific SNPs may improve the prediction of CBT outcomes (i.e. a decrease in measures of severity). The most widely assessed SNP have been the serotonin transporter gene functional length polymorphism (5HTTLPR), and the functional Val66Met (rs6265) polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene [9, 10].

Both preclinical and clinical data suggest that Val66Met is involved in response to CBT (and more specifically, to exposure-based interventions) for anxiety and related disorders. Val66Met, which involves substitution of valine (Val) with methionine (Met), affects intracellular trafficking and secretion of *BDNF*, and Met carriers show decreased activity-dependent secretion of this neurotrophin [14]. Consistent with animal studies, this variation may be associated with anxiety or fear in humans [15]. Recent research suggests that extinction learning, which is the experimental model for exposure therapy, may be modulated by genetic variation in *BDNF*, and both mouse and human carriers of the Met variant show impaired extinction learning [16]. Moreover, humans carriers show a different pattern of activation of brain regions that are essential for fear extinction (including the ventromedial prefrontal cortex and the amygdala), which is consistent with impaired extinction learning [16, 17]. Preliminary translation of these basic results is provided by two recent studies showing that among adults with post-traumatic stress disorder (PTSD) [18] and obsessive-compulsive disorder (OCD) [19], those with the Met allele had a poorer response to exposure-based CBT than those with the

Val/Val genotype. However, this association was not replicated in a study in adults with social anxiety disorder (SAD) who received internet-based or group CBT [20], or in a study in children with mixed anxiety disorders who were receiving CBT [21].

Regarding environmental factors, childhood maltreatment has been the focus of extensive research. Beyond its established role as a risk factor for many mental disorders [22, 23], childhood maltreatment may also influence treatment outcomes. There is a well established association between childhood maltreatment and poor response to treatment for depression, and this association seems to be independent of treatment modality (pharmacological or psychological) [24]. However, this issue has not been investigated in detail for anxiety disorders, and very few studies have considered whether specific forms of maltreatment are relevant. To our knowledge, only two studies in patients with SAD have examined the impact of specific types of childhood maltreatment on CBT outcomes in anxiety disorders [25, 26]. Alden *et al.* [25] found that parental abuse increased risk of poor treatment outcome, while Bruce *et al.* [26] found no association between specific types of childhood maltreatment and response to CBT.

There has been at least one preliminary attempt to combine genetic and clinical variables to predict outcomes of psychological treatment in children with anxiety disorders [9]. To our knowledge, however, the role of genetics and early developmental experiences such as maltreatment in predicting the outcome of CBT in adults has not yet been explored.

Our aim was to study whether the *BDNF* Val66Met polymorphism and/or childhood maltreatment were associated with the outcome of exposure-based CBT for panic disorder (PD) in a naturalistic setting. Based on growth mixture models (GMM), we operationalized treatment outcome with trajectories of change in panic symptoms. Trajectory analyses have recently been used in psychological treatment research to identify patterns of change and to examine treatment effects in different patients subgroups [27–32]. This approach has several methodological advantages and is probably more clinically informative [28, 30, 33, 34].

Based on previous research, we predicted the existence of distinct response trajectories in patients receiving exposure-based CBT, and we hypothetised that genetic variation (presence of the *BDNF* Met allele) and childhood maltreatment (both abuse and neglect) would be associated with a less favourable response trajectory.

Method

Participants

Our sample consisted of 97 patients who completed (i.e., attended $\geq$ 8 sessions) a 9-week intervention of manualized exposure-based group CBT (GCBT) for PD at one of two treatment centres in Barcelona (Spain) between February 2011 and January 2014. During the recruitment period, 132 patients were assessed, and the following exclusion criteria were applied: age $<$18 or $>$60 years; presence or history of any organic mental disorder, bipolar disorder or psychosis; substance abuse or dependence in the previous three months (except for nicotine); intellectual disability; and language barriers. A Consort flow diagram of the recruitment process is shown in Fig 1.

All participants had a primary diagnosis of PD (89.7% with agoraphobia) according to the DSM-IV-TR [35], and had a score of $\geq$6 on the Spanish self-report version [36] of the *Panic Disorder Severity Scale* (PDSS-SR) [37]. Diagnosis was established by one experienced clinician using a semi-structured interview, and was confirmed by another clinician using the validated Spanish version [38] of the *Mini International Neuropsychiatric Interview* (MINI) [39].

The final sample included 61 women (62.9%), and the mean age was 36.19 years (range 18–60, *SD* = 9.23). Twenty-two participants (22.7%) presented one or more additional axis-I disorders. The most common comorbidities were SAD (7.2%), specific phobia (6.2%), generalized

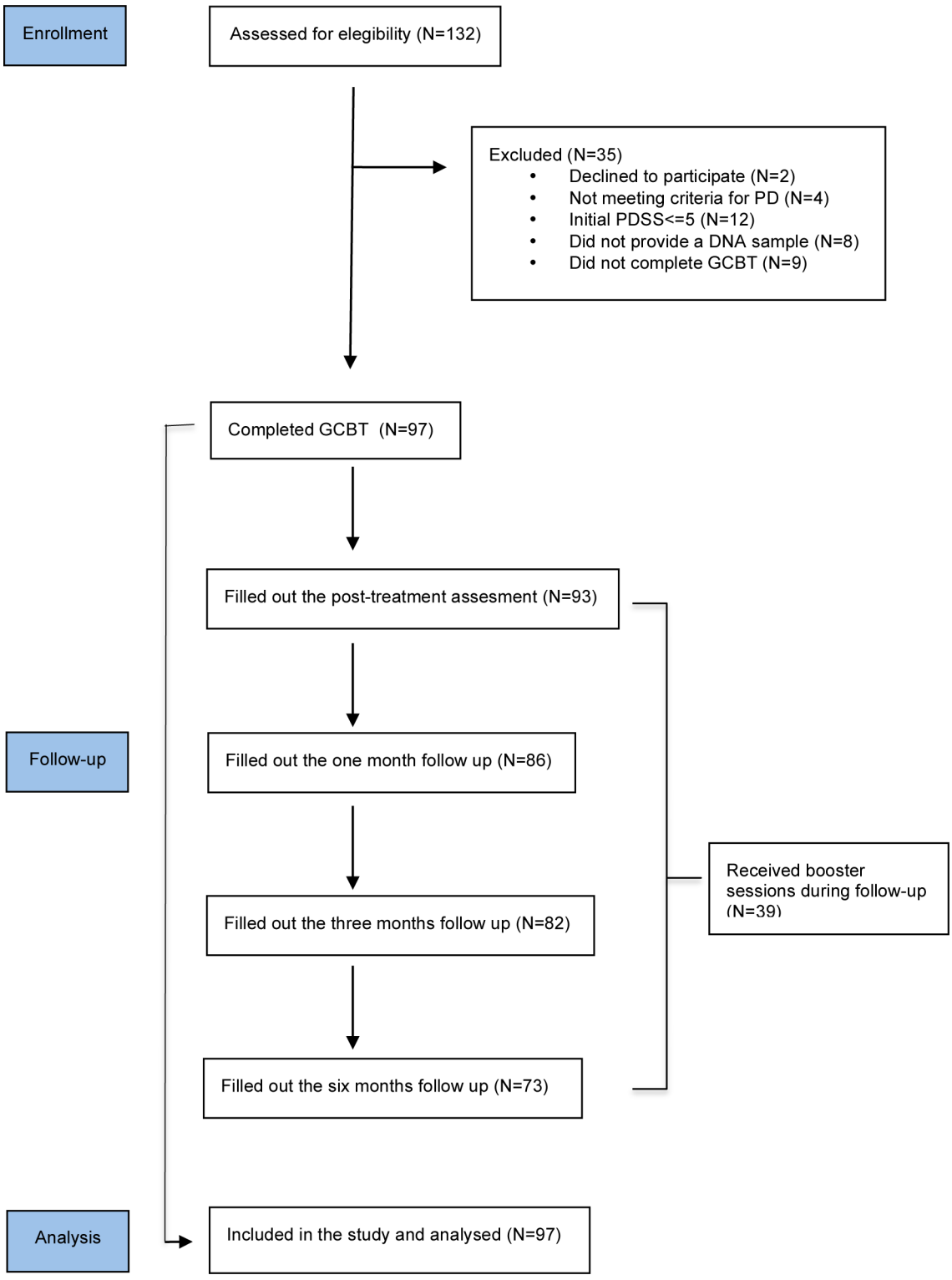

Fig 1. Consort flow diagram.

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anxiety disorder (3.1%), and others (6.2%). On admission, eighty-two patients (84.5%) were taking psychiatric medication (mainly antidepressants) continually for at least two months prior to beginning treatment, and 40 (41.2%) were taking PRN benzodiazepines. Participants were asked to maintain their medication regime during the GCBT. Table 1 shows a demographic and clinical summary of the sample.

The study fulfilled the principles of the World Medical Association Declaration of Helsinki and was approved by the Clinical Research Ethical Committee of the Parc de Salut Mar (Barcelona, Spain) and by the Clinical Research Ethical Committee of the Consorci Sanitari de Terrassa (Barcelona, Spain). All participants provided voluntary informed written consent.

Assessment

The MINI (Spanish version 5.0.0) is a brief structured interview that evaluates the presence of Axis I disorders according to DSM-IV criteria [39], and is a widely used instrument in clinical and research settings. The Spanish version of the MINI has shown to have sound psychometric properties [40].

Table 1. Demographic and clinical characteristics of the sample (N = 97).

		% / Mean (*sd*)
Gender		
	Men	37.1%
	Women	62.9%
Age (years)		36.19 (9.23)
Marital status		
	Single	30.5%
	Married/in a relationship	69.5%
Education level		
	Elementary school	28.4%
	High school	45.3%
	University	26.3%
Unemployed		45.8%
Age of onset (panic symptoms)		25.58 (9.13)
Duration of current episode (in years)		4.13 (5.58)
Presence of agoraphobia		89.7%
Axis-I comorbidity		22.7%
Pharmacological treatment		
	No medication	15.5%
	Antidepressant + benzodiazepine	41.2%
	Antidepressant	19.6%
	Benzodiazepine	23.7%
BDNF Val66Met genotypes		
	Val-Val	61.9%
	Met carriers	38.1%
CTQ-SF scores		
	Emotional abuse	9.64 (5.24)
	Physical abuse	6.44 (3.30)
	Sexual abuse	5.69 (1.56)
	Emotional neglect	10.66 (4.82)
	Physical neglect	6.59 (2.46)

M = mean, *sd* = standard deviation, CTQ-SF = Childhood Trauma Questionnaire-Short Form

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The self-report version of the *Panic Disorder Severity Scale* (PDSS-SR) is a 7-item instrument that assesses the frequency of panic attacks, associated distress, anticipatory anxiety, agoraphobic fear and avoidance, body-sensation fear and avoidance, and impaired work and social function [37] during the previous week. Each item is scored on a 5-point ordinal scale (0–4), and the total score ranges between 0 and 28. The Spanish PDSS-SR has shown excellent internal consistency, good test-retest reliability, adequate convergent and divergent validity, and good sensitivity to change [36].

The *Childhood Trauma Questionnaire-Short Form* (CTQ-SF) is a 28-item instrument that measures five types of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect [41, 42]. Each item ranges from 1 to 5, and the total score of each subscale ranges from 5 to 25. Following previous research [43], childhood maltreatment was grouped into two main types: childhood abuse (including emotional, physical and sexual abuse) and childhood neglect (including emotional and physical neglect). Childhood abuse and childhood neglect were calculated by summing the items of the corresponding subscales. The Spanish CTQ-SF has been shown to be a reliable and valid instrument [44].

Treatment

Group CBT consisted of nine one-hour sessions administered on a weekly basis. Groups were conducted by a main therapist (a PhD level clinical psychologist) and a co-therapist (a clinical psychology trainee or psychiatric nurse), and ranged from 4 to 7 patients each. Treatment was mannualized and the protocol was a modified version of the *Panic Control Treatment* by Barlow and Craske [45], adapted by the last author. Sessions 1 to 3 were devoted to education about anxiety and panic; sessions 4 and 5 consisted of in-session interoceptive exposure exercises, and progressive withdrawal of safety behaviors; and sessions 6 to 9 focused on graded exposure to avoided situations and activities. The treatment included homework exercises that varied depending on the phase of therapy, and did not include specific cognitive therapy tasks. To maximize treatment integrity and adherence to the protocol, fortnightly meetings between the main therapists were scheduled and checklists with the items to be covered at each session were provided to the co-therapists. Thirty-nine patients (40.2%) had at least one individual "booster" session during the six month follow-up period. Previous research has established the effectiveness of this treatment protocol [46].

Procedure

At the beginning of each session and at one, three and six months follow-up, participants completed the PDSS-SR to assess panic symptoms during the previous week. Additionally, participants also completed the CTQ-SF during the initial assessment session.

Genetic analyses

Genomic DNA was extracted from buccal mucosa on a cotton swab, or from blood samples using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain). The rs6265 SNP (Val66-Met) of the *BDNF* gene was determined using the Taqman 5' exonuclease assay -Applied Biosystems (AB)- and genotyped using AB TaqMan technology. The probe for genotyping the rs6265 was ordered through the TaqMan SNP Genotyping assays AB assay-on-demand service (code C_11592758_10). The final volume of the polymerase chain reaction (PCR) reaction was 5 mL, which contained 10 ng of genomic DNA, 2.5 ml of TaqMan Master Mix, and 0.125 ml of 40x genotyping assay. The cycling parameters were as follows: 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s and annealing/extension at 60°C for 1 min. PCR plates

were read on an ABI PRISM 7900HT instrument with SDS v2.1 software (AB). The genotype frequencies of rs6265-*BDNF* were in Hardy-Weinberg equilibrium ($\chi^2 = 0.53$; $p = 0.467$).

Statistical analyses

In the first step, we used growth mixture models (GMM) analysis to empirically identify latent subpopulations of patients with similar change trajectories ('trajectory classes') in panic symptoms, as measured using the PDSS-SR (baseline, plus 9 weekly ratings, plus three follow-up sessions). In GMM, trajectory classes are characterized by two parameters: intercept (i.e. initial severity) and slope (i.e. rate of change). GMM allows us to test for an *a priori* unknown number of latent subpopulations with different intercepts and slopes, as well as class-specific variations around these parameters.

To determine the optimal number of trajectory classes, we compared different linear models, starting with a one-class model (i.e. assuming that all participants followed the same trajectory) and then adding classes in each subsequent run. For each model, allocation of individuals was based on maximum posterior probability [47]. Models were estimated with 2000 random starting values, using MPLUS software (version 7.0). To decide on the number of trajectory classes, we examined the following indices of goodness of fit: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted BIC (SSBIC) and the bootstrap likelihood ratio test (BLRT). The model with the lowest SSBIC was chosen [48]. The BLRT was used to assess differences in log-likelihood between models with k and k+1 classes, where $p<0.05$ indicates the benefit of adding an additional class [49]. We also computed the entropy value for each class solution. In addition to the indices of goodness of fit, the optimal number of latent trajectory classes was also based on group membership posterior probabilities, distinctiveness of classes and how well the PDSS-SR profiles of subjects from one class matched the class average. For all intercept and slope coefficients, we report unstandardized coefficients.

In the second step of the analyses, we conducted logistic regression analysis to test whether genetic background (presence/absence of the *BDNF* 66Met allele) and trauma-related variables (childhood abuse and childhood neglect) predicted class membership. To control for the potential effect of pharmacological treatment, this variable was included in the model as a covariate. Finally, the model also included variables for interaction effects between childhood abuse and *BDNF* genotype, and between childhood neglect and *BDNF* gentoype.

Results

Genetic and trauma-related variables

Carriers of one or two *BDNF*66Met alleles were combined as a "Met-carrier group", consistent with previous studies [18, 19, 50]. The genotype frequencies for the *BDNF* Val66Met polymorphism were: 31.8% (N = 37) Met allele carriers (including 6 Met/Met homozygotes), and 61.9% (N = 60) Val-Val homozygotes. In line with previous reports [51–53], we evaluated the prevalence of childhood maltreatment was evaluated using the following cut-off scores: emotional abuse $\geq$9, physical abuse $\geq$8, sexual abuse $\geq$6, emotional neglect $\geq$10 and physical neglect $\geq$8. In the current sample, 53 participants (55.2%) had been exposed to at least one type (emotional, physical, or sexual) of childhood abuse, and 51 (53.7%) to at least one type (emotional or physical) of childhood neglect.

Identification of trajectory classes

Preliminary sensitivity analyses showed that the models including and excluding participants with more than 3 missing data points gave the same class structures. Since missing data did not

Table 2. Model fit indices, *p*-value in Bootstrap Likelihood Ratio Test and entropy for up to three latent classes.

Model	AIC	BIC	SSBIC	BLRT difference (number of parameters)	*p*	Entropy
1-class	6549.88	6629.05	6531.18	--	--	
2-class	6547.61	6652.32	6522.80	23.46 (4)	0.037	0.851
3-class	6583.56	6636.18	6548.89	16.85 (4)	0.092	0.873

AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, SSBIC = sample-size adjusted BIC, BLRT = Bootstrap Likelihood Ratio Test

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affect results substantially, two participants with missing data were excluded, leaving 95 participants for the the trajectory analyses.

Table 2 shows the fit indices for models with 1 to 3 trajectory classes for the PDSS-SR. BLRT was only significant in the change between the 1-class and the 2-class models, which was not significantly different to the the 3-class model. The 2-class solution was therefore selected because it had the lowest SSBIC and a high entropy, which was 0.85, over the recommended cut-off of 0.80 [54].

Fig 2 shows that one class ("high response") included patients (N = 76; 80.3% of the sample) with lower baseline panic symptoms (intercept = 12.12, SE = 2.061, $p<0.01$) and a tendency to improve over time (slope = -0.329, SE = 0.12, $p = 0.01$). The other class ("low response") included patients (N = 19; 19.7% of the sample) with greater panic symptoms at baseline

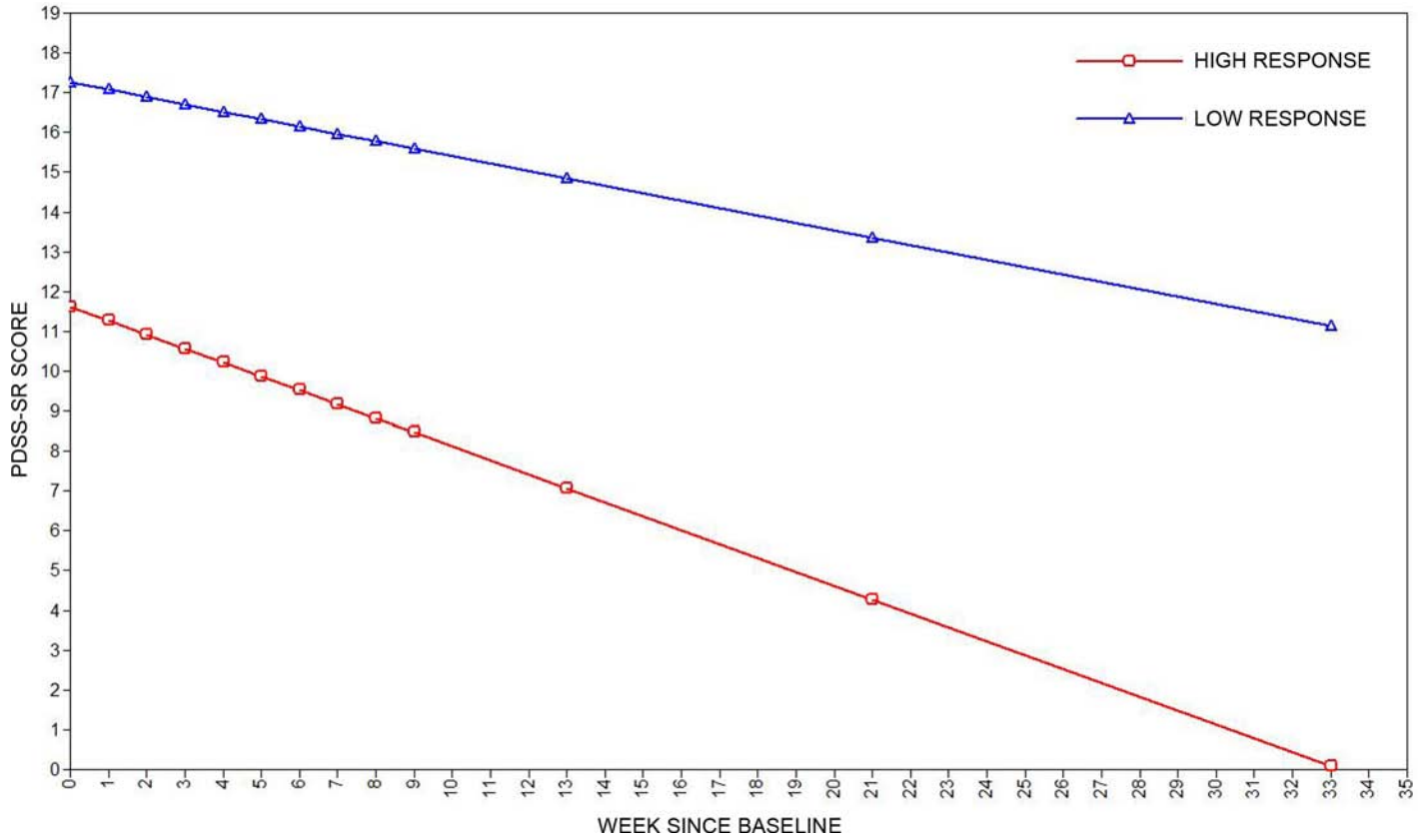

Fig 2. Estimated mean scores for panic symptoms (PDSS-SR) in the two-class model during exposure-based CBT and follow-up.

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Table 3. Main effects and interactions of genetic and trauma-related variables on trajectory class membership.

	B	SE	*p*
Main effects			
BDNF Met allele	0.078	0.550	0.887
Childhood abuse	0.003	0.046	0.946
Childhood neglect	-0.058	0.058	0.319
Interaction effects			
*BDNF**childhood abuse	-0.060	0.098	0.544
*BDNF**childhood neglect	0.059	0.123	0.631

SE = standard error

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(intercept = 18.36, SE = 2.76, $p<0.01$) and which did not improve across time (slope = -0.17, SE = 0.15, $p = 0.26$).

Effects of genetic background and trauma on trajectory classes

Table 3 shows that neither the *BDNF* Val66Met polymorphism nor the specific types of trauma analysed (abuse and neglect) predicted membership of any specific trajectory class. We found no significant evidence to suggest that trajectory class membsership was affected by gene-environment interaction between the *BDNF* Met allele and childhood abuse, nor between the *BDNF* Met allele and childhood neglect.

Discussion

To our knowledge, this is the first study to evaluate the effects of the *BDNF* Val66Met polymorphism and childhood maltreatment as possible predictors of CBT outcome in PD (assessed using trajectories of change). We found no evidence that either *BDNF* Val66Met or childhood maltreatment were significant predictors of CBT outcome.

In our sample PD patients followed two different trajectories during treatment. Many patients (80.3%) showed a tendency to improve as a result of CBT, whereas a significant proportion (19.7%) did not. While there is a general paucity of data on trajectories of change during CBT for PD, our results are consistent with data from a previous study that highlighted a group of PD patients with high baseline symptoms that tend not to improve with CBT [28]. We observed a similar percentage of patients with this non-remitting course (19.7%) to that reported by Lutz et al. (17.2%).

We did not find a significant association between the *BDNF* Val66Met polymorphism and CBT treatment outcome. In light of previous reports, our results show that there is no compelling evidence to suggest that this genetic variation can be used to predict response to exposure-based CBT. In previous studies in adults, PTSD [18] and OCD patients [19] who carried the Met allele showed a poorer response than Val/Val homozygotes, although effects of *BDNF* in the OCD study were apparent in the percentage of responders, but not in the pre- to post-treatment severity scores. In addition, no association has been found between the *BDNF* Met allele and CBT outcome in SAD [20] or in mixed child anxiety disorders [21]. Thus, based on ours and previous studies, it seems that the relatively well established association between the *BDNF* gene and learning and memory, and specifically with fear extinction [16, 55], does not translate easily into clinical practice. One possible explanation is that the BNDF effect may be observed in very controlled experiments, but may be diluted among the multiple variables involved in clinical studies [56]. In an extensive review of the association between the *BDNF* Val66Met

polymorphism and mental disorders, Notaras and van den Buuse [57] highlight some of the possible methodological shortcomings as an explanation for previous inconsistent results, including small sample sizes and ethnicity-specific effects. It may also be the case that the *BNDF* gene provokes a poorer response in some anxiety-related disorders but not in others. For example, Hedman *et al.* [12] have recently proposed that exposure might have a more decisive role in some anxiety-related disorders (e.g., PTSD) than in others (e.g., SAD).

Another possibility is that other polymorphisms (rather than the one studied here) may be more important for predicting CBT outcome. A recent large study (N = 829) did not replicate the previously reported association [12] between the functional serotonin transporter promoter polymorphism and CBT outcome [58]. The authors of this study recommended abandoning the single-variant approach and moving towards a whole-genome array-based therapygenomics approach. A recent study from the same group also found no evidence of an effect of hypothalamic-pituitary-adrenal axis-related genes on response to CBT [59]. These authors also invesitgated epigenetic factors (changes in DNA methylation) and suggested that epigenetic variables may be a better predictor of CBT outcome than genetic factors. Regardless, it would be necessary to evaluate the clinical relevance of any positive association between (epi)genetic variation and psychological treatment [21].

We also found no evidence to suggest that childhood abuse and childhood neglect predict CBT outcome. Only two previous studies have investigated the effects of childhood maltreatment on CBT outcome in anxiety disorders, specifically in SAD patients [25, 26]. Bruce *et al.* did not find an association between childhood maltreatment and CBT outcome, as Alden *et al.* had previoulsy observed. However, in the study by Bruce *et al*., the patients who reported emotional abuse, emotional neglect and sexual abuse showed greater severity before and throughout treatment. Here, we focused on symptom reduction as our index of CBT outcome, and it remains possible that other variables (e.g. attrition rates or relapse/recurrence rates) may be affected by childhood abuse/neglect. Future studies that include these and other treatment-related outcomes may provide additional insights.

Finally, we detected no interaction between the polymorphism of interest and childhood abuse or neglect. As suggested by Keers *et al.* [60], inconsistent findings in previous studies on stressful life events may be due to unmeasured genetic moderators. Again, epigenetic factors have recently been identified in individuals with a history of abuse [61] and in institutionalized children [62], and it would be interesting for future studies to add epigenetics to the prediction of psychological treatment outcomes.

Several limitations of this study should be noted. First, a limitation of reporting negative results is that they could be due to a lack of statistical power rather than a real lack of effect in the population. However, the present study reports on a larger or similar sample (N = 97) than several previous studies that have found significant effects of genetic polymorphisms (the *BDNF* Val66Met and others) on the psychological [18, 19, 63] or pharmacological treatment [64, 65, 66] of anxiety and related disorders. Our sample is also much larger than a previous study that did find an effect of chilldhood maltreatment on CBT outcome [25]. A formal estimate of power in our study was hampered by the fact that we measured the effects of treatment using response trajectories, and the previous literature could not offer sufficient guidance to provide such calculations. Be as it is, one possibility to increase the sample size in future studies would be to include patients with different anxiety-related diagnoses and/or using different CBT modalities. This strategy was followed in Lester *et al.* [58], where children with mixed anxiety disorders receiving individual CBT, group-based CBT or parent-supported guided self-help were included. Second, most of the patients were receiving pharmacological treatment during CBT. While medication was kept stable for at least two months before the treatment started, we cannot exclude the possibility that improvement in panic symptoms was due to

maintaining pharmacotherapy over time. However, this was controlled for by including drug treatment as a covariate in our analyses. Third, our sample consisted mainly of non-responders to pharmacotherapy, which could represent a subgroup with different (including genetic) characteristics than the entire spectrum of patients with PD. Fourth, due to the low frequency of the *BDNF* Met allele in the European population [67], our Met/Met group was too small to be tested. Fifth, although we accounted for some environmental factors, the *BDNF* Val66Met polymorphism is unlikely to adhere to a simple genetic model [57], and so future studies involving genetic combinations may be warranted.

In conclusion, we found no evidence to support the effect of either the *BDNF* Val66Met polymorphism or childhood trauma-related variables on CBT outcome. Future studies that address the role of other (including epigenetic) variables may shed light on the neurobiological prediction of psychological treatment outcomes.

Supporting Information

S1 Fig. Mean scores of the PDSS-SR throughout the treatment and follow-up for Met-carriers and Val-Val.
(JPG)

Author Contributions

Conceived and designed the experiments: MS BA MAF. Performed the experiments: MS M. Mitjans M. Montoro SR MAF. Analyzed the data: MS BA AB CGF. Wrote the paper: MS CGF MAF. Critical revision of the manuscript for important intellectual content: BA CGF. Final approval of the version to be published: BA AB RG VV VP CGF.

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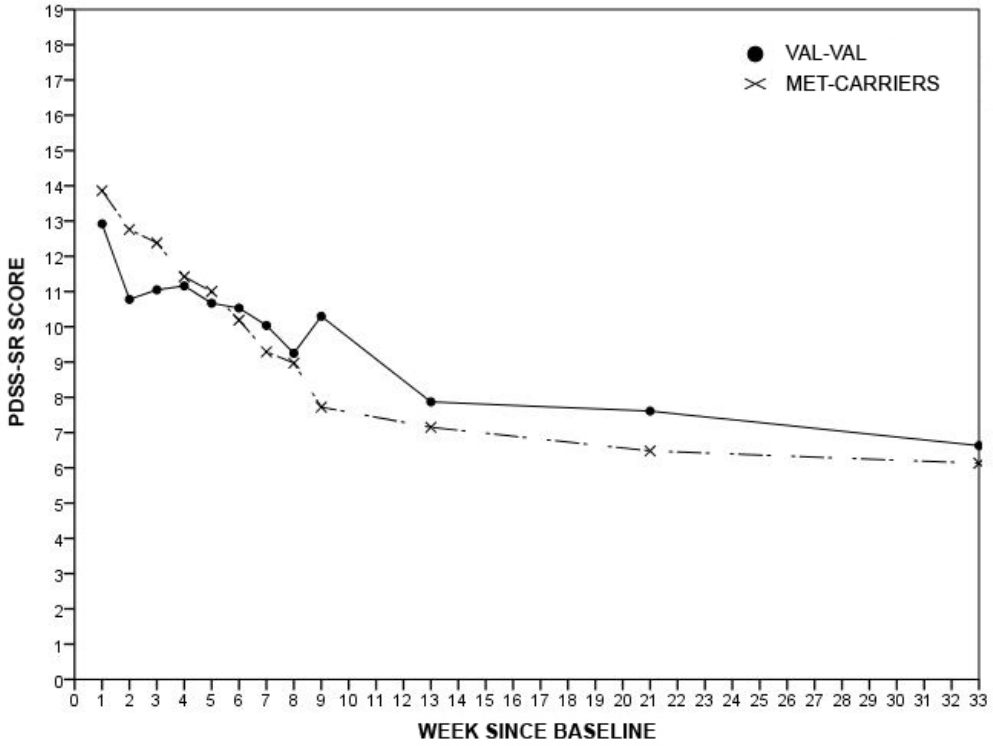
Annex estudi 2

Mean scores of the PDSS-SR throughout the treatment and follow-up for Met-carriers and Val-Val.



IV. Discussió general

Tal i com s'ha comentat, els trastorns d'ansietat suposen una gran càrrega social i econòmica, i una davallada molt important en la qualitat de vida dels pacients afectats. Per sort, actualment es disposa de tractaments eficaços per aquests trastorns, com per exemple els ISRS o la TCC.

Segons dades nostres amb la mostra de l'estudi 2 lleugerament ampliada (N=116, dades no publicades), i a partir dels criteris de Furukawa *et al.* (90), un 51% dels pacients que completen el protocol de 10 sessions de TCCG (assistència en 8 sessions o més) compleix criteris de resposta al post-tractament, percentatge que s'incrementa fins al 68.8% al seguiment als sis mesos. Aplicant una anàlisi per intenció de tractar (*last observation carried forward*), un 47.4% compleix criteris de resposta al post-tractament i un 57.8% al seguiment a 6 mesos. A les figures 1 i 2 es mostren les taxes completes de resposta i remissió, i a les taules 3 i 4 es mostra la mida de l'efecte (*d* de Cohen) al post-tractament i als diferents seguiments, tant per *completers* com a partir d'una aproximació *intention-to-treat*.

Així doncs, es reafirma l'efectivitat de la TCCG pel TP en entorns naturalístics (38), amb les típiques condicions complexes del dia a dia (91). És a dir, sense utilitzar la típica mostra "hiperseleccionada" dels estudis controlats realitzats en centres de recerca. En aquest cas, per exemple, la mostra incloïa un 23% de pacients amb comorbiditat a l'eix-I, un 13% amb comorbiditat a l'eix-II, un 84% rebia tractament farmacològic (a dosis estables) i 38% tenia pautades benzodiazepines a demanda. En aquest sentit, doncs, les condicions

Figura 1. Taxes de resposta i remissió dels pacients que van completar la TCCG.

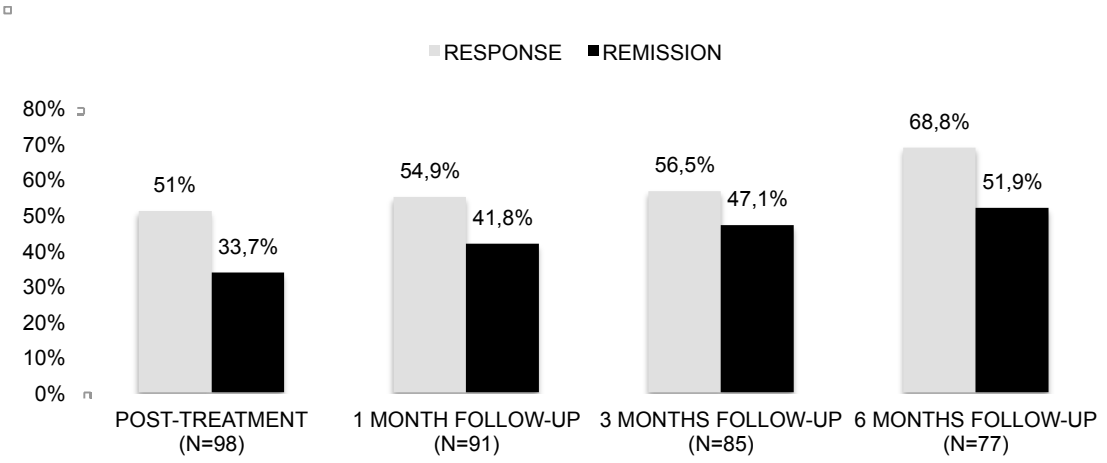
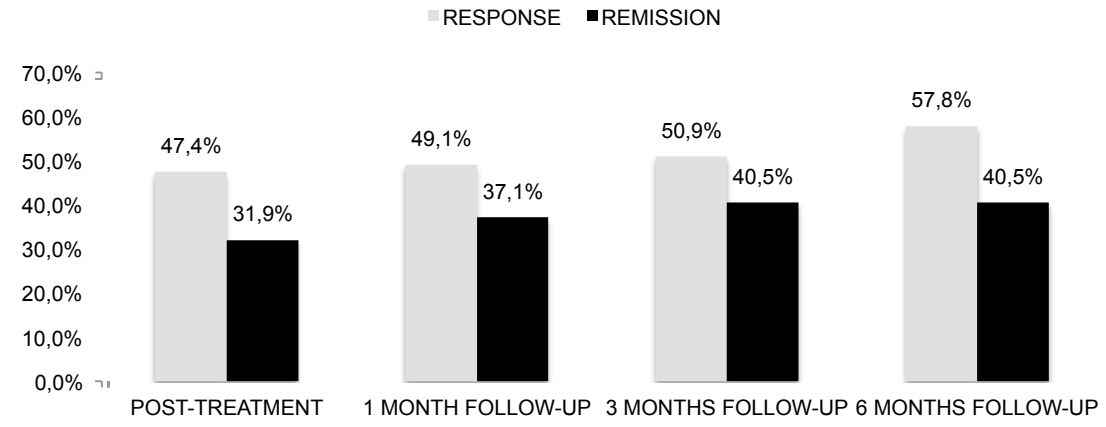


Figura 2. Taxes de resposta i remissió amb una anàlisi per intenció de tractar (N=116).



Taula 3. Mida de l'efecte (*d* de Cohen) amb els pacients que van completar la TCCG (N=103).

	Pre → Post	Pre → 1M FU	Pre → 3M FU	Pre → 6M FU
PDSS-SR	0.78	1.05	1.06	1.11
SDI	0.77	0.99	0.94	1.06
ASI-3 Total	0.59	0.90	0.92	0.95
ASI-3 Physical concerns	0.60	0.84	1.00	0.96
ASI-3 Cognitive concerns	0.45	0.67	0.58	0.56
ASI-3 Social Concerns	0.30	0.58	0.71	0.85
BDI-II	0.39	0.58	0.67	0.66

1M FU = one-month follow-up, 3M FU = three-month follow-up, 6M FU = six month- follow-up, PDSS-SR = Panic Disorder Severity Scale, Self-Report Version, SDI = Sheehan Disability Inventory, ASI-3 = Anxiety Sensitivity Index-3, BDI-II = Beck Depression Inventory-II

Taula 4. Mida de l'efecte (*d* de Cohen) amb una anàlisi per intenció de tractar (N=116).

	Pre → Post	Pre → 1M FU	Pre → 3M FU	Pre → 6M FU
PDSS-SR	0.81	0.91	0.91	0.99
SDI	0.83	0.92	0.89	1.04

1M FU = one month follow-up, 3M FU = three months follow-up, 6M FU = six months follow-up, PDSS-SR = Panic Disorder Severity Scale, Self-Report Version, SDI = Sheehan Disability Inventory

complexes del sistema sanitari públic no haurien de ser una “excusa” a l'hora d'implementar la TCCG i perseguir bons resultats en el TP.

Tanmateix, un part considerable dels pacients no milloren amb aquests tractaments. Per aquest motiu, la identificació dels factors implicats en una pitjor resposta terapèutica és ara per ara una prioritat en el món de la recerca. Emmarcada en aquest context, i des d'una òptica translacional -és a dir, posant a prova en entorns clínics "reals" troballes provinents del laboratori-, aquesta tesi pretén ser una contribució a l'estudi dels predictors de resposta.

Inicialment, i enllaçant amb el fil conductor de l'avaluació i el tractament del TP, es va portar a terme un primer treball (estudi 1) per a validar la versió castellana de la PDSS-SR. Tot i que els resultats ja s'han discutit amb més detall a l'estudi en qüestió (inclòs en aquesta tesi), es confirma que la PDSS-SR és un instrument adequat per valorar símptomes de pànic/agorafòbia en contextos de parla castellana. El fet que es tracti d'un instrument fàcil d'utilitzar ha de permetre la seva aplicació de forma àmplia, i poder portar a terme comparacions entre diferents cultures, cosa que fins ara no era possible degut a l'absència d'una versió en castellà validada. Per altra banda, seria desitjable desenvolupar en el futur una guia per interpretar canvis en la PDSS-SR en termes de millora/empitjorament, tal i com Furukawa *et al.* (90) van fer amb la PDSS. Una guia que permeti, per exemple, establir una correspondència entre la PDSS-SR i la *Clinical Global Impression* (CGI). Tenint en compte que aquest instrument es va dissenyar per monitoritzar símptomes del TP, l'elaboració d'aquesta guia semblaria un objectiu especialment important per a propers estudis.

Pel que fa a l'estructura factorial de l'escala, les nostres dades suggereixen un model de dos factors, amb un primer factor relacionat amb els atacs de pànic *per se*, i un segon factor amb els components cognitius i conductuals del trastorn. Tanmateix, aquests resultats contrasten amb els de Sánchez-Arribas *et al.* (24), que defensen una estructura unifactorial. Futurs estudis hauran d'abordar aquesta qüestió, ja que pot tenir importants implicacions en la conceptualització del TP. De fet, a la literatura, mentre alguns autors presenten el TP com un sol bloc (14, 92), altres autors plantegen una certa independència entre diferents grups de símptomes (93).

A partir de recerca prèvia (78-81), en l'estudi 2 vam avaluar la relació entre el polimorfisme Val66Met del gen del *BDNF* i dues formes de maltractament infantil (abús i negligència) amb les trajectòries de canvi durant la TCC pel TP. Cal destacar que aquesta és la primera vegada que s'avaluen en un mateix estudi aquests possibles predictors de resposta en el TP. Tanmateix, a partir de les nostres dades no vam obtenir un resultat positiu entre aquestes variables i la resposta al tractament. Anàlogament amb l'estudi anterior, els resultats ja han estat comentats amb precisió a l'apartat corresponent. Tot i així, valdria la pena destacar una sèrie d'observacions.

En primer lloc, la relació entre el gen del *BDNF* i els processos d'extinció -ben establerta en estudis previs- no sembla traslladar-se de forma robusta en la pràctica clínica. Si bé aquesta relació s'ha pogut observat en TOC (80) i TPEP (81), no ha estat així en ansietat social (82), TP (estudi 2 de la present tesi doctoral), o amb una mostra d'infants/adolescents amb diversos trastorns d'ansietat (83). Una possible explicació és que l'efecte del *BDNF*, observat en experiments de laboratori molt controlats, podria quedar diluït entre les

múltiples variables de confusió implicades en els estudis clínics (91). Una altra possible explicació, tal i com apunten Hedman *et al.* (82), seria que l'exposició podria tenir un rol més decisiu en alguns trastorns d'ansietat (p.e., TPEP) que en d'altres (p.e., ansietat social), fet que podria explicar les diferències en l'efecte del *BDNF*. Per altra banda, Roberts *et al.* (94) suggereixen que determinades variables epigenètiques podrien tenir un pes més important en la predicció de la resposta a la TCC que no pas determinats factors genètics. En el seu cas, per exemple, no troben efectes amb gens implicats en l'eix hipotalàmic-pituïtari-adrenal però si amb variables epigenètiques associades a aquests gens.

En segon lloc, igual que en l'estudi de Bruce *et al.* (89) amb ansietat social, tenir una història prèvia de maltractament infantil no sembla predir una pitjor resposta a la TCC. Tanmateix, resta pendent avaluar la relació entre el maltractament infantil i altres formes de mala evolució clínica (p.e., a partir d'índexs de recaiguda o abandonament). En tot cas, aquests resultats contrasten amb els d'Alden *et al.* (88) també amb ansietat social, segons els quals haver patit abusos durant la infància incrementa el risc de presentar una pitjor resposta a la TCC. Segons Keers *et al*. (95), els resultats inconsistents en estudis sobre esdeveniments vitals estressants es podrien explicar per la possible presència de moderadors no identificats (és dir, variables "intermèdies" que modulen l'efecte dels predictors). En aquest context, cal destacar que diversos autors ja han detectat alteracions epigenètiques en persones amb història d'abús (96) i en nens institucionalitzats (97). Tot apunta, per tant, que els treballs futurs en aquest terreny hauran d'incloure també variables epigenètiques.

I en tercer lloc, la interacció entre el gen del *BDNF* i les variables de maltractament infantil tampoc no va resultar estar associada amb la resposta al tractament. Tanmateix, aquest últim resultat no és sorprenent tenint en compte l'absència de significació en els efectes principals.

Tot i tractar-se de resultats negatius, aquestes dades s'afegeixen al creixent cos de coneixement sobre predictors de resposta en els trastorns d'ansietat, informació que ha d'acabar derivant en un futur cap a intervencions més ajustades a determinats perfils de pacients. A més, donat que la hipòtesi de partida no es va poder confirmar, aquest treball orienta la recerca en aquest camp cap a altres variables (p.e., epigenètiques) que podrien modular la resposta al tractament psicològic en el TP, i possiblement també en altres trastorns.

Finalment, destacar que la resposta al tractament es va mesurar a partir d'anàlisis de trajectòries. Tot i que la mostra era massa petita per posar a prova models amb trajectòries curvilínies (quadràtics o cúbics), aquesta aproximació metodològica suposa una de les fortaleses d'aquesta tesi. A partir de les anàlisis de trajectòries s'obté informació sobre els diferents patrons de canvi en el TP. Tal i com ja s'ha comentat, aquesta informació pot ser potencialment molt útil en el camí cap a una medicina més "personalitzada. A més, aquesta informació longitudinal de la simptomatologia del TP també pot ser especialment útil en la pràctica clínica, on rarament s'apliquen protocols predeterminats, sinó que es van modificant els tractaments sobre la marxa, en funció de l'evolució del pacients. A partir d'aquesta informació es podria anticipar què cal anar introduint a cada fase del tractament o en quins moments serà necessari algun tipus de potenciació. En tot cas, aquest treball contribueix

a impulsar aquesta nova aproximació metodològica i encoratja a la seva utilització en d'altres trastorns i tractaments.

V. Conclusions

Segons les nostres dades, podem concloure que:

- La versió castellana de la PDSS-SR presenta unes propietats psicomètriques adequades.
- Tenint en compte que la PDSS-SR és d'administració ràpida i fàcil, pot ser una eina útil en entorns clínics i de recerca de parla castellana, i ha de poder permetre comparacions entre diferents contextos culturals.
- S'identifiquen dues *trajectory classes* durant la TCC pel TP: un gran grup format pel 80% dels pacients i que millora amb el tractament, i un grup més reduït -format pel 20% dels pacients- que es caracteritza per presentar una major gravetat inicial i que no millora significativament amb el tractament.
- No hi ha evidència que l'al·lel Met del gen del *BDNF* ni les formes de maltractament infantil avaluades (abús i negligència) s'associïn a una pitjor resposta a la TCC pel TP.
- Futurs estudis que incloguin altres variables (incloses variables epigenètiques) podran aportar més llum sobre els factors implicats en una pitjor resposta terapèutica.

VI. Referències de la introducció i discussió general

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