Universitat Autònoma de Barcelona

Noves perspectives en l'extinció de la por: similituds amb la teràpia d'exposició i el paper del control atencional

Eduard Forcadell López

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TESI DOCTORAL

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A la Cristina, les Júlies i la Lluna.

Anyway the wind blows.

Bohemian Rhapsody, Queen

Agraïments

Això de la tesi és com anar a comprar al "súper": un sap quan entra però mai quan sortirà. Portes la llista de la compra ben pensada, organitzada per productes, passadissos o en ordre alfabètic. No importa, mai la completaràs al 100%, ni seguiràs el recorregut que havies planificat amb tanta cura. Ja sigui perquè volies meló i no n'és temporada, perquè se t'indigesten les ANOVA's, potser és que han canviat les begudes de lloc, o perquè el *reviewer* 2 opina que cal reestructurar tot el supermercat i tot i així no pot garantir que es torni a obrir el local. Cal paciència (que mai ha estat el meu fort) i cintura. Però tot s'entrena.

Però si una cosa molesta del "súper" és l'alteració premeditada de les rodes del carret, que fa que a vegades vagis donant bandades d'un costat a l'altre del passadís. En aquest sentit, la gran compra que ha estat la tesi es pot entendre *només* perquè 4 mans han dirigit el meu carret per evitar derrapades o col·lisions contra la muntanya de torrons. Deu ser que a Mallorca els carrets tenen ABS i tracció a les 4 rodes. Sigui com sigui, mai no podré agrair prou al Miquel Àngel i al Miquel el fet d'haver-me dirigit a través de l'establiment fins a la zona de caixes. M'han acompanyat en tot moment, m'han dirigit i re-dirigit, fins a completar tota la compra.

Menció especial als diferents empleats del supermercat que acostumen a facilitar el procés de compra. El David, l'especialista en productes porcins i de l'àrea de psicofisiologia i condicionament avançat, ha estat un suport fonamental sense el qual la compra mai no hagués finalitzat. També he de donar les gràcies a altres empleats (família i amics) que mai han acabat d'entendre de què anava la meva tesi però que m'han recolzat i respectat igualment. Finalment, he gaudit d'una espècie de *personal shoppers* (Cristina i Lluna) que m'han ajudat/recolzat/suportat en tot el procés, ja sigui ajustant el fil musical de la tenda, recomanant un producte o un altre, recordant-me la necessitat d'alimentar-me de tant en tant o obligant-me a agafar aire entre compra i compra. Sempre amb un somriure i amb una paciència infinita, les dues.

Ha sigut dur, però estic molt satisfet amb la compra. Moltes gràcies a tots!

Índex

Abreviacions

ACS	*Attentional Control Scale*
ANT-I	*Attentional Network Test for Interactions*
CA	Control atencional
CC	Condicionament clàssic
eACS	*Emotional Attentional Control Scale*
EC	Estímul condicionat
EC+	Estímul condicionat excitatori
EC-	Estímul condicionat inhibitori
EI	Estímul incondicionat
EN	Estímul neutre
TCC	Teràpia cognitivoconductual

I. Introducció

1. L'Aprenentatge de la por al laboratori

La por és una emoció que proporciona una resposta adaptativa per protegir-se d'alguna amenaça. No obstant això, quan la por apareix sense una amenaça "real", ho fa de manera desproporcionada, o amb una intensitat i freqüència excessives, pot acabar desembocant en un trastorn d'ansietat. A les últimes dècades, els models d'aprenentatge de la por al laboratori han estat rellevants per a la comprensió dels trastorns d'ansietat (Graham i Milad, 2011; VanElzakker, Dahlgren, Davis, Dubois, i Shin, 2014), ja que permeten l'estudi d'aquests trastorns en el laboratori. El treball de Pitman i Orr (1986) és un dels primers en estudiar i donar suport al model d'Eysenck (1979) que sostenia que les alteracions en l'aprenentatge de la por constituïen la base dels trastorns d'ansietat (en aquella època englobats en el constructe "neurosi"). Aquest model rebia el nom de "condicionament de la neurosi".

Un dels paradigmes més emprats en la recerca sobre la por és el condicionament clàssic (CC), en el que un estímul inicialment neutre (EN) es converteix en un estímul condicionat (EC) després de ser associat repetidament amb un estímul incondicionat (EI) aversiu, de manera que l'EC provoca una resposta de por condicionada que genera una memòria de por (*adquisició* de la por). Després d'aquesta fase, si l'EC es presenta repetidament sense l'EI, l'amplitud i la freqüència de la resposta de por mostren una disminució. Aquest procés, en el qual es genera una memòria "de seguretat", rep el nom d'*extinció dins la sessió*. Finalment, el *record de l'extinció* descriu la reaparició de la memòria de l'extinció de la por, que s'estudia habitualment quan el participant torna al context on es va realitzar aquesta.

L'aprenentatge de la por al laboratori es pot estudiar mitjançant paradigmes de condicionament simple (com el descrit anteriorment) o diferencial (els més emprats en estudis amb humans). En el condicionament diferencial, s'anomena estímul condicionat excitatori (EC+) aquell EN que s'ha associat amb l'EI i que per tant, provocarà una resposta de por condicionada. Per altra banda, també es presenta un altre EN que mai s'associarà a l'EI, i que anomenem estímul condicionat inhibitori (EC-), ja que es converteix en un senyal d'absència de l'EI. En els paradigmes de condicionament diferencial, l'adquisició de la por es mesura habitualment comparant les respostes entre l'EC+ i l'EC-. D'aquesta manera, al final de la fase d'adquisició s'espera que la diferència entre EC+ i EC- sigui màxima (ja que el primer estímul provocarà respostes de por i el segon no). A la fase d'extinció, s'espera que les diferències entre l'EC+ i l'EC- vagin desapareixent, ja que el participant haurà après que l'EC+ ja no és un senyal de perill associat a l'EI.

Els paradigmes d'aprenentatge de la por al laboratori poden variar en un nombre important de paràmetres, com per exemple, el tipus i nombre d'estímuls utilitzats, així com l'ús d'un tipus d'EI o un altre (Lissek et al. 2005). La figura 1 mostra el paradigma d'aprenentatge de la por de 2 dies basat en Milad, Orr, Pitman, i Rauch (2005) emprat en el nostre estudi. Els contexts d'adquisició i d'extinció eren imatges de dues habitacions diferents que contenien una làmpada que s'encenia amb dos colors (blau o groc) que eren els EC (EC+ i EC-). El primer dia constava d'una fase d'adquisició, en la que l'EC+ (en el cas de la figura 1 es tracta de la llum blava) s'associava amb un xoc elèctric. Immediatament després començava la fase d'extinció dins la sessió (ja en un altre context) en la que l'EC+ no s'associava a l'EI. El segon dia (24 hores després) constava de la fase de record de l'extinció, en la que es presentaven un altre cop els estímuls en el context d'extinció sense l'EI.

Figura 1. Paradigma d'aprenentatge de la por emprat en el nostre estudi.

EI: estímul incondicionat; EC: estímul condicionat.

1.1. Anomalies en l'aprenentatge de la por en l'etiologia dels trastorns d'ansietat

S'han descrit diverses anomalies en els processos d'aprenentatge de la por que podrien caracteritzar els individus amb trastorns d'ansietat i que serien també un probable factor en l'etiologia d'aquests trastorns (Mineka i Zinbarg, 2006). Duits et al. (2015) examinaren de forma sistemàtica aquestes diferències en l'aprenentatge de la por comparant pacients amb trastorns d'ansietat (trastorn de pànic, trastorn d'ansietat generalitzada, trastorn d'estrès posttraumàtic, fòbia social i fòbia específica) i controls sans mitjançant una metaanàlisi de 44 estudis. Els resultats indicaven que, durant la fase d'adquisició de la por, els pacients amb trastorns d'ansietat mostraven un augment de les respostes de por davant els senyals de seguretat (EC-) quan se'ls comparava amb el grup control. Per contra, durant la fase d'extinció dins la sessió, els pacients mostraven un augment de les respostes de por davant l'EC+, així com una tendència cap a l'augment de les diferències entre EC+ i EC-, quan se'ls comparava amb un grup control.

Tot i que la majoria d'estudis, fins ara, s'han centrat en les diferències entre pacients i controls sans en les fases d'adquisició i extinció dins la sessió, hi ha certa evidència que els pacients amb trastorns d'ansietat també mostrarien anomalies durant el record de l'extinció. Un estudi interessant de Milad et al. (2008), que comparava pacients amb trastorn per estrès posttraumàtic amb els seus bessons sans en un paradigma d'aprenentatge de la por, va trobar que els pacients mostraven deficiències en el record de l'extinció (respostes de por més elevades tant a l'EC+ com a l'EC-) quan se'ls comparava amb els seus germans sans.

La figura 2 il·lustra de manera esquemàtica alguns d'aquests dèficits durant les fases d'extinció dins la sessió i record de l'extinció.

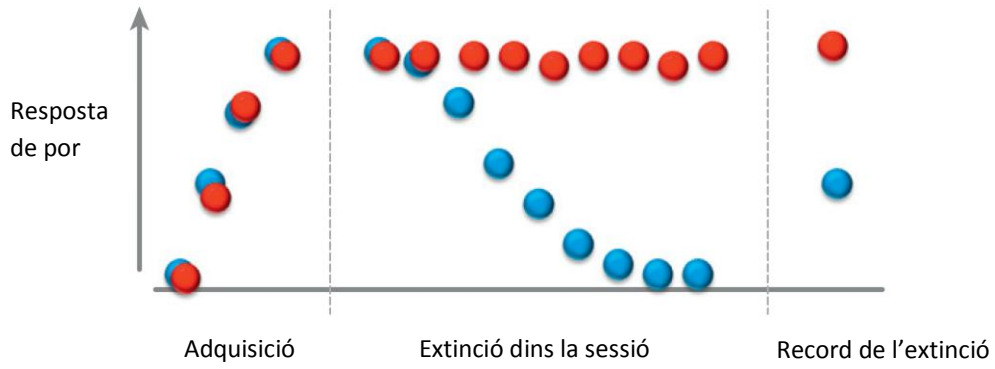

Figura 2. Exemples d'anomalies en les diferents fases d'aprenentatge de la por.

El gràfic il·lustra diferències individuals en diferents processos de l'aprenentatge de la por. Els punts blaus representarien respostes de por "normals", mentre que els vermells mostren alteracions en les respostes de por.

Diverses teories han intentat explicar l'associació entre anomalies en l'aprenentatge de la por al laboratori i els trastorns d'ansietat. Lissek et al. (2005) en descriu breument algunes:

Condicionament clàssic aversiu: Inicialment es considerava que l'ansietat patològica era conseqüència directa d'un procés de condicionament clàssic aversiu (de manera que un EN associant-se amb un EI aversiu es convertia amb un EC). No obstant això, des de fa anys aquestes teories han estat matisades pel seu plantejament massa reduccionista (Rachman, 1997).

Condicionament augmentat: Un estudi d'Orr et al. (2000) va mostrar com pacients amb trastorns per estrès posttraumàtic desenvolupaven un major condicionament diferencial (i.e. majors diferències entre EC+ i EC-) comparat amb controls sans, tant durant la fase d'adquisició com a la fase d'extinció de la por. Els autors concloïen que aquest patró de respostes podria ser un fenomen característic dels trastorns d'ansietat.

Errors en la inhibició de la por davant de senyals de seguretat: Alguns autors també han explicat les anomalies en l'aprenentatge de la por com un dèficit per a considerar els EC- (aquells estímuls no associats amb un EI) com un senyal de seguretat (no relacionada amb el "perill") (Davis, Falls i Gewirtz, 2000). Un estudi de Grillon i Morgan (1999) amb pacients amb estrès posttraumàtic va confirmar aquesta hipòtesi.

Sobregeneralització de la por: Un altre factor que podria explicar les dificultats en l'aprenentatge de la por seria el procés de generalització, en el que la por condicionada davant d'un estímul es "generalitzaria" a un altre amb característiques perceptuals semblants. En aquest sentit, Lissek et al. (2010) va mostrar que els pacients amb trastorn de pànic exhibien més generalització que un grup control, el que explicaria en part perquè aquests pacients estendrien algunes pors condicionades en un entorn concret durant un atac de pànic (com per exemple un centre comercial concret) a altres ambients similars (tots els centres comercials). Malgrat l'estudi de Lissek et al. (2014) demostrava que la sobregeneralització també apareixia amb pacients amb trastorn d'ansietat generalitzada, altres estudis han trobat resultats oposats (Tinoco-González et al., 2015).

1.2. Similituds entre l'extinció de la por i la teràpia d'exposició

A part del paper important que poden tenir en l'origen dels trastorns d'ansietat, els processos d'aprenentatge de la por també podrien tenir un rol destacat en el tractament d'aquests trastorns. La teràpia d'exposició és el tractament més eficaç per a la majoria de trastorns d'ansietat, ja sigui com a element únic o com a component central de la teràpia cognitivoconductual (TCC) (Hofmann i Smits, 2008). Malgrat l'elevada eficàcia de la teràpia d'exposició en la reducció dels nivell de por, la retenció a llarg termini d'aquesta reducció és un aspecte encara a millorar. Així doncs, la prevenció de recaigudes (i.e. evitar el retorn de la por) és un dels aspectes en el qual la recerca està centrant més esforços. La teràpia d'exposició i l'extinció al laboratori comparteixen algunes característiques en relació al retorn de la por (Vervliet, Craske i Hermans, 2013). Per exemple, en ambdós processos el context hi juga un paper crucial. Durant la teràpia, els següents aspectes probablement comportaran un retorn de la por:

- quan la teràpia es duu a terme en un context i s'avalua els nivell d'ansietat post-tractament en un ambient diferent.

- quan l'estat intern del pacient (com per exemple, l'"arousal") és diferent durant la teràpia i durant l'avaluació post-tractament.

Durant l'aprenentatge de la por al laboratori, s'han definit tres processos (íntimament lligats amb l'extinció i el context) que comporten un retorn de la por:

- Renovació de la por ("renewal"): presentar l'EC+ en un context diferent al de la fase d'extinció comporta normalment un retorn de la por condicionada.

- Recuperació espontània: quan es presenta l'EC+ un altre cop, un període de temps després de l'extinció, el participant pot tornar a presentar respostes de por.

- Reinstauració ("reinstatement"): la presentació de l'EI (de manera inesperada) pot comportar un retorn de la por davant l'EC extingit.

Hi ha altres similituds entre l'extinció de la por i la teràpia d'exposició. La teràpia d'exposició utilitza principis del procés d'extinció de la por, atès que el pacient ha d'afrontar de manera repetida una situació temuda (EC) en l'absència de perill (EI). Per altra banda, alguns models teòrics d'extinció de la por explicarien els mecanismes a través dels quals actua la teràpia d'exposició. Una de les teories més representatives d'aquest enfocament és la *Teoria de l'aprenentatge inhibitori*. De forma breu, aquesta teoria explica que la memòria original entre EC i EI apresa durant la fase d'adquisició no és esborrada durant la fase d'extinció, sinó que es conserva de manera intacta i se'n crea una de nova: l'EC ja no prediu l'EI (es tracta d'una memòria inhibitòria, que competirà amb l'anterior) (Bouton, 1993). En l'actualitat, aquest model teòric és el que ha rebut més suport en la descripció dels principis bàsics a través dels quals operaria la teràpia d'exposició i es basa de forma directa en la investigació sobre l'extinció de la por en el laboratori.

Un dels motius pels quals aquest model teòric ha rebut suport per part de la comunitat científica és el fet que descriu millor un seguit de processos (com la renovació de la por o la importància del context) que els anteriors models no podien explicar. Per exemple, un dels primers models que intentava descriure el funcionament de la teràpia d'exposició (que inicialment formava part de la desensibilització sistemàtica, una intervenció en la que habitualment es combina l'exposició en imaginació amb la relaxació), era el contra-condicionament o inhibició recíproca, descrit per Wolpe (1958). Segons aquest autor, proporcionar una resposta antagònica a l'ansietat (com la relaxació) en presència de l'estímul que la provoca farà que el vincle entre l'estímul i la resposta d'ansietat es debiliti. Malgrat la importància d'establir un primer marc teòric sobre la teràpia d'exposició, la inhibició

recíproca no va poder explicar alguns fenòmens (com l'eficàcia de l'exposició sense incloure la relaxació) que sí es podien justificar des dels models d'habituació. L'habituació (reducció de la intensitat de les respostes de por per la presentació repetida de les situacions temudes) va esdevenir el component central dels models dominants en la descripció dels processos de canvi de la teràpia d'exposició. En aquest context apareix la *Teoria del processament emocional* (Foa i Kozak, 1986) que descrivia l'habituació de la por com el procés principal que determinava l'èxit de la teràpia d'exposició. Aquesta teoria descriu que els efectes de la teràpia serien conseqüència de l'activació d'una "estructura de por" que s'integraria amb informació incompatible, resultant en la creació d'una estructura de no-por que reemplaçaria l'original. La informació incompatible s'aconseguiria mitjançant la reducció de la por després d'una exposició prolongada als estímuls temuts, de manera que els clínics haurien de fer èmfasi en l'augment inicial de la por seguit d'una reducció de la mateixa, que seria un senyal d'èxit terapèutic. No obstant això, l'evidència no ha donat suport a aquest mecanisme, atès que la reducció de la por durant la teràpia no sempre prediu els nivell de por expressats en els seguiments post-tractament (Craske et al., 2008).

Com s'apuntava més amunt, aquestes limitacions van ser superades per la teoria de l'aprenentatge inhibitori, la qual es basa en la recerca de l'extinció de la por. Aquesta teoria argumenta que el funcionament de la teràpia d'exposició no s'explica per la debilitació de l'estructura original de la por, sinó per la creació de noves memòries que competiran amb la memòria original. Des d'aquest model, autores com Craske, Treanor, Conway, Zbozinek i Vervliet (2014) han proposat estratègies per maximitzar els resultats de la teràpia d'exposició que es deriven directament de la teoria i dels models d'extinció de la por al laboratori i que permetrien "augmentar" l'aprenentatge inhibitori (i per tant, augmentar l'eficàcia de la teràpia d'exposició). Algunes d'aquestes estratègies són:

Violació d'expectatives: consisteix en trencar al màxim les expectatives en relació a l'aparició d'esdeveniments aversius a través de l'experiència (per exemple, l'expectativa d'un pacient amb trastorn de pànic a tenir un atac de cor quan està a un ascensor). El que es pretén és dissenyar una teràpia d'exposició que potenciï l'aprenentatge inhibitori per sobre de l'excitatori. En l'exemple anterior, la violació de les expectatives consistiria en exposar al pacient a l'ascensor i fer èmfasi en la *no aparició* de l'esdeveniment aversiu (l'atac de cor), i no tant en la disminució de la por (com es faria des dels models d'habituació de la por).

Retirar senyals de seguretat: quan els pacients amb trastorns d'ansietat retiren aquells senyals o conductes de seguretat que ajuden a alleujar el malestar a curt termini (com ara la presència d'una altra persona, portar aigua o medicació) podríem millorar els resultats de la teràpia, ja que aquests senyals interferirien en la creació de la memòria inhibitòria.

Variabilitat: introduir variabilitat d'estímuls temuts durant la teràpia d'exposició podria millorar la capacitat d'emmagatzemar informació nova, de la mateixa manera que s'incrementaria la memòria inhibitòria ja que l'individu aprendria que molts més estímuls estan associats amb situacions sense perill.

Introduir senyals de recuperació: es tracta de senyals sobre la memòria "l'EC no està relacionat amb l'EI" que s'aprenen durant la teràpia i el pacient podria fer servir després, en una fase de prevenció de recaigudes.

Múltiples contextos: per evitar el fenomen de la renovació (ja descrit abans) caldria realitzar la teràpia d'exposició en diverses situacions i contextos.

Com s'ha descrit anteriorment, hi ha moltes similituds entre la teràpia d'exposició i l'extinció de la por. Tant és així, que la literatura clàssicament ha considerat ambdós processos com a equivalents (Hermans, Craske, Mineka, i Lovibond, 2006). Així, s'ha assumit que les diferències individuals en l'extinció de la por podrien predir el resultat de la

teràpia d'exposició (és a dir, una major capacitat per extingir la por estaria relacionada amb millors resultats durant la teràpia). No obstant això, aquesta relació pràcticament no ha estat estudiada experimentalment.

Dos estudis recents s'han aproximat a la qüestió. Waters i Pine (2016) van avaluar els processos d'adquisició i extinció dins la sessió amb un paradigma de condicionament diferencial, amb mesures subjectives i d'activitat electrodermal, en un grup de nens amb trastorns d'ansietat que van ser tractats amb TCC en grup. Els resultats indicaven que aquells nens que no van respondre a la teràpia no van mostrar una reducció significativa de la por durant la fase d'extinció dins la sessió, comparat amb aquells nens que sí van respondre al tractament i amb el grup control. Tot i que aquest estudi fa una primera aproximació a la relació entre l'extinció dins la sessió i els resultats de la TCC en nens amb trastorns d'ansietat, el treball no investiga el paper que hi juga el record de l'extinció. Per altra banda, no queda clar que aquests resultats es puguin replicar amb població adulta, atès que la literatura prèvia indica que les capacitats d'extinció poden canviar al llarg de la vida (Baker, Bisby, i Richardson, 2016; Pattwell et al., 2012).

El segon d'aquests estudis (Ball, Knapp, Paulus, i Stein, 2016) explorava la relació entre l'extinció dins la sessió i la teràpia d'exposició en una mostra de 24 adults amb por de parlar en públic. En aquest cas, la por es va avaluar mitjançant respostes subjectives i activació cerebral (durant la fase d'extinció dins la sessió) i amb autoinformes sobre els canvis en la por experimentada (durant la sessió de teràpia). Els resultats mostraven que les persones amb major capacitat d'extinció dins la sessió i amb canvis en l'activació de regions cerebrals associades amb l'extinció de la por (còrtex prefrontal ventromedial, amígdala, ínsula i substància gris periaqüeductal) presentaven majors reduccions de por durant la teràpia d'exposició. En aquest cas també es va obviar el possible paper de la fase del record de l'extinció en relació a la teràpia d'exposició.

2. El control atencional

De la mateixa manera que passa amb l'aprenentatge de la por, diferents processos atencionals s'han identificat com a variables que tindrien un paper important en els trastorns d'ansietat i també en els processos d'aprenentatge de la por. Fins ara, la majoria d'estudis s'han centrat en analitzar com la distribució atencional canvia durant o després de la fase d'adquisició (Beaver, Mogg, i Bradley, 2005; Koster, Crombez, Van Damme, Verschuere, i De Houwer, 2005), o durant la fase d'extinció dins la sessió (Barry, Vervliet, i Hermans, 2016; Robbins, 1990; Van Damme, Crombez, Hermans, Koster, i Eccleston, 2006) i com aquests desplaçaments del focus atencional afecten a la magnitud de l'aprenentatge de la por.

A partir d'aquests estudis s'ha iniciat una línia de recerca, encara poc prolífica, que s'ha plantejat la qüestió de si, i de quina manera, les diferències individuals en les capacitats atencionals basals poden predir alguns paràmetres de l'aprenentatge de la por i, més en concret, de l'extinció de la por (Barry, Griffith, Vervliet, i Hermans, 2016; Barry, Vervliet, i Hermans, 2017; Waters i Kershaw, 2015).

Una part d'aquests treballs s'ha adreçat a analitzar de quina manera els biaixos atencionals cap a l'amenaça es relacionen també amb l'aprenentatge de la por, en tant que puguin modular la preferència atencional cap a un tipus o altre d'estímuls (e.g. EC+ o EC-) i/o afavorint l'evitació atencional. L'anàlisi de les relacions entre els processos atencionals davant estímuls amb càrrega emocional i la presència de símptomes d'ansietat ha estat una qüestió força estudiada (e.g. Cisler i Koster, 2010).

D'altres, s'alineen amb una segona tradició de recerca centrada en l'anàlisi de com les capacitats de control cognitiu i control inhibitori, ja sigui davant estímuls emocionals o davant estímuls sense càrrega emocional - aspecte sobre el que abundarem més endavant - s'associen amb una major vulnerabilitat a l'ansietat, posant-los també en relació a la presència

de diferències individuals en l'aprenentatge de la por. En aquest marc, el control atencional (CA) ha esdevingut el constructe probablement més destacat en la investigació sobre com les diferències individuals en les capacitats atencionals es relacionen amb els processos d'ansietat (Hadwin, Visu-Petra, Muris, Derakshan, i McLeod, 2016; Heeren, De Raedt, Koster, i Philipott, 2013).

2.1. Control atencional, ansietat i processos relacionats

El CA és un constructe que defineix l'habilitat de regular la distribució atencional, incloent les habilitats per a mantenir l'atenció sostinguda, ignorar distractors i desplaçar el focus atencional entre diferents tasques (Derryberry i Reed, 2002).

Tradicionalment, el CA s'ha equiparat amb el funcionament de la xarxa de control executiu del model de Posner i Petersen (1990), que inclou dues xarxes atencionals més: la d'orientació i la d'alerta. No obstant això, en l'actualitat alguns autors defensen que el constructe de CA es caracteritza millor incloent-hi les tres xarxes atencionals i no només la de control executiu (Heeren i McNally, 2016).

La xarxa de control executiu està especialitzada en resolució de conflictes i en el control voluntari de l'atenció i seria la responsable de resistir distraccions provocades per la interferència d'altres estímuls no relacionats amb la tasca prioritària a la qual s'ha d'atendre. La xarxa d'orientació està involucrada en la selecció d'informació rellevant d'entre els estímuls sensorials de l'entorn immediat, incloent-hi les operacions de captació atencional i de retirada de l'atenció. Finalment, la xarxa d'alerta seria l'encarregada de mantenir una sensibilitat adequada per percebre i processar estímuls.

Com ja s'ha apuntat abans, hi ha prou evidències a la literatura que les diferències individuals en les capacitats de CA s'associen amb variacions a l'afectivitat negativa (i.e.

reactivitat emocional davant d'estímuls aversius o estressors), la simptomatologia ansiosodepressiva i d'altres processos relacionats. Concretament, una baixa capacitat de CA s'ha relacionat amb una major afectivitat negativa (e.g. Fajkowska i Derryberry, 2010) i amb major simptomatologia ansiosodepressiva (e.g. Olatunji, Ciesielski, Armstrong, Zhao, i Zald, 2011). En aquest sentit, Sportel, Nauta, de Hullu i de Jong (2013) en un estudi longitudinal amb una mostra de 1811 participants sans, van trobar que una baixa capacitat de CA predeia l'aparició de símptomes ansiosos al cap de 2 anys.

La literatura prèvia també ha mostrat que una menor capacitat de CA, incloent-hi una menor eficiència en el funcionament d'algunes xarxes atencionals (com les de control executiu i la d'orientació) s'associa amb ansietat clínica i amb major ansietat tret (Heeren, Maurage, i Philippot, 2015; Heeren i McNally, 2016; Moriya i Tanno, 2009; Pacheco-Unguetti, Acosta, Callejas, i Lupiáñez, 2010; Pacheco-Unguetti, Acosta, Marqués, i Lupiáñez, 2011).

De la mateixa manera, la literatura ha relacionat la presència de dificultats de CA amb una major resposta davant d'estressors (e.g. Richey, Keough, i Schmidt, 2012), més biaixos atencionals cap a l'amenaça característics de les persones amb ansietat (e.g. Massar, Mol, Kenemans, i Baas, 2011) i majors dificultats de regulació emocional (veure, més endavant, l'apartat sobre la qüestió). A més, un estudi recent de Basanovic, Notebaert, Grafton, Hirsch i Clarke (2017) va mostrar que les diferències individuals basals en CA es relacionaven amb la magnitud dels canvis en els biaixos atencionals cap a l'amenaça després de participar en una tasca de modificació d'aquests biaixos. En concret, les persones amb major CA inicial van experimentar reduccions més grans en els biaixos atencionals, és a dir, es van beneficiar més de la intervenció.

De tota manera, una de les assumpcions bàsiques de la teoria del control atencional (Eysenck i Derakshan, 2011) indica que és l'ansietat la que provoca dificultats en la capacitat

general de control cognitiu, bàsicament perquè erosiona l'eficiència de funcions executives com són les d'inhibició i canvi del focus atencional. Atenent aquest plantejament, no serien tant les diferències individuals en el CA les que porten a variacions en les manifestacions d'ansietat i processos relacionats sinó més aviat a l'inrevés. De tota manera, hi ha diverses evidències que plantegen la possibilitat de que les dificultats de CA puguin ser vistes com a resultat de dèficits en el temperament regulatori i que la capacitat de CA, per ella mateixa, pugui ser responsable, almenys parcialment, de la qualitat dels processos atencionals de dalt a baix, un cop descomptats els efectes perniciosos de l'ansietat elevada sobre l'atenció (e.g. Rueda, Posner, i Rothbart, 2005; White, Helfinstein, Reeb-Sutherland, Degnan, i Fox, 2009). La forma amb la qual s'ha avaluat el CA, a la qual cosa dedicarem el següent apartat, també ha tingut molt a veure amb aquestes concepcions.

2.2. Mesures del control atencional

El CA pot ser avaluat en condicions emocionals o neutres. Aquesta diferenciació és important perquè tradicionalment la investigació sobre el paper de les variables atencionals en els trastorns d'ansietat s'ha basat en paradigmes de biaixos atencionals cap a l'amenaça (Hadwin et al., 2016) i, per tant, es tracta d'estudis que utilitzen estímuls amb càrrega emocional. Un dels focus de debat en els últims anys és, precisament, si aquests biaixos atencionals cap a l'amenaça (propis de les persones amb ansietat elevada) podrien estar reflectint una desregulació més general de la capacitat de CA que pogués ser observable quan són avaluats en absència de càrrega emocional, és a dir, utilitzant estímuls neutres (Bishop, 2009; Moriya i Tanno, 2009; Pacheco-Unguetti et al., 2011).

La recerca sobre CA ha emprat diversos instruments per a la seva mesura. Els dos més rellevants, que permeten avaluar el CA en condicions no emocionals, són l'*Attentional*

Control Scale (ACS; Derryberry i Reed, 2002) i l'*Attentional Network Test for Interactions* (ANT-I; Callejas, Lupiáñez, i Tudela, 2004).

L'ACS consta de 20 ítems amb 4 opcions de resposta. A part d'una puntuació global, també ofereix dues subescales: focalització (habilitat per a mantenir el focus atencional intencionadament) i canvi atencional (habilitat per a canviar el focus atencional de forma voluntària). Puntuacions més altes indiquen majors capacitats de CA. Posteriorment ha aparegut una versió de l'instrument per avaluar el CA davant situacions emocionals, l'*Emotional Attentional Control Scale* (eACS; Barry, Hermans, Leanert, Debeer, i Griffith, 2013).

L'ANT-I és una tasca de rendiment que permet quantificar el funcionament de les tres xarxes atencionals abans descrites (control executiu, orientació i alerta) així com dos components de la xarxa d'orientació (costos: la capacitat de retirar l'atenció de senyals no vàlids; i beneficis: orientació facilitada per senyals vàlids), tant si es fan servir estímuls neutres com estímuls amb càrrega emocional. La tasca consisteix en quatre blocs de 48 assajos. A cada assaig, un senyal (un to d'alerta i/o un asterisc) precedeix una fletxa flanquejada per altres fletxes distractores. El participant ha d'indicar la direcció de la fletxa objectiu prement una tecla amb la major precisió i rapidesa possibles. Valors més alts dels índexs de les diferent xarxes indiquen una major capacitat d'aquella xarxa (excepte per control executiu i costos d'orientació, on valors més alts indiquen una menor capacitat). La figura 2A del segon estudi que forma part d'aquesta tesi mostra una representació gràfica dels diferents components i del procediment de l'ANT-I.

2.3. Control atencional i regulació emocional

En apartats anteriors s'ha parlat de la relació existent entre el CA i l'afectivitat negativa, la simptomatologia ansiosodepressiva i altres processos associats, entre els quals hi destaca la regulació emocional. La regulació emocional es pot definir com la capacitat de modular la reactivitat emocional mitjançant diversos processos, tant voluntaris com no intencionals. Les capacitats de focalitzar l'atenció, de canviar el focus atencional o d'activar o inhibir respostes subdominants, incloses les atencionals, són components centrals per a una regulació emocional eficient (e.g., Rothbart i Rueda, 2005; Sulik et al., 2010).

Així, no ens ha d'estranyar que la literatura també hagi trobat associacions entre la presència de dèficits en les capacitats de CA, ja siguin avaluades mitjançant autoinforme o amb tasques d'execució com l'ANT-I, amb certes dificultats de regulació emocional tant cognitiva (Armstrong, Zald, i Olatunji, 2011; Fajkowska i Derryberry, 2010; Koster, De Lissnyder, Derakshan, i De Raedt, 2011; Tortella-Feliu et al., 2014), com espontània (Morillas-Romero, Tortella-Feliu, Balle, i Bornas, 2015). Per tant, semblaria que el CA, un cop controlats els efectes de l'ansietat sobre les capacitats atencionals, podria explicar aquests mecanismes involucrats en una major o menor eficiència de la regulació emocional.

Com s'ha avançat una mica més amunt, dins la regulació emocional podríem diferenciar-hi processos de caràcter més aviat voluntari o intencional i altres de caràcter més automàtic. Entre aquests últims trobem la regulació emocional espontània, que es defineix com un procés natural, no intencional, i relativament lliure d'esforç que resulta en canvis en les propietats d'una resposta emocional (Gyurak, Gross, i Etkin, 2011). Tenint en compte que l'extinció de la por és una forma de regulació emocional espontània (Hartley i Phelps, 2010) i la relació identificada en la literatura entre dèficits en CA i dificultats en la regulació

emocional, és probable que les diferències individuals en CA estiguin associades amb diferències individuals en l'extinció de la por.

2.4. Control atencional i extinció de la por

La possible relació entre CA i extinció de la por ha rebut molt poca atenció en la literatura prèvia. Un estudi de Waters i Kershaw (2015), que se centrava en analitzar l'associació entre biaixos atencionals cap a l'amenaça i l'adquisició i l'extinció de la por en infants amb ansietat clínica, va trobar que aquells nens que mostraven atenció preferent cap a l'amenaça en una tasca de detecció visual exhibien major capacitat d'extinció dins la sessió que aquells que evitaven l'amenaça.

Per altra banda, els estudis de Barry i el seu equip (Barry, Griffith et al., 2016; Barry et al., 2017) han explorat com els dèficits en CA emocional (fent servir l'eACS, que explora CA davant situacions amb contingut emocional) s'associaven amb l'extinció dins la sessió en participants sans. En el primer dels estudis, es presentava als participants un estímul perceptualment similar a un EC original prèviament extingit. Els autors van observar que aquells amb un CA emocional més elevat extingien la por més ràpidament i mostraven un major retorn de la por (Barry, Griffith et al., 2016). En el segon estudi, durant la fase d'extinció dins la sessió es presentava als participants un estímul similar al de la fase d'adquisició, i se'ls demanava o bé fixar-se en las característiques que tenien en comú ambdós estímuls, o bé en les característiques úniques de l'estímul de la fase d'extinció dins la sessió. En els participants d'aquesta última condició (els que s'havien de fixar en les característiques úniques de l'estímul fet servir durant l'extinció) es va trobar una tendència a la significació en l'associació entre baix CA emocional i major retorn de la por (Barry et al., 2017). La conclusió dels autors és que aquells amb un menor CA emocional no haurien estat

capaços de desplaçar l'atenció cap a les característiques pròpies de l'estímul emprat durant l'extinció, el que hauria facilitat el retorn de la por quan se'ls presentava un estímul similar.

Així doncs, l'evidència sembla apuntar cap a una relació entre el CA emocional i la capacitat d'extingir la por. No obstant això, com s'ha apuntat anteriorment, seria interessant poder extrapolar aquests resultats a dificultats de CA més bàsiques que es podrien evidenciar en el maneig d'informació sense contingut emocional (i.e. neutra). Per altra banda, seria rellevant també veure quin paper jugarien les diferents xarxes de CA avaluades a través de tasques de rendiment (i no només a través d'autoinforme) així com explorar la relació entre CA i el record de l'extinció.

3. Objectius

Els objectius de la present tesi doctoral eren estudiar la relació entre diferències individuals en l'extinció de la por (extinció dins la sessió i record de l'extinció) al laboratori i la reducció de la por durant la teràpia d'exposició (estudi 1); i estudiar la relació entre diferències individuals en l'extinció de la por (extinció dins la sessió i record de l'extinció) al laboratori i el control atencional (avaluat de forma autoinformada i a través d'una tasca de rendiment que inclou les xarxes de control executiu, orientació i alerta) en condicions no emocionals (i.e. neutres) (estudi 2).

Basant-nos en la investigació prèvia, la hipòtesi de l'estudi 1 era que existiria una relació entre la capacitat d'extinció de la por al laboratori i la reducció de la por durant la teràpia. Més concretament, esperàvem que una millor capacitat per extingir la por (extinció dins la sessió i record de l'extinció) estaria associada amb una major reducció de la por durant la teràpia d'exposició. Pel que fa a l'estudi 2, aquest era de caràcter exploratori ja que l'evidència de la literatura prèvia era limitada.

II. Estudi 1:

Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study

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Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study

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ABSTRACT

Fear extinction models have a key role in our understanding of anxiety disorders and their treatment with exposure therapy. Here, we tested whether individual differences in fear extinction learning and fear extinction recall in the laboratory were associated with the outcomes of an exposure therapy analog (ETA). Fifty adults with fear of spiders participated in a two-day fear-learning paradigm assessing fear extinction learning and fear extinction recall, and then underwent a brief ETA. Correlational analyses indicated that enhanced extinction learning was associated with better ETA outcome. Our results partially support the idea that individual differences in fear extinction learning may be associated with exposure therapy outcome, but suggest that further research in this area is needed.

1. Introduction

Fear learning models are important for our understanding of anxiety disorders and their treatment (Graham and Milad, 2011; VanElzakker et al., 2014). In a typical fear learning experiment, an initially neutral stimulus (conditioned stimulus, CS) elicits a conditioned fear response (CR) and generates a fear memory (*conditioning*) after being repeatedly paired with an aversive unconditioned stimulus (US). In humans, most fear learning experiments use a differential conditioning paradigm, where one CS (CS+) is followed by the US and another is not (CS−).

After conditioning, if the CS is presented repeatedly without the US, the CR decays and a safety memory is formed (*extinction learning*). In experiments where conditioning and extinction learning occur in different contexts, if the CS is presented later in the context where extinction learning took place, this extinction memory is expressed again (*extinction recall*).

Abnormalities in some of these fear-learning processes could characterize anxious individuals in comparison to healthy controls and be a hallmark of anxiety disorders. For example, impaired extinction learning has been observed in individuals with panic disorder or generalized anxiety disorder (Michael et al., 2007; Otto et al., 2014; Pitman and Orr, 1986), while impaired extinction recall could characterize individuals with post-traumatic stress disorder (Milad et al., 2008). Several theories have been proposed to explain the association between fear learning and anxiety disorders, including failure to inhibit fear to safety cues (Davis et al., 2000), deficits in associative learning (Grillon, 2002), stimulus generalization (Mineka and Zinbarg, 1996), and enhanced conditionability (Orr et al., 2000) (reviewed by Lissek et al., 2005).

Apart from their possible role in the origin of anxiety disorders, fear-learning variables may have also an important role in the treatment of these disorders. In fact, there are many similarities between exposure therapy and fear extinction learning. Exposure therapy (one of the central components of cognitive-behavioral therapy - CBT - for anxiety-

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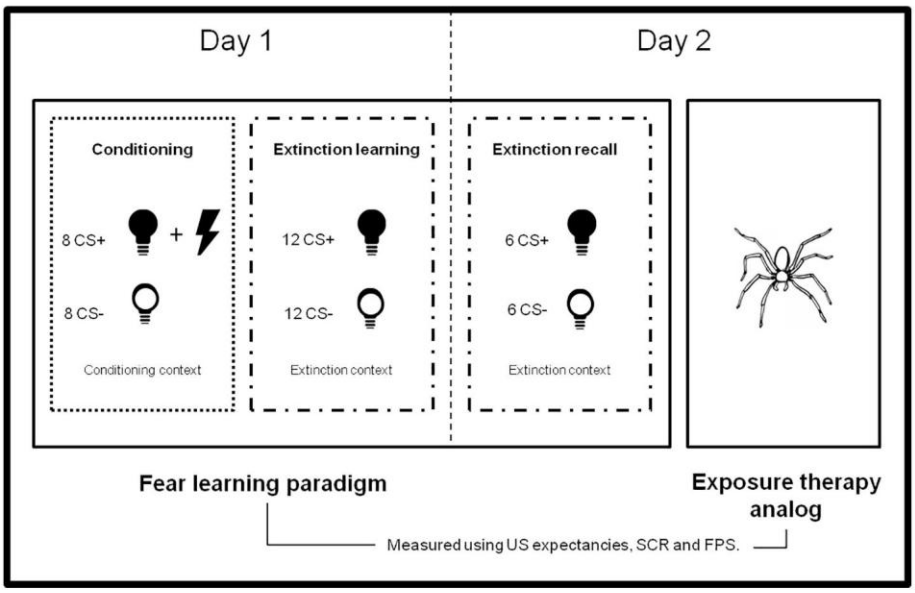

Fig. 1. Summary of experimental design.
US: unconditioned stimulus; SCR: Skin Conductance Response; FPS: Fear-Potentiated startle; CS +, conditioned stimulus associated with the unconditioned stimulus during the conditioning phase; CS −, conditioned stimulus never associated with the unconditioned stimulus.

related disorders) uses extinction learning principles by having the patient repeatedly confront a feared situation (CS) in the absence of danger (US) until fear diminishes (Myers and Davis, 2007). Moreover, extinction learning models may explain the mechanisms through which exposure therapy acts. For example, according to the inhibitory learning theory the original CS-US association learned during fear conditioning is not erased during fear extinction learning, but rather a new association (that the CS no longer predicts the US) is developed (Craske et al., 2008).

Research on fear extinction has gained momentum in recent years thanks to the exciting possibilities offered by translational research (Kindt, 2014; Milad and Quirk, 2012; Morrison and Ressler, 2014). Neuroimaging studies have shown that structural or functional variability in brain areas related to fear extinction is associated with the outcome of exposure therapy/CBT (Bryant et al., 2008; Fullana et al., 2014; Hoexter et al., 2013). Moreover, new pharmacological (Singewald et al., 2015) and behavioral (Schiller et al., 2010) approaches have been developed that focus on optimizing fear extinction abilities.

An important assumption from this research is that extinction learning in the laboratory is (almost) equivalent to exposure therapy (Berry et al., 2009; Hermans et al., 2006), and that the former should predict the latter (i.e. enhanced extinction learning would be associated with better outcomes from exposure therapy); however, this assumption has rarely been tested. One exception is a recent study by Waters and Pine (2016), who assessed fear conditioning and extinction learning in the laboratory using a differential conditioning paradigm and evaluative ratings (arousal and valence) and Skin Conductance Responses (SCR) as measures of fear in a group of clinically anxious children who then underwent CBT. The results showed that, during extinction learning, treatment non-responders did not show a significant decrease in fear (measured with the SCR) compared to responders and healthy controls. Waters and Pine (2016) assessed fear learning psychophysiologically using the SCR, and there is evidence that Fear-Potentiated startle (FPS) could be a more selective (i.e. less sensitive to declarative knowledge) measure of fear (Hamm and Weike, 2005; Sevenster et al., 2014; but see Luck and Lipp, 2015; Purkis and Lipp, 2001). Moreover, this study did not assess fear extinction recall, which may also be associated with exposure therapy outcomes (Milad and Quirk, 2012). Finally, it is not clear whether these findings can be replicated in adults, which is important because translational evidence suggests that extinction learning capacities may change over the life span (Baker et al., 2016; Pattwell et al., 2012).

Another recent study by Ball et al. (2016) explored the link between extinction learning and exposure therapy in a sample of 24 adults with public speaking anxiety. Brain activation and subjective ratings were assessed during extinction learning, and self-reported anxiety changes were collected during a massed exposure session, mimicking exposure therapy. Results showed that those with better extinction learning and changes in activation in brain regions associated with fear extinction (ventromedial prefrontal cortex, amygdala, insula, and periaqueductal gray) reported greater anxiety reduction during exposure therapy. This study focused only on extinction learning and did not assess extinction recall. Moreover, Ball et al. (2016) did not use psychophysiological measures of fear learning or anxiety reduction.

In the present study, we used a differential conditioning paradigm in adults with fear of spiders to test the hypothesis that individual differences in fear extinction in the laboratory would be associated with the outcome of an analog of exposure therapy (exposure therapy analog, ETA). Specifically, we expected that an enhanced fear extinction learning and fear extinction recall would be associated with a greater fear reduction from pre- to post-ETA. Following previous research (e.g. Pineles et al., 2016; Rabinak et al., 2013), we operationalized fear extinction as the difference between the CS + and CS − during extinction learning and extinction recall.

2. Materials and methods

See Fig. 1 for a summary of the experimental design.

2.1. Participants

We selected individuals with moderate to strong fear of spiders, as assessed by a dimensional instrument. Participants were recruited by advertisements to participate in a study on "physiological responses to anxiety". Initially, 1504 individuals were screened with the validated Spanish version (Forcadell et al., 2014) of the *Fear of Spiders Questionnaire* (FSQ; Szymanski and O'Donohue, 1995) via a secure web system. Participants who scored in the top quartile of the study distribution (FSQ ≥ 33; n = 386) were invited to participate. Of those, 92 accepted to be interviewed by a doctoral-level clinical psychologist using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998).

Exclusion criteria were: (a) current or lifetime history of mental disorders other than specific phobia (animal type, spiders), as determined by the MINI, supplemented with the specific phobia section of

the Structured Clinical Interview for DSM (SCID; First et al., 2002); (b) use of medication/illicit drugs or medical problems that could interfere with study performance or interpretation; (c) alcohol abuse; (d) pregnancy; (e) not being Spanish-speaker. Female participants had regular menstrual cycles (self-report), had not used oral contraceptives or hormone replacement therapy during the previous three months, and participated in the study during their early follicular phase (days 3–8 of a 28 to 30-day cycle) to avoid possible confounding by sex hormones in fear extinction (Merz et al., 2012; Milad et al., 2006; Pineles et al., 2016). All participants were tested between 5 and 8 PM.

The final sample consisted of 50 participants with moderate to strong fear of spiders (M_{FSQ} = 58.98, SD = 17.94; M_{age} = 21.50 years, SD = 2.93; 25 women). Participants gave written informed consent to take part in the study, which was approved by the corresponding institution's Clinical Research Ethics Committee. Participants were paid €25.

2.2. Procedure overview

Participants took part in two experimental sessions on two consecutive days. On day one, they rated their fear of spiders (FSQ pre-ETA score), participated in the first part of the fear learning paradigm (conditioning and extinction learning), and selected the two phobic stimuli (two most fearful images from a pre-selected set of 30 spider images; see Supplementary Materials-Methods) that would be used during ETA. On day two, they participated in the second part of the fear learning paradigm (extinction recall), underwent ETA, and rated their fear of spiders again (FSQ post-ETA score). Psychophysiological responses were recorded continually during the fear learning paradigm and during ETA (see below).

2.3. Fear learning paradigm

We adapted the paradigm developed by Milad et al. (2005), which allows us to assess conditioning, extinction learning, and extinction recall separately. The original task used SCR as the only measure of conditioned fear, but we added two other measures (US expectancies and FPS) (see Supplementary Materials-Methods). Briefly, the visual contexts were photographs of two different rooms (conditioning context, CX+; extinction context, CX−) containing a lamp that switched on to one of two different colors (blue or yellow), which were the CSs (CS+ and CS−). Contexts and CSs were displayed on a computer monitor in front of the participant. On day 1, a conditioning phase (in CX+) was followed by an extinction learning phase (in CX−). During conditioning, the CS+ co-terminated with an electric shock (US). The US was individually adjusted before the experiment (day 1) presenting shocks of gradually increasing intensity until a 'definitely annoying but not painful' shock was selected ($M_{shock\ level}$ = 4.9 milliamperes (mA), SD = 3.3). Participants were not instructed about the CS-US contingency. During extinction learning (immediately after conditioning), the CS+ was not followed by the US. The CS− was never followed by the US. The extinction learning phase was divided in two equal parts by a 1-minute pause (early and late extinction learning). Day 2 consisted of an extinction recall phase in CX−. During day 2, the CS+ and the CS− were never followed by the US. The US was not recalibrated during day 2.

Each trial of the experiment started with presentation of the context for 10, 12 or 14 s. Then the CS was presented (i.e. the lamp switched on) for 8 s, and a startle probe (50 ms duration, 100 dB) was delivered 7 s after CS onset. Between trials, a fixation cross was shown for 1 s. In one third of the trials (noise-alone trials, NA), no CS was presented, and instead the context was present for 8 more seconds; the startle probe was presented at second 7 of this extra time. The inter-probe interval varied between 18, 20, and 22 s. Eight trials of each type (CS+, CS−, and NA) were presented during conditioning, and six trials of each were presented during each of the remaining phases (early and late extinction learning, and extinction recall). SCR, FPS and US expectancy ratings were calculated for each trial type.

The SCR signal was sampled at a rate of 125 Hz. SCR magnitudes were computed in microsiemens (μS) as the difference between the maximum SCR value and the value at response onset, occurring 1 to 7 s after CS onset. Trials in which no response was detected or with a response magnitude of < 0.02 μS were considered non-response trials (see Dunsmoor et al., 2009), and trials showing interference or excessive baseline activity (1.3%) were rejected after visual inspection. To normalize the distribution of the SCR data, we applied a square root transformation.

Startle amplitudes were computed in microvolts (μV) as the difference between the EMG value at response peak and the average EMG during the 50 ms preceding the probe. If no response was detected in a given trial, the amplitude was scored as 0 μV. To be considered a valid response, elevations in the EMG recording had to start between 20 and 100 ms, and their peak had to occur between 20 and 150 ms after the probe. After visual inspection, trials with excessive noise (3.2%) were rejected. Raw data were transformed into T-scores to control for differences in reactivity. Scorers of SCR and FPS data were blind to the stimuli presented.

Regarding US expectancy ratings, for each trial participants were told to try to predict whether the shock would occur in the following seconds each time the lamps in the rooms turned blue or yellow. They had to answer as quickly as possible by clicking on the scale from 0 (no shock) to 10 (shock) displayed at the bottom of the screen (see Supplementary Materials-Methods for further information).

2.4. Fear extinction indices

Based on previous literature (Garfinkel et al., 2014; Pineles et al., 2016; Rabinak et al., 2013, 2014), we calculated for each participant and for each measure (US expectancies, SCR and FPS) an index expressing the "amount of learning" reflecting differences between CS+ and CS− during extinction learning (using early extinction and operationalized as a percentage), and extinction recall (using the first two trials) (see Supplementary Materials Table S1). Since the extinction learning index was calculated as a percentage, higher scores indicated enhanced extinction learning (i.e. less discrimination between CS+ and CS−). Since the extinction recall index was calculated as a simple subtraction it had the opposite interpretation (i.e. lower scores indicated enhanced extinction recall).

2.5. Exposure therapy analog (ETA)

We developed a one-session computer-assisted ETA based on exposure therapy principles (i.e. repeated presentation of phobic stimuli). Single-session exposure therapy (Tsao and Craske, 2000; Vasey et al., 2012), including computer-assisted protocols (Andersson et al., 2009; Dewis et al., 2001; Gilroy et al., 2000; Heading et al., 2001; Müller et al., 2011), are effective for treating specific fears and phobias. Our ETA was very similar to that used by Müller et al. (2011) in a randomized controlled trial, and similar effect sizes in fear reduction (see below) as those obtained by Müller et al. (2011) were also observed in the present study.

During ETA, participants were presented on a computer screen with the two previously selected phobic images (10 min each for a total of 20 min) and two neutral images (of a pen and a fork; 2,5 min each for a total of 5 min; see Supplementary Material-Methods). Neutral and phobic images were interleaved and presented 10 times each. To avoid order effects, participants were randomized into two groups that began with either a phobic or a neutral image. Neutral images were included to confirm that phobic images were subjectively and psychophysiologically more aversive.

Participants received brief psychoeducation in which they were instructed to confront phobic stimuli without using overt (i.e. avoid

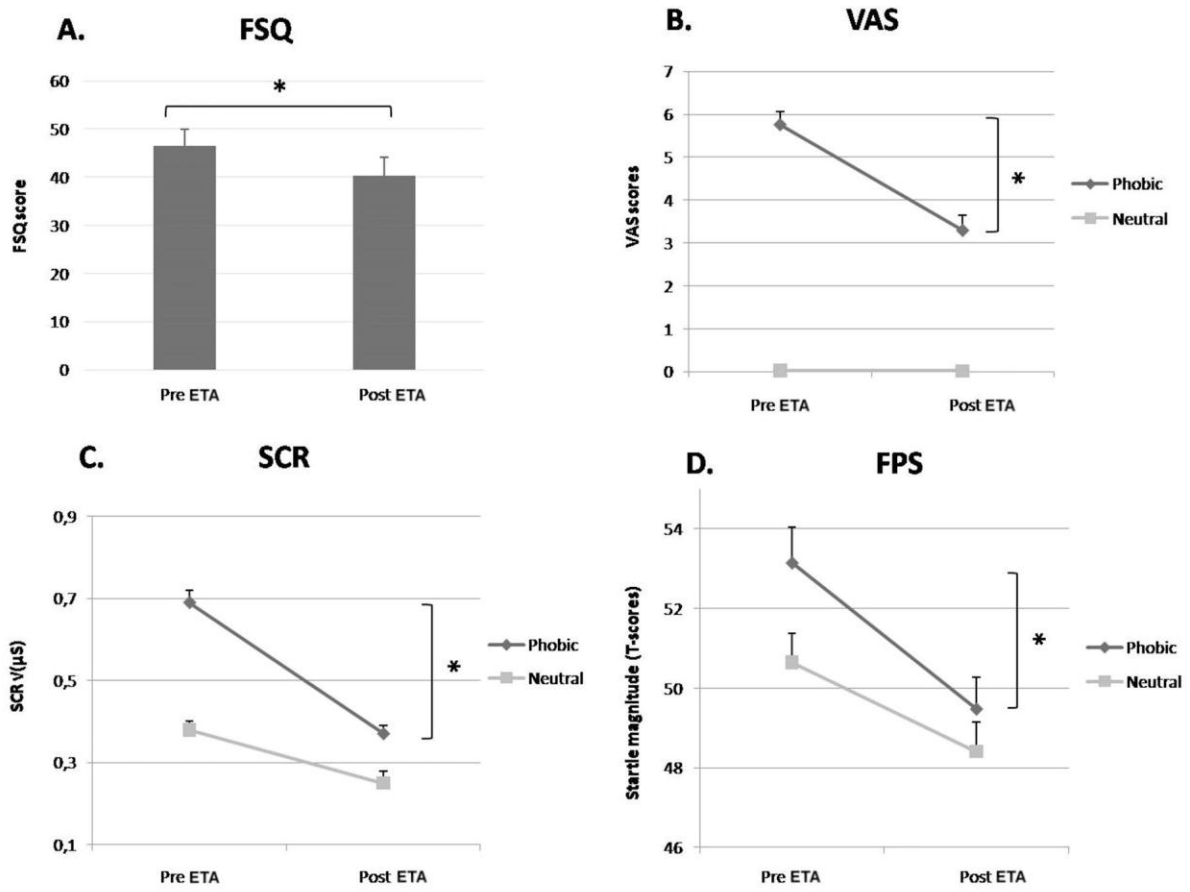

Fig. 2. Effectiveness of ETA (exposure therapy analog) on different outcome measures: (a) Fear of Spiders Questionnaire (FSQ), (b) Visual Analog Scale (VAS), (c) Skin Conductance Response (SCR), and (d) Fear-Potentiated startle (FPS). Bars represent standard errors of the mean. Asterisks indicate significant differences, $^{*}p < 0.05$.

looking) or covert (i.e. distracting) avoidance behaviors. We assessed SCR, FPS and subjective responses (using a visual analog scale, VAS) during ETA. SCR and FPS responses for each stimulus during ETA were quantified off-line using the same procedures as for the fear learning paradigm, with the exception that for the SCR, due to design constraints, we used the maximum score occurring at 1 to 6 s (not 1 to 7 s) after onset of the stimulus. We obtained 20 SCR scores for the phobic and 20 for the neutral stimuli. Two startle probes were presented at the end of each image, with an inter-probe interval of 8, 9, 10, 12, or 14 s. These two scores were averaged to obtain 20 FPS scores for the phobic and 20 for the neutral stimuli (see Supplementary Materials-Methods for further information).

2.6. ETA outcome variables

We evaluated ETA outcomes using three different measures of fear reduction, where higher scores indicated greater fear reduction:

FSQ: Difference between pre- and post-ETA, as measured by the FSQ.

ABS-Fear reduction: Absolute difference between the first response (average of the first two responses to phobic image 1 and phobic image 2) and the last response (average of the last two responses to phobic image 1 and phobic image 2) for VAS, SCR and FPS responses during ETA.

% Fear reduction: Percentage of fear reduction for VAS, SCR and FPS obtained by dividing the last response during ETA (average of phobic image 1 and phobic image 2) by the first response during ETA (average of phobic image 1 and phobic image 2), multiplied by 100 and then subtracted from 100%.

2.7. Statistical analyses

In preliminary analyses, we tested for differences in responses to phobic and neutral stimuli during ETA using three separate (VAS, SCR, and FPS) repeated-measures *t*-tests. We also assessed the effectiveness of ETA on fear reduction using four separate (FSQ, VAS, SCR, and FPS) repeated-measures *t*-tests to compare pre- and post-ETA scores. We report Cohen's *d* (calculated as the difference between means divided by the standard deviation) as an estimate of effect size for these analyses. We studied the performance of the sample during the fear learning paradigm using repeated-measures ANOVA for each phase (conditioning, extinction learning and extinction recall) and for each measure (US expectancies, SCR and FPS), with CS type (CS + vs. CS −) and Block as within-subjects factors. We averaged SCR and FPS responses over two consecutive trials of the same type (blocks), and applied Greenhouse–Geisser corrections for main effects and interactions involving repeated measures. We report η_p^2 as an estimate of effect size for these analyses.

We used Pearson correlations to test the significance of associations between fear extinction indices and ETA outcome for the whole sample. Following our main hypothesis, we expected our extinction learning index to be positively correlated and our extinction recall index to be negatively correlated with ETA outcome.

Finally, following recent guidelines for the analyses of fear learning data in humans (Lonsdorf et al., 2017), we repeated our extinction learning analyses using only those participants showing evidence of conditioning (i.e., one participant was excluded for the US expectancies analyses, 23 for SCR, and 21 for FPS). Similarly, we calculated extinction recall only for participants who showed evidence of extinction learning (i.e., five participants were excluded for the US expectancies analyses, 32 for SCR, and 35 for FPS) (see Supplementary Materials for

the criteria of "successful" conditioning and extinction learning).

3. Results

3.1. Preliminary analyses

As expected, phobic stimuli were more fearful than neutral stimuli, both subjectively (M_{phobic} = 4.37, SD = 2.25; $M_{neutral}$ = 0.03, SD = 0.09; $t(49)$ = 13.65; $p < 0.001$; d = 2.38) and psychophysiologically [SCR (M_{phobic} = 0.47, SD = 0.17; $M_{neutral}$ = 0.29, SD = 0.15; $t(49)$ = 10.59; $p < 0.001$; d = 1.12); FPS (M_{phobic} = 50.77, SD = 1.89; $M_{neutral}$ = 49.32, SD = 1.85; $t(49)$ = 2.74; p = 0.009; d = 0.78)].

ETA was effective in reducing fear (see Fig. 2), as indicated by a significant pre-post ETA reduction in FSQ (M_{pre} = 46.54, SD = 23.78; M_{post} = 40.38, SD = 26.38; $t(49)$ = 2.70; p = 0.009; d = 0.25) and VAS scores (M_{pre} = 5.76, SD = 2.22; M_{post} = 3.30, SD = 2.37; $t(49)$ = 11.40; $p < 0.001$; d = 1.07), as well as in SCR (M_{pre} = 0.69, SD = 0.20; M_{post} = 0.37, SD = 0.17; $t(49)$ = 12.16; $p < 0.001$; d = 1.72) and FPS responses (M_{pre} = 53.15, SD = 6.36, M_{post} = 49.48, SD = 5.67; $t(49)$ = 2.71; p = 0.009; d = 0.61).

For all measures (US expectancies, SCR, and FPS) and for the whole sample, we found evidence of successful conditioning (i.e. higher response to the CS + than to the CS − in the last block of conditioning), as shown by a significant main effect of CS type ($ps < 0.001$) and significant [US expectancies: $F(2.71, 130.23) = 79.76$, $p < 0.001$, $\eta_p^2 = 0.62$; SCR: $F(2.87, 136.17) = 3.59$, $p = 0.021$, $\eta_p^2 = 0.07$] or almost significant (FPS: $F(2.31, 101.48) = 2.66$, $p = 0.072$, $\eta_p^2 = 0.06$) CS type × Block interactions, as well as follow-up analyses indicating larger responses to the CS + than to the CS − in the last block of conditioning ($ps < 0.001$; ds ranging from 0.62 to 4). For SCR and FPS and for the whole sample there was evidence of successful extinction learning (i.e. similar response to the CS + and CS − in the last block of extinction), as evidenced by a non-significant CS type main effect and a non-significant CS type × Block interaction ($ps > 0.108$). Analyses of US expectancies for the whole sample revealed a main effect of CS type, $F(1, 48) = 7.04$, $p = 0.011$, $\eta_p^2 = 0.128$, but a non-significant CS type × Block interaction ($p = 0.080$). For FPS and for the whole sample, there was evidence of successful extinction recall (i.e. similar response to the CS + and CS − in the extinction context during the first block of extinction recall), as shown by a non-significant CS type main effect and a non-significant CS type × Block interaction ($ps = 0.277$). For US expectancies and SCR we found no evidence of extinction recall for the whole sample [significant CS type × Block interaction for US expectancies: $F(2, 96) = 14.77$, $p < 0.001$, $\eta_p^2 = 0.24$; and for SCR: $F(2, 96) = 4.92$, $p = 0.009$, $\eta_p^2 = 0.09$].

3.2. Fear extinction indices and ETA outcome

Consistent with our hypothesis, our index of fear extinction learning (as measured with US expectancies) was positively associated with one of our measures of fear reduction (ABS-Fear reduction), i.e. predicted a greater fear reduction from pre-to post-ETA. The extinction recall index was, however, not significantly associated with ETA outcome (see Table 1). Results did not change when we conducted partial correlations controlling for the intensity of the US (data not shown).

3.3. Additional analyses

We repeated the analyses related to ETA outcome described above excluding individuals who showed no conditioning for the extinction learning analyses, or those who did not show extinction learning for the extinction recall analyses (Table 2). We replicated the significant positive correlation between extinction learning (measured with US expectancies and FPS) and ABS-Fear reduction (r = 0.358, p = 0.032; r = 0.667, p = 0.013) and we also found a significant positive correlation between extinction learning and % Fear reduction as measured with FPS, r = 0.704, p = 0.007). Unexpectedly, in these additional analyses our index of fear extinction recall (as measured with FPS) was positively associated with ABS-Fear reduction (r = 0.527, p = 0.044) and % Fear reduction (r = 0.548, p = 0.035) (i.e. those showing less extinction recall showed greater fear reduction from pre-to post-ETA). We also repeated our correlational analyses excluding one possible outlier (a participant with a pre-post ETA change score in the FSQ 2 standard deviations above the mean) and our results remained unchanged.

Finally, since there is a lot of variability in how researchers have operationalized and calculated fear-learning indices, we calculated alternative fear extinction indices (Supplementary Materials-Table S2). We found that two alternative indices of extinction recall (based on Pineles et al., 2016) were positively correlated with ABS-Fear reduction (extinction recall: r = 0.325, p = 0.021; r = 0.305, p = 0.031). When we excluded participants individuals without successful fear conditioning and extinction learning, none of these alternative indices was significantly associated with ETA outcome, except an extinction learning index using SCR (based on Rabinak et al., 2014), which was positively associated with % fear reduction (r = 0.455, p = 0.022).

4. Discussion

In this study, we examined the association between fear extinction in the laboratory and the outcomes of an ETA. Our analyses suggest that individual differences in fear extinction may be associated with fear reduction during an ETA, although they seem to diminish previous assumptions about the magnitude of the association between extinction and exposure therapy. We found the expected association and in the expected direction for fear extinction learning, i.e. individuals with higher extinction learning capacity (as assessed by the discrimination between the CS + and CS −) showed greater fear reduction from pre- to post-ETA. However, these results must be interpreted with caution since they were obtained only for some of our fear measures (US expectancies for the whole sample analyses, and US expectancies and FPS when we excluded individuals without successful fear conditioning and extinction learning).

Our results are partially in agreement with Waters and Pine (2016), who found that individual differences in fear extinction learning might moderate response to CBT. However, there are important methodological differences between the studies: we tested healthy individuals in a purely experimental setting and using an analog of exposure therapy, whereas Waters and Pine (2016) tested anxious children in a clinical setting and using a 10-week group-based CBT program. We also used a different fear-learning paradigm. Our results are also consistent with those of Ball et al. (2016), who found that individuals with fear of public speaking and higher extinction learning reported better outcomes during a massed exposure therapy session. However, we note some differences here, in that Ball et al. (2016) did not assess fear extinction recall and did not explore psychophysiological variables.

Taken together, these results seem consistent with models that consider extinction learning to be a central process to exposure therapy (e.g. Craske et al., 2012), and support the predictive validity of the fear extinction model in anxiety disorders (Vervliet and Raes, 2013). From a clinical perspective, our results indicate that laboratory studies of extinction learning may indeed provide insights into exposure therapy, e.g. by helping to identify patients who will benefit or not from exposure-based therapies, and thereby adapt therapeutic strategies. Moreover, these results support current translational efforts to "boost" fear extinction learning as a way to improve CBT therapeutic outcomes (Fitzgerald et al., 2014; Pittig et al., 2015; Rodrigues et al., 2014).

Unexpectedly, in our additional analyses, we found that enhanced extinction recall was associated with a more negative outcome during the ETA. This contrasts with a previous report showing association between enhanced extinction recall and a positive CBT outcome in

Table 1
Correlations between fear extinction indices and ETA.

	ETA outcome variables	Pearson correlation	*p*
Extinction learning			
US expectancies	FSQ-Fear reduction	− 0.098	0.563
	ABS-Fear reduction (VAS)	**0.338**	**0.041**
	% Fear reduction (VAS)	0.242	0.149
SCR	FSQ-Fear reduction	− 0.154	0.530
	ABS-Fear reduction (SCR)	− 0.096	0.697
	% Fear reduction (SCR)	− 0.060	0.808
FPS	FSQ-Fear reduction	0.256	0.250
	ABS-Fear reduction (FP)	0.039	0.863
	% Fear reduction (FPS)	0.061	0.787
Extinction recall			
US expectancies	FSQ-Fear reduction	0.069	0.635
	ABS-Fear reduction (VAS)	0.276	0.052
	% Fear reduction (VAS)	0.171	0.236
SCR	FSQ-Fear reduction	− 0.002	0.988
	ABS-Fear reduction (SCR)	− 0.132	0.361
	% Fear reduction (SCR)	− 0.100	0.503
FPS	FSQ-Fear reduction	− 0.018	0.903
	ABS-Fear reduction (FPS)	0.137	0.342
	% Fear reduction (FPS)	0.145	0.316

ETA: exposure therapy analog; US: unconditioned stimulus; SCR: Skin Conductance Response; FPS: Fear-Potentiated startle; VAS: Visual Analog Scale; FSQ: Fear of Spiders Questionnaire; % Fear reduction: percentage of fear reduction; ABS-Fear reduction: absolute fear reduction. Significant values in bold.

social anxiety disorder (Berry et al., 2009). However, there are important differences between our experimental measure of extinction recall (focusing on discriminative learning between a CS + and CS −) and that used by Berry et al. (2009), which focused on between-session fear reduction. Moreover, in previous experimental fear-learning studies, the operationalization of extinction recall has varied a lot, and it is possible that the different ways of measuring the process affect its association with other variables. Notably, when we used alternative indices of extinction recall, the direction of the association (greater extinction recall = more negative outcome) remained the same. A previous study in patients with obsessive-compulsive disorder (OCD) (Milad et al., 2013) found that OCD severity was positively correlated with extinction recall (i.e. better extinction recall was associated with higher severity), which is also counterintuitive. Therefore, clarifying the association between fear extinction recall and therapy outcome is an important topic for future research.

The finding that extinction learning has a different predictive capacity than extinction recall is consistent with neurobiological studies showing that these two processes are independent (Milad et al., 2007; Phelps et al., 2004; Quirk and Mueller, 2008). Moreover, from a methodological perspective, the fact that extinction learning may predict ETA outcomes could make the assessment of extinction recall redundant. This is important because of the time cost of separate experimental sessions to assess extinction recall.

Table 2
Correlations between fear extinction indices and ETA. Results excluding individuals without successful fear conditioning and extinction learning.

	ETA outcome variables	Pearson correlation	*p*
Extinction learning			
US expectancies	FSQ-Fear reduction	− 0.111	0.521
	ABS-Fear reduction (VAS)	**0.358**	**0.032**
	% Fear reduction (VAS)	0.266	0.117
SCR	FSQ-Fear reduction	0.119	0.761
	ABS-Fear reduction (SCR)	0.409	0.275
	% Fear reduction (SCR)	0.298	0.436
FPS	FSQ-Fear reduction	0.007	0.982
	ABS-Fear reduction (FPS)	**0.667**	**0.013**
	% Fear reduction (FPS)	**0.704**	**0.007**
Extinction recall			
US expectancies	FSQ-Fear reduction	0.023	0.883
	ABS-Fear reduction (VAS)	0.246	0.103
	% Fear reduction (VAS)	0.151	0.323
SCR	FSQ-Fear reduction	0.367	0.134
	ABS-Fear reduction (SCR)	− 0.109	0.667
	% Fear reduction (SCR)	− 0.161	0.551
FPS	FSQ-Fear reduction	0.005	0.985
	ABS-Fear reduction (FPS)	**0.527**	**0.044**
	% Fear reduction (FPS)	**0.548**	**0.035**

ETA: exposure therapy analog; US: unconditioned stimulus; SCR: Skin Conductance Response; FPS: Fear-Potentiated startle; VAS: Visual Analog Scale; FSQ: Fear of Spiders Questionnaire; % Fear reduction: percentage of fear reduction; ABS-Fear reduction: absolute fear reduction. Significant values in bold.

Furthermore, some measures in our study (e.g. US expectancies) had a better predictive value than others (e.g. SCR). This is consistent with many previous fear-learning studies reporting a dissociation between fear measures (e.g. Sevenster et al., 2014). Importantly, our US expectancies-based indices remained the most robustly associated with our ETA, which supports the use of US expectancies as measures of fear extinction with clinical relevance (Boddez et al., 2013). Although this has important practical implications because US ratings are easier to collect than psychophysiological measures, caution is warranted since such association was found for only one of the three ETA outcomes tested.

In this study we used an "analog" sample, which is consistent with new initiatives in mental health research that focus on domains or constructs across a dimension of function rather than on clinical diagnoses (Haro et al., 2014; Insel et al., 2010). Previous research on the use of D-cycloserine as an "extinction enhancer" in phobic fears has produced contradictory results in clinical (where positive results have been achieved, e.g. Ressler et al., 2004) and analog (where mostly negative results have been achieved, e.g. Guastella et al., 2007) samples. When interpreting this contradiction, Grillon (2009) has proposed a "dual-model theory" of fear learning, according to which two systems would be involved in fear learning in humans: a higher-order cognitive system (associated with the conscious awareness of danger) and an "automatic" lower-order system (independent of conscious awareness processes, and where D-cycloserine would act on). Lower-order processes could play a more important role in clinical than in analog phobic samples. Although exposure therapy probably taps into both higher order and lower order mechanisms (see Grillon, 2009), it is possible that some of our negative findings on the association between extinction measures and fear reduction measures depend on the use of an analog rather than a clinical sample. In a similar way, this could explain why our "higher order measures" (i.e. risk ratings) were a better predictor of fear reduction that our "lower order measures" (i.e. FPS).

Our study has several strengths. We measured fear learning using a well-established paradigm with three different fear measures, while controlling for variables that are known to affect fear learning (menstrual cycle, time of the day). Moreover, our recruitment strategy avoided typical factors that confound fear learning experiments in anxious individuals (comorbidity, medication).

In addition, we note various limitations. First, our sample was relatively small for some of the analyses, but is still much larger ($n = 50$ versus $n = 24$) than that used in a previous study on the association between fear extinction and exposure therapy (Ball et al., 2016).We computed post-hoc power (two-tailed) for our significant bivariate correlations using the sample size, the effect size, and the alpha error (0.05). We had 68% power to detect a significant correlation between extinction learning and ETA (one-tailed 79%), and 59% to 82% (one-tailed from 71% to 90%) for the other additional significant correlations. Thus, we had only moderate true power to accept our hypothesis. Second, in the paradigm employed here, conditioning and extinction learning occurred consecutively with no time for longer consolidation of fear conditioning. Third, our ETA was much shorter than the average exposure therapy "in the clinic". Our ETA cannot therefore be equated with exposure therapy, but rather as *a model of exposure therapy* that focuses on exposure principles. However, our data support a significant reduction in fear, and previous research has shown a significant fear reduction with similar "doses" of exposure therapy (e.g. Ball et al., 2016; Kleim et al., 2014; Müller et al., 2011). Single-day exposures have been proposed as a laboratory analog for clinical exposure therapy (Tsao and Craske, 2000). Importantly, there was sufficient variability in our ETA outcomes to examine individual differences. Fourth, fear of spiders involves also disgust, not only fear (Cisler et al., 2009). Although exposure-based treatments are effective in reducing spider fear (Olatunji et al., 2011), it is unclear whether our results would replicate in other phobic fears. Finally, we did not conduct a follow-up study, and thus were unable to test whether these associations would remain significant over time. This is especially important for processes such as extinction recall.

Notwithstanding these limitations, we have shown that fear extinction learning assessed in the laboratory is associated with the outcome of an ETA. These data may help to confirm that extinction learning is a valid pre-clinical model of exposure therapy and support current efforts to improve therapeutic outcomes by focusing on this process. Clarifying the role of other fear-learning processes (i.e., extinction recall) in the prediction of exposure-based interventions awaits further research.

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Conflict of interests

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijpsycho.2017.09.001.

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III. Estudi 2:

Attentional control and fear extinction in subclinical fear: An exploratory study

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Attentional Control and Fear Extinction in Subclinical Fear: An Exploratory Study

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Attentional control (AC) and fear extinction learning are known to be involved in pathological anxiety. In this study we explored whether individual differences in non-emotional AC were associated with individual differences in the magnitude and gradient of fear extinction (learning and recall). In 50 individuals with fear of spiders, we collected measures of non-emotional AC by means of self-report and by assessing the functioning of the major attention networks (executive control, orienting, and alerting). The participants then underwent a paradigm assessing fear extinction learning and extinction recall. The two components of the orienting network functioning (costs and benefits) were significantly associated with fear extinction gradient over and above the effects of trait anxiety. Specifically, participants with enhanced orienting costs (i.e., difficulties in disengaging attention from cues not relevant for the task) showed faster extinction learning, while those with enhanced orienting benefits (i.e., attention facilitated by valid cues) exhibited faster extinction recall as measured by fear-potentiated startle and Unconditioned Stimulus expectancies, respectively. Our findings suggest that, in non-emotional conditions, the orienting component of attention may be predictive of fear extinction. They also show that the use of fear extinction gradients and the exploration of individual differences in non-emotional AC (using performance-based measures of attentional network functioning) can provide a better understanding of individual differences in fear learning. Our findings also may help to understand differences in exposure therapy outcomes.

Keywords: attentional control, attentional network functioning, fear extinction, extinction learning, extinction recall, anxiety disorders

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INTRODUCTION

Several attentional and learning processes have been found to play a major role in pathological anxiety (i.e., anxiety disorders). Recent research suggests that attentional control (AC) and fear extinction learning feature prominently among such processes (e.g., Bar-Haim et al., 2007; Cisler and Koster, 2010; Eysenck and Derakshan, 2011; Milad and Quirk, 2012; Heeren et al., 2013;

VanElzakker et al., 2014; Duits et al., 2015; Hadwin et al., 2016). In this study, we explore the possible association between these two processes.

Attentional control is a construct that defines our ability to regulate attention allocation, including our ability to maintain sustained attention, ignore distractors, and shift attention between tasks (Derryberry and Reed, 2002). Deficient AC has been found to characterize both clinical (Olatunji et al., 2011) and subclinical anxiety (e.g., Fajkowska and Derryberry, 2010; Sportel et al., 2013). Such deficits may also account for the attention bias to threat commonly observed in anxious individuals (Hadwin et al., 2016). Moreover, such deficits are associated with reduced ability to regulate emotion (Fajkowska and Derryberry, 2010; Armstrong et al., 2011; Tortella-Feliu et al., 2014; Hsu et al., 2015; Morillas-Romero et al., 2015; O'Bryan et al., 2017). AC can be assessed under emotional conditions (emotional AC, e.g., Barry et al., 2013) or neutral conditions (non-emotional AC, e.g., Derryberry and Reed, 2002; Pacheco-Unguetti et al., 2011; Richey et al., 2016).

Fear extinction learning refers to the decrease in fear following non-reinforced exposure to a feared conditioned stimulus (CS) and is typically investigated in humans within a differential fear learning paradigm preceded by a conditioning (i.e., acquisition) phase. The test of how fear extinction learning is retrieved after re-exposure to the extinguished CS is usually called extinction recall. Deficient fear extinction learning (Duits et al., 2015) or extinction recall (Graham and Milad, 2011; Milad and Quirk, 2012) could be a marker of anxiety disorders (e.g., Graham and Milad, 2011). Importantly, fear extinction is a form of emotion regulation (Hartley and Phelps, 2010) and there is evidence that similar neurobiological mechanisms (i.e., hipoactivity of the prefrontal cortex) may be involved in fear extinction, reduced emotion regulation capabilities, and low AC in non-emotional conditions (Bishop, 2007, 2008, 2009; Hartley and Phelps, 2010; Milad and Quirk, 2012; Ochsner et al., 2012; Shiba et al., 2016; Ball et al., 2017). Therefore, individual differences in AC under non-emotional conditions may be associated with individual differences in fear extinction, although this has not been investigated so far, as far as we are aware.

Moreover, fear extinction learning procedures are considered experimental models for exposure therapy (Craske et al., 2014: Pittig et al., 2016) and both fear extinction learning (e.g., Waters and Pine, 2016; Ball et al., 2017; Forcadell et al., 2017) and attentional functioning (e.g., Barry et al., 2015a) may be associated with the outcomes of exposure therapy, and constitute putative targets for improving such outcomes (Bar-Haim, 2010; Craske et al., 2012, 2014; Barry et al., 2015b; Mogg and Bradley, 2016; Pittig et al., 2016). A better understanding of the association between AC and fear extinction may therefore have important therapeutic implications.

The role of attention in fear learning has been a topic of research for years (e.g., Mackintosh, 1975; Wagner, 1981; Le Pelley et al., 2016). Most studies have focused on how attention allocation changes during or after acquisition (e.g., Beaver et al., 2005; Koster et al., 2005) or extinction (e.g., Robbins, 1990; Van Damme et al., 2006; Barry et al., 2016b) affect the magnitude of learning. Moreover, attentional biases to threat in anxiety could reflect a much broader dysregulation of AC (Bishop, 2009; Moriya and Tanno, 2009; Pacheco-Unguetti et al., 2011). The use of non-emotional stimuli allows to isolate potential general attention deficits beyond those observed when individuals face emotional materials (see further below). A few recent studies have focused on how baseline individual differences in attention predict the magnitude or gradient ("speed") of fear extinction learning (Waters and Kershaw, 2015; Barry et al., 2016a, 2017).

The study by Waters and Kershaw (2015) belongs to the research tradition that focuses on analyzing how attentional bias to threat-related information is associated with increased anxiety (valence-specific models) (for a review see Heeren et al., 2013; Hadwin et al., 2016). Waters and Kershaw (2015) found that clinically anxious children who showed attention to threat in a visual probe task exhibited greater fear extinction learning than those who avoided threat.

The studies by Barry and colleagues (Barry et al., 2016a, 2017) represent a second research tradition that has explored how deficient AC is associated with anxiety vulnerability, and more specifically with cognitive and inhibitory control impairments observed in anxious individuals. In two separate studies in healthy participants, these authors investigated how emotional AC, as measured by self-report (Barry et al., 2013), was associated with fear extinction learning (Barry et al., 2016a, 2017). In the first study, participants were confronted with a perceptually similar stimulus presented after extinction of the original CS, and it was observed that higher emotional AC was associated with faster extinction learning and greater return of fear (Barry et al., 2016a). In the second study, during extinction learning participants were confronted with a similar stimulus as during acquisition, and were instructed to attend toward the common features between the acquisition and extinction stimuli, or toward the unique features of the extinction stimulus. For participants who, during extinction, were instructed to attend toward the unique features of the extinction stimulus, lower emotional AC tended to be associated with a greater return of fear (Barry et al., 2017). The authors suggested that those with low emotional AC may have been unable to shift attention to other features of the extinction stimulus, which may have facilitated the return of fear when confronted with a perceptually similar stimulus.

In the studies mentioned above, individual differences in attention functioning were investigated using emotional conditions. We share the view of Heeren et al. (2015b, p. 136) that the focus on emotional materials has "neglected the empirical exploration of basic attentional deficits from non-emotional material," and precludes the assessment of general attentional abilities that may be relevant to several clinical phenomena (see also Snyder et al., 2015). Furthermore, in the two studies investigating the association between AC and extinction learning, AC was assessed by self-report (Barry et al., 2016a, 2017). The use of performance-based tasks (see below) may provide important information on the role of different attentional networks beyond general AC (see Heeren et al., 2015a; Heeren and McNally, 2016).

According to the *attention system model* (Posner and Petersen, 1990; Posner and Rothbart, 2007), attention consists of three major networks, which can be assessed separately: *executive control*, *orienting*, and *alerting* (see Posner et al., 2007 for

a review). The *executive control* network is specialized in conflict resolution and voluntary control of attention while resisting distraction by other competing stimuli. While the executive control network has traditionally been equated to AC, some authors have recently expanded the definition of AC to include the orienting and alerting networks (e.g., Heeren and McNally, 2016). The *orienting network* is involved in attention engagement to new stimuli and attention disengagement from the current focus. Finally, the *alerting network* is devoted to maintaining adequate sensitivity to perceive and process stimuli. The functioning of these three attentional networks when facing non-emotional cues has been related to anxiety and emotion regulation. For example, reduced efficiency of the executive control and orienting networks has been associated with high trait and clinical anxiety (Moriya and Tanno, 2009; Pacheco-Unguetti et al., 2010; Pacheco-Unguetti et al., 2011; Heeren et al., 2015b; Heeren and McNally, 2016), and faster spontaneous emotion regulation (Morillas-Romero et al., 2015). Finally, increased efficiency of the alerting network has been associated with state anxiety (Pacheco-Unguetti et al., 2010).

In this present study, we explore whether individual differences in non-emotional AC (defined as a multifaceted construct including executive control, orienting, and alerting attentional networks), are associated with individual differences in fear extinction (learning and recall) in a sample of subclinical phobic participants (individuals with moderate to strong fear of spiders). The use of subclinical samples is a valid strategy for studying anxiety-related processes, can be generalized to individuals with an anxiety diagnosis (Stopa and Clark, 2001; Abramowitz et al., 2014) and also has some advantages (e.g., avoid comorbidity, medications or the impact from previous treatments) compared to clinical samples. Furthermore, previous studies exploring the association between attentional bias to threat and fear extinction (Waters and Kershaw, 2015) and between fear learning and treatment outcome (Waters and Pine, 2016) included children with specific phobias, but to the best of our knowledge, ours is the first study exploring the role of non-emotional attention and its association with fear extinction in (subclinical) adult phobic individuals using "truly" non-emotional stimuli.

We used self-report and performance-based measures of AC under non-emotional conditions. Fear extinction was assessed using three different measures: Unconditioned Stimulus (US) expectancies, Skin Conductance Response (SCR), and Fear-Potentiated Startle (FPS). Given the well-established association between trait anxiety and AC (e.g., Pacheco-Unguetti et al., 2010, 2011; Sportel et al., 2011), and between trait anxiety and fear extinction (Sehlmeyer et al., 2011; Gazendam et al., 2013; Haaker et al., 2015), we tested the magnitude of these associations after controlling for trait anxiety.

MATERIALS AND METHODS

Participants

We selected individuals with moderate to strong fear of spiders, as assessed by a dimensional instrument. Participants were recruited by advertisement to participate in a study on "physiological responses to anxiety" (see participants flow chart in **Figure 1**). Initially, 1504 individuals were screened with the validated Spanish version (Forcadell et al., 2014) of the *Fear of Spiders Questionnaire* (FSQ; Szymanski and O'Donohue, 1995) via a secure web system. In the online stage we used online forms with encryption technology that guaranteed the privacy of the participants. The information could only be processed by a person with access to the matrix and passwords. Participants who scored in the top quartile of the study distribution (FSQ $\geq$ 33; $n = 386$) were invited to participate. Of those, 92 agreed to be interviewed by a doctoral-level clinical psychologist using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998).

Exclusion criteria were: (a) current or lifetime history of mental disorders other than specific phobia (animal type, spiders), as determined by the MINI, supplemented with the specific phobia section of the Structured Clinical Interview for DSM (SCID; First et al., 2002); (b) use of medication/illicit drugs or medical problems that could interfere with study performance or interpretation; (c) alcohol abuse; (d) pregnancy; (e) not being Spanish-speaker. Female participants had regular menstrual cycles (as per self-report), had not used oral contraceptives or hormone replacement therapy during the previous 3 months (as per self-report), and participated in the study during their early follicular phase (days 3–8 of a 28–30-day cycle) to avoid possible confounding by sex hormones in fear extinction (Milad et al., 2006; Merz et al., 2012; Pineles et al., 2016). All participants were tested between 5 and 8 PM.

The final sample consisted of 50 participants with moderate to strong fear of spiders ($M_{FSQ} = 58.98$, $SD = 17.94$; $M_{age} = 21.50$ years, $SD = 2.93$; 25 women). The number of participants included in each analysis is reported in **Figure 1**. Participants gave written informed consent to take part in the study, which was approved by the corresponding institution's Clinical Research Ethics Committee. Participants were paid €25.

Procedure Overview

Participants took part in two experimental sessions on 2 consecutive days. On day 1, they completed (a) a self-report measure of AC (Attentional Control Scale; ACS; Derryberry and Reed, 2002), (b) the trait version of the State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1970), (c) a task assessing attentional network functioning (Attentional Network Test-Interactions task, ANT-I, Callejas et al., 2004) (see below and **Figure 2A**), and they underwent the first part of the fear learning paradigm (conditioning and extinction learning) (see below and **Figure 2B**). On day 2, they participated in the second part of the fear learning paradigm (extinction recall) (**Figure 2C**). Psychophysiological responses were recorded continually during the fear learning paradigm (see below).

Self-report Measures

Attentional Control

We used the Spanish version (Pacheco-Unguetti et al., 2011) of the Attentional Control Scale (ACS; Derryberry and Reed, 2002) to measure individual differences in non-emotional AC (e.g., "My

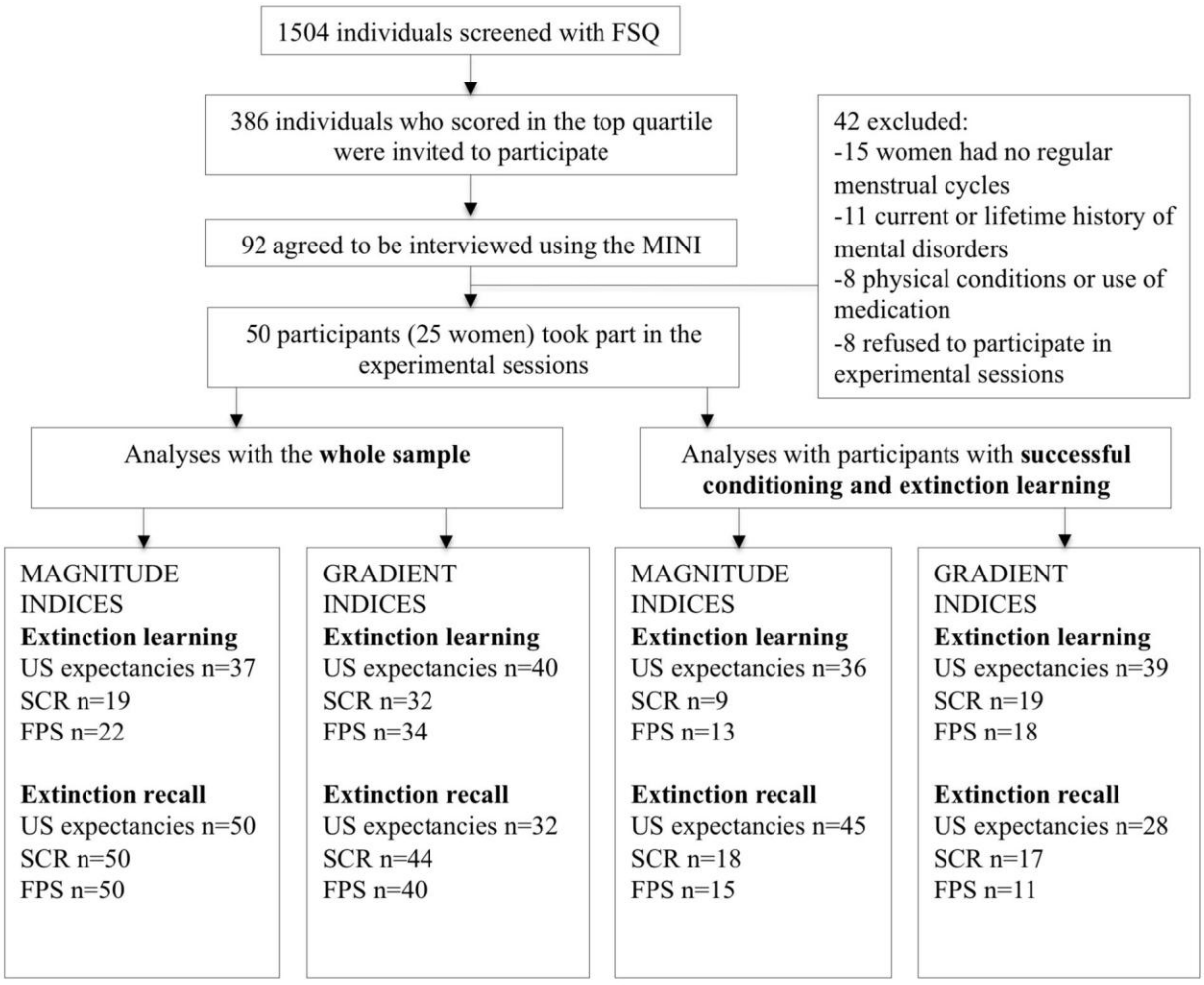

FIGURE 1 | Diagram of the sample selection procedure and participants included in each analysis. FSQ, Fear of Spiders Questionnaire; MINI, Mini International Neuropsychiatric Interview; US, Unconditioned stimulus; SCR, Skin Conductance Response; FPS, Fear-Potentiated startle.

concentration is good even if there is music in the room around me," "It is easy for me to read or write while I am also talking on the phone"). The scale consists of 20 4-point items (1 = *Almost never*; 4 = *Always*), with higher scores indicating higher AC. The scale is divided into two subscales: focusing (i.e., ability to intentionally hold attentional focus) and shifting (i.e., ability to intentionally shift attentional focus). In line with Ólafsson et al. (2011), item 9 was excluded when calculating the total score. Cronbach's alpha for the ACS was 0.70.

Trait Anxiety

We used the Spanish version (Spielberger et al., 1982) of the STAI-trait (STAI-T; Spielberger et al., 1970) to measure trait anxiety (e.g., "I worry too much over something that really does not matter," "I am content"). It consists of 20 4-point items (1 = *Almost never*; 4 = *Almost always*). Scores range from 0 to 60 in the Spanish version of the STAI-T, with higher scores indicating higher trait anxiety. Cronbach's alpha for the STAI-T was 0.87.

Performance-Based Measures

Attentional Network Functioning

We used the Attentional Network Test for Interactions (ANT-I; Callejas et al., 2004), a modified version of the Attentional Network Test (Fan et al., 2002), to assess the functioning of the three major attentional networks (executive control, orienting and alerting), and the two components of orienting, namely costs (i.e., disengagement of attention from invalid cues), and benefits (i.e., facilitated orientation from valid cues). The task consisted of four blocks of 48 trials. On each trial, a non-emotional cue (an alerting tone and/or an asterisk) preceded an arrow flanked by other distractor arrows (see **Figure 2A**). Participants had to indicate the direction of the target arrow by pressing one of two keys as quickly and accurately as possible (we measured reaction time and error rate; see below). Following previous research (Callejas et al., 2004; Pacheco-Unguetti et al., 2010, 2011) we computed an efficiency index for each attentional network, and for the two components of orienting (see Supplementary Methods), where higher scores

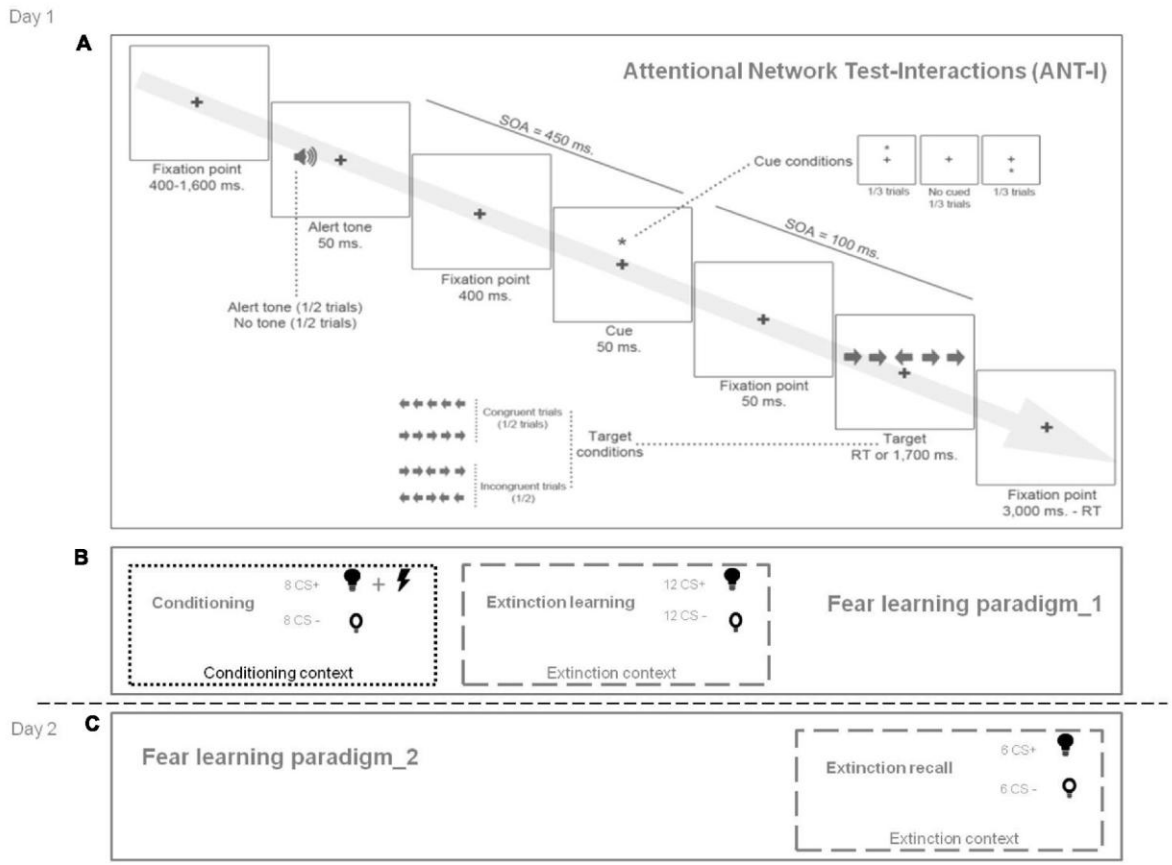

FIGURE 2 | Summary of experimental design. **(A)** Attentional Network Test-Interactions (ANT-I): Trials began with a fixation point (400–1600 ms). Then, in half of the trials, an alerting tone is presented (50 ms). In two-thirds of the trials, this is followed after 400 ms by an asterisk as an orienting signal (50 ms) either above or below the fixation point (cued trials). No asterisk is presented in the remaining third of the trials (uncued condition). Then, the asterisk disappears leaving only the fixation point. After 50 ms, an arrow flanked by four distractor arrows (two on each side) is presented. The distractors point either in the same direction as the arrow target (i.e., congruent trials) or in the opposite direction (i.e., incongruent trials), and in the same position as the orienting cue (i.e., valid trials) or at the opposite location (i.e., invalid trials). Participants have to indicate the direction in which the target was pointing (right or left). After the response, the fixation point is presented for up to 3000 ms. **(B)** Fear learning paradigm, day 1 (conditioning and extinction learning). A conditioning phase was followed by an extinction learning phase. The visual contexts were photographs of two different rooms (i.e., conditioning context and extinction context). A lamp switched on to one of two different colors (blue or yellow), which were the CS+ and the CS–. Participants were not instructed about the CS-US contingency. During conditioning, the CS+ co-terminated with an electric shock (US). During extinction learning (immediately after conditioning), the CS+ was not followed by the US. The CS– was never followed by the US. **(C)** Fear learning paradigm, day 2 (extinction recall). This phase was identical to extinction learning on day 1. The extinguished CS+ and the CS- were presented again in the extinction context. SOA, stimulus onset asynchrony; RT, reaction time; CS+, conditioned stimulus associated with the unconditioned stimulus during the conditioning phase; CS–, conditioned stimulus never associated with the unconditioned stimulus; US, unconditioned stimulus.

indicated enhanced functioning of the network (except for executive control and orienting costs, where higher scores indicated diminished functioning).

Fear Learning Paradigm

We adapted the paradigm developed by Milad et al. (2005) which assesses conditioning, extinction learning, and extinction recall separately. The original task used Skin Conductance Response (SCR) as the only measure of conditioned fear, and we added two other measures (Unconditioned Stimulus [US] expectancies and Fear-Potentiated Startle [FPS]). Briefly, the visual contexts were photographs of two different rooms (conditioning context, CX+; extinction context, CX−) containing a lamp that switched on to one of two different colors (blue or yellow), which were the CS+ and the CS− (CS not paired with the US). Contexts and CSs were displayed on a computer monitor in front of the participant. On day 1, a conditioning phase (in CX+) was followed by an extinction learning phase (in CX−). During conditioning, the CS+ co-terminated with an electric shock (US). The US was individually adjusted before the experiment (day 1), presenting shocks of gradually increasing intensity until a 'definitely annoying but not painful' shock was selected [$M_{\text{shock level}} = 4.9$ milliamperes (mA), $SD = 3.3$]. Participants were not instructed about the CS-US contingency. During extinction learning (immediately after conditioning), the CS+ was not followed by the US. The CS– was never followed by the US. The extinction learning phase was divided in two equal parts by a 1-min pause (early and late extinction learning). Day

2 consisted of an extinction recall phase (in CX−). During day 2, the CS+ and the CS– were never followed by the US. The US was not recalibrated during day 2.

Each trial of the experiment started with presentation of the context for 10, 12, or 14 s. Then the CS was presented (i.e., the lamp switched on) for 8 s, and a startle probe (50 ms duration, 100 dB) was delivered 7 s after CS onset. Between trials, a fixation cross was shown for 1 s. In one third of the trials (noise-alone trials, NA), no CS was presented, and instead the context was present for 8 more seconds; the startle probe was presented at second 7 of this extra time. The inter-probe interval varied between 18, 20, and 22 s. Eight trials of each type (CS+, CS–, and NA) were presented during conditioning, and six trials of each type were presented during each of the remaining phases (early and late extinction learning and extinction recall). Trial order was randomized across participants in blocks of nine trials (three of each type), with the restriction that no more than two trials of the same type occurred consecutively. Assignment of the photographs of the rooms to the conditioning and the extinction contexts, and of the CS+ and the CS–, was counterbalanced across participants.

SCR, FPS, and US expectancy ratings were calculated for each trial type. The SCR signal was sampled at a rate of 125 Hz. SCR magnitudes were computed in microsiemens (μS) as the difference between the maximum SCR value and the value at response onset, occurring 1–7 s after CS onset. Trials in which no response was detected or with a response magnitude of <0.02 μS were considered non-response trials (see Dunsmoor et al., 2009), and trials showing interference or excessive baseline activity (1.3%) were rejected after visual inspection. To normalize the distribution of the SCR data, we applied a square root transformation.

Startle amplitudes were computed in microvolts (μV) as the difference between the EMG value at response peak and the average EMG during the 50 ms preceding the probe. If no response was detected in a given trial, the amplitude was scored as 0 μV. To be considered a valid response, elevations in the EMG recording had to start between 20 and 100 ms, and their peak had to occur between 20 and 150 ms after the probe. After visual inspection, trials with excessive noise (3.2%) were rejected. Raw data were transformed into T-scores to control for differences in reactivity. Scorers of SCR and FPS data were blinded to the stimuli presented.

Regarding US expectancy ratings, for each trial participants were told to try to predict whether the shock would occur in the following seconds each time the lamps in the rooms turned blue or yellow. They had to answer as quickly as possible by clicking on the scale from 0 (no shock) to 10 (shock) displayed at the bottom of the screen (see Supplementary Materials-Methods for further information).

Fear Extinction Indices

For each participant, we calculated an index based on the magnitude (amount of learning) and an index based on the gradient (slope of change, i.e., "speed") for both extinction learning and extinction recall.

Magnitude-Based Indices

Based on previous research (Rabinak et al., 2013, 2014; Garfinkel et al., 2014; Pineles et al., 2016), for each participant and each measure (US expectancies, SCR and FPS) we calculated an index expressing the "amount of learning," reflecting differences between CS+ and CS− during extinction learning and extinction recall.

The extinction learning index was calculated according to Pineles et al. (2016): Extinction learning = 100 – ([Mean [CS+]-[CS−] during the last two trials of early extinction/Mean [CS+]-[CS−] during the first two trials of early extinction × 100]). Since the extinction learning index was calculated as a percentage, higher scores indicated enhanced extinction learning (i.e., less discrimination between CS+ and CS−).

The extinction recall index was calculated, based on Rabinak et al. (2013), as the mean of (CS+)-(CS−) in the first two extinction recall trials. Lower scores indicated enhanced extinction recall.

Gradient-Based Indices

In line with Barry et al. (2016a, 2017), we computed the slope of change (i.e., gradient) across extinction learning and extinction recall trials using the area under the curve with respect to the decrease in US expectancies, SCR, and FPS scores. For each participant we calculated the percentage change in the difference between CS+ and CS− in each trial during extinction learning and recall relative to the first extinction trial. We used the percentage change between the first and last extinction trials as the baseline to account for individual differences in the intercept of the extinction curves. Lower scores in the gradient-based indices indicated faster fear extinction learning and extinction recall.

Statistical Analyses

In manipulation checks, we examined main effects and interactions between networks and reaction time in the ANT-I using a factorial mixed ANOVA with executive control (congruent and incongruent), orienting (valid, invalid, uncued), and alerting (no alerting, alerting tone) as within-subject factors, and reaction time as the dependent variable. We also studied the association between trait anxiety and AC variables using Pearson bivariate correlations. We also studied the performance of the sample during the fear learning paradigm using repeated-measures ANOVA for each phase (conditioning, extinction learning and extinction recall) and for each measure (US expectancies, SCR and FPS), with CS type (CS+ vs. CS−) and Block as within-subject factors. We averaged SCR and FPS responses over two consecutive trials of the same type (blocks), and applied Greenhouse–Geisser corrections for main effects and interactions involving repeated measures. For indices calculated as a percentage, extreme values (>150% or <−150%) were excluded.

We used Pearson bivariate correlation analyses to test for association between AC with fear extinction indices. Following recent guidelines for the analyses of fear learning data in humans (Lonsdorf et al., 2017), we performed those analyses with the whole sample. Since extinction learning can theoretically only

occur if there is conditioning, and extinction recall can occur only if there is extinction learning, we repeated our extinction learning analyses using only those participants showing successful conditioning, and our extinction recall analyses using only those participants showing successful extinction learning. The criteria for establishing successful fear conditioning/extinction learning were based on Schiller et al. (2012): the differential SCR to the CS+ and CS− by the end of the conditioning phase (mean of second half of the conditioning trials) had to be in the right direction (i.e., CS+ > CS−) and >0.1 μs for SCR, >1 μV for FPS, or >1 point for US expectancies. Similarly, the criteria for establishing successful extinction learning were: differential SCR to the CS+ and CS− by the end of the late extinction learning phase (last trial) had to be ≤0.1 μs for SCR, ≤1 μV for FPS, or ≤1 for US expectancies.

For associations that were significant at $p < 0.10$, we conducted hierarchical regression analyses using AC as the independent variables and fear extinction indices as the dependent variables. For these analyses, trait anxiety was entered in Step 1, and the AC variables were entered independently in Step 2.

Finally, we conducted additional analyses using an alternative method to calculate indices based on fear extinction gradients (see Barry et al., 2016a,b).

RESULTS

Manipulation Checks

Our manipulation checks on the ANT-I confirmed (see Supplementary Table S1 in Supplementary Results) the typically observed pattern for this task (i.e., reaction times were significantly shorter in: (i) trials including an alerting tone than in trials without this tone, (ii) trials including an orienting signal, and (iii) trials where distractors pointed in the same direction as the arrow target) (e.g., Callejas et al., 2004; Pacheco-Unguetti et al., 2010, 2011). Also consistent with previous literature, trait anxiety was significantly and negatively correlated with AC (see Supplementary Results). Regarding the associations between performance-based and self-reported AC, the overall AC scale was only significantly correlated with performance-based executive control ($r = -0.438$; $p = 0.001$), with a higher self-reported AC indicating a lower interference (i.e., greater executive control). The focusing AC subscale was positively associated with interference (i.e., lower executive control) ($r = 0.323$; $p = 0.022$). No significant correlations were found between self-reported AC and the orienting and alerting networks functioning. All the correlations are depicted in Supplementary Materials, Supplementary Table S2.

For all measures (US expectancies, SCR, FPS), we found evidence of successful conditioning (i.e., higher response to the CS+ than the CS− in the last block of conditioning), which allowed us to investigate fear extinction learning. We also found evidence of extinction learning (i.e., similar response to the CS+ and CS− in the last block of extinction) for all measures (US expectancies, SCR, FPS), which allowed us to investigate extinction recall. For further details, see Supplementary Results.

Correlational Analyses

Relationship between AC and Fear Extinction Magnitude-Based Indices

None of the AC variables investigated was significantly correlated with fear extinction learning or recall, as measured by the magnitude-based indices (**Table 1**).

Relationship between AC and Fear Extinction Gradient-Based Indices

The two orienting network components (costs and benefits) showed a significant negative association with fear extinction (see **Table 2**). For the whole sample, orienting benefits (i.e., facilitated orientation) were inversely correlated with our gradient-based index of extinction recall, as measured with US expectancies ($r = -0.358$; $p = 0.044$), indicating that enhanced facilitated orientation was associated with faster extinction recall (see **Table 2**). When only those participants with successful conditioning and extinction learning were included in the analyses, orienting costs were inversely correlated with our gradient-based index of extinction learning using FPS ($r = -0.493$; $p = 0.038$), indicating that greater difficulty in disengaging attention from invalid cues was associated with faster extinction learning. Moreover, orienting benefits were inversely correlated again with our gradient-based index of extinction recall, as measured by US expectancies ($r = -0.424$; $p = 0.025$). We found no other significant associations between AC and fear extinction learning or recall.

Scatter plots for the main findings can be found in the Supplementary Materials (Supplementary Figure S1).

Predictive Power of AC on Magnitude and Gradient of Fear Extinction

Results from the hierarchical regression analyses (**Table 3**) showed that, after controlling for trait anxiety, orienting costs were a significant predictor of extinction learning gradient (as measured by FPS), accounting for 27.4% of its variance ($F[2,15] = 4.91$, $p = 0.023$, $R^2_{\text{Adjusted}} = 0.27$). In other words, greater difficulty in disengaging attention from invalid neutral cues predicted faster extinction learning beyond what is attributable to trait anxiety.

After controlling for trait anxiety, orienting benefits were also a significant predictor of extinction recall gradient (as measured by US expectancies), accounting for 12% of its variance ($F[2,25] = 3.50$, $p = 0.046$, $R^2_{\text{Adjusted}} = 0.12$). Thus, facilitated orientation by valid neutral cues predicted faster extinction recall beyond what is attributable to trait anxiety.

Additional Analyses

When we calculated the gradient of fear extinction considering only the response to the CS+ (instead of the difference between CS+ and CS−) (Barry et al., 2017), we found that enhanced alerting was associated with faster extinction recall (as measured by FPS) ($r = -0.695$; $p = 0.008$) (see Supplementary Table S3).

TABLE 1 | Bivariate correlation between attentional control and fear extinction **magnitude**-based indices (results for the whole group and for participants with successful fear conditioning and extinction learning).

	AC total	AC focusing	AC shifting	Executive control	Orienting	Orienting-costs	Orienting-benefits	Alerting
Extinction learning magnitude								
Whole group								
US expectancies $n = 37$	−0.037 ($p = 0.828$)	−0.035 ($p = 0.838$)	−0.026 ($p = 0.878$)	−0.007 ($p = 0.967$)	0.069 ($p = 0.683$)	0.045 ($p = 0.789$)	0.042 ($p = 0.804$)	−0.022 ($p = 0.898$)
SCR $n = 19$	0.104 ($p = 0.671$)	0.154 ($p = 0.529$)	0.035 ($p = 0.888$)	−0.147 ($p = 0.549$)	−0.055 ($p = 0.824$)	0.081 ($p = 0.742$)	−0.133 ($p = 0.587$)	−0.047 ($p = 0.849$)
FPS $n = 22$	0.237 ($p = 0.289$)	0.265 ($p = 0.234$)	0.203 ($p = 0.365$)	−0.282 ($p = 0.204$)	−0.312 ($p = 0.157$)	−0.137 ($p = 0.543$)	−0.253 ($p = 0.255$)	−0.100 ($p = 0.658$)
Successful conditioning and extinction learning								
US expectancies $n = 36$	−0.009 ($p = 0.957$)	−0.016 ($p = 0.926$)	−0.014 ($p = 0.936$)	−0.036 ($p = 0.836$)	0.041 ($p = 0.813$)	0.053 ($p = 0.761$)	0.000 ($p = 0.999$)	−0.050 ($p = 0.773$)
SCR $n = 9$	0.172 ($p = 0.657$)	0.292 ($p = 0.447$)	0.035 ($p = 0.929$)	−0.477 ($p = 0.194$)	0.417 ($p = 0.264$)	0.171 ($p = 0.660$)	0.445 ($p = 0.230$)	0.361 ($p = 0.340$)
FPS $n = 13$	−0.030 ($p = 0.922$)	0.101 ($p = 0.743$)	−0.042 ($p = 0.890$)	0.013 ($p = 0.965$)	−0.097 ($p = 0.752$)	−0.045 ($p = 0.885$)	−0.077 ($p = 0.802$)	0.045 ($p = 0.885$)
Extinction recall magnitude								
Whole group								
US expectancies $n = 50$	−0.185 ($p = 0.198$)	−0.275 ($p = 0.053$)	−0.088 ($p = 0.545$)	0.222 ($p = 0.122$)	0.103 ($p = 0.475$)	0.097 ($p = 0.501$)	0.028 ($p = 0.848$)	−0.230 ($p = 0.109$)
SCR $n = 50$	−0.051 ($p = 0.723$)	−0.210 ($p = 0.144$)	0.126 ($p = 0.384$)	0.221 ($p = 0.123$)	0.088 ($p = 0.545$)	0.190 ($p = 0.187$)	−0.080 ($p = 0.579$)	−0.203 ($p = 0.158$)
FPS $n = 50$	0.049 ($p = 0.737$)	0.111 ($p = 0.444$)	−0.002 ($p = 0.987$)	0.032 ($p = 0.823$)	0.040 ($p = 0.784$)	−0.079 ($p = 0.585$)	0.123 ($p = 0.393$)	0.043 ($p = 0.765$)
Successful conditioning and extinction learning								
US expectancies $n = 45$	−0.202 ($p = 0.184$)	−0.278 ($p = 0.064$)	−0.099 ($p = 0.517$)	0.224 ($p = 0.139$)	0.157 ($p = 0.304$)	0.113 ($p = 0.458$)	0.072 ($p = 0.640$)	−0.212 ($p = 0.163$)
SCR $n = 18$	0.134 ($p = 0.596$)	−0.158 ($p = 0.532$)	0.349 ($p = 0.156$)	−0.021 ($p = 0.934$)	0.305 ($p = 0.218$)	0.463 ($p = 0.053$)	−0.014 ($p = 0.957$)	−0.317 ($p = 0.200$)
FPS $n = 15$	0.164 ($p = 0.560$)	0.253 ($p = 0.363$)	0.102 ($p = 0.716$)	−0.001 ($p = 0.996$)	0.144 ($p = 0.609$)	−0.193 ($p = 0.491$)	0.497 ($p = 0.060$)	−0.206 ($p = 0.461$)

US, unconditioned stimulus; SCR, skin conductance response; FPS, fear-potentiated startle; AC, attentional control.

TABLE 2 | Bivariate correlation between attentional control and fear extinction **gradient**-based indices (results for the whole group and for participants with successful fear conditioning and extinction learning).

	AC total	AC focusing	AC shifting	Executive control	Orienting	Orienting-costs	Orienting-benefits	Alerting
Extinction learning gradient								
Whole group								
US expectancies $n = 40$	0.109 ($p = 0.505$)	0.136 ($p = 0.401$)	0.089 ($p = 0.583$)	0.056 ($p = 0.730$)	−0.005 ($p = 0.974$)	−0.121 ($p = 0.457$)	0.111 ($p = 0.495$)	0.223 ($p = 0.167$)
SCR $n = 32$	0.260 ($p = 0.151$)	0.313 ($p = 0.081$)	0.030 ($p = 0.872$)	0.178 ($p = 0.330$)	0.054 ($p = 0.767$)	0.028 ($p = 0.880$)	0.037 ($p = 0.842$)	−0.094 ($p = 0.607$)
FPS $n = 34$	0.376 ($p = 0.129$)	0.321 ($p = 0.064$)	0.256 ($p = 0.143$)	−0.032 ($p = 0.858$)	0.051 ($p = 0.776$)	−0.082 ($p = 0.644$)	0.137 ($p = 0.441$)	0.273 ($p = 0.118$)
Successful conditioning and extinction learning								
US expectancies $n = 39$	0.115 ($p = 0.486$)	0.140 ($p = 0.396$)	0.094 ($p = 0.571$)	0.051 ($p = 0.757$)	−0.012 ($p = 0.944$)	−0.121 ($p = 0.464$)	0.105 ($p = 0.524$)	0.219 ($p = 0.180$)
SCR $n = 19$	−0.066 ($p = 0.788$)	−0.081 ($p = 0.742$)	−0.112 ($p = 0.647$)	0.453 ($p = 0.052$)	0.203 ($p = 0.405$)	−0.060 ($p = 0.808$)	0.278 ($p = 0.249$)	0.144 ($p = 0.558$)
FPS $n = 18$	0.297 ($p = 0.232$)	0.231 ($p = 0.356$)	0.223 ($p = 0.373$)	−0.122 ($p = 0.628$)	−0.408 ($p = 0.093$)	**−0.493 ($p = 0.038$)**	0.098 ($p = 0.698$)	0.432 ($p = 0.073$)
Extinction recall gradient								
Whole group								
US expectancies $n = 32$	−0.149 ($p = 0.417$)	−0.094 ($p = 0.609$)	−0.183 ($p = 0.315$)	−0.063 ($p = 0.733$)	−0.300 ($p = 0.095$)	0.014 ($p = 0.938$)	**−0.358 ($p = 0.044$)**	−0.221 ($p = 0.223$)
SCR $n = 44$	−0.153 ($p = 0.322$)	−0.092 ($p = 0.551$)	−0.171 ($p = 0.267$)	0.153 ($p = 0.320$)	−0.095 ($p = 0.541$)	0.086 ($p = 0.577$)	−0.192 ($p = 0.212$)	−0.070 ($p = 0.651$)
FPS $n = 40$	0.220 ($p = 0.173$)	0.012 ($p = 0.944$)	0.347 ($p = 0.228$)	−0.146 ($p = 0.369$)	−0.067 ($p = 0.681$)	0.041 ($p = 0.801$)	−0.121 ($p = 0.459$)	−0.264 ($p = 0.099$)
Successful conditioning and extinction learning								
US expectancies $n = 28$	−0.217 ($p = 0.266$)	−0.117 ($p = 0.554$)	−0.275 ($p = 0.157$)	−0.080 ($p = 0.687$)	−0.359 ($p = 0.061$)	−0.012 ($p = 0.951$)	**−0.424 ($p = 0.025$)**	−0.178 ($p = 0.366$)
SCR $n = 17$	0.095 ($p = 0.716$)	0.066 ($p = 0.800$)	0.026 ($p = 0.921$)	0.204 ($p = 0.433$)	−0.213 ($p = 0.411$)	−0.028 ($p = 0.915$)	−0.250 ($p = 0.333$)	0.251 ($p = 0.332$)
FPS $n = 11$	0.192 ($p = 0.571$)	0.171 ($p = 0.614$)	0.268 ($p = 0.426$)	−0.564 ($p = 0.071$)	−0.283 ($p = 0.400$)	−0.283 ($p = 0.400$)	0.092 ($p = 0.787$)	0.010 ($p = 0.976$)

US, unconditioned stimulus; SCR, skin conductance response; FPS, fear-potentiated startle; AC, attentional control. Significant values in bold.

TABLE 3 | Summary of hierarchical multiple regression analyses predicting fear extinction.

	$\Delta R^2_{adjusted}$	*B*	*SE B*	*95% CI*	β		*p*
Extinction recall magnitude							
US expectancies							
STAIT	−0.021	−0.030	0.066	[−0.16, 0.10]	−0.030		
ACS Focusing	0.017	−0.259	0.135	[−0.53, 0.01]	−0.259		0.166
						$F(2,42) = 1.87$	
SCR							
STAIT	−0.060	0.002	0.005	[−0.009, 0.013]	0.101		
Orienting_ Costs	0.061	0.006	0.003	[0.000, 0.011]	0.475		0.149
						$F(2,15) = 2.17$	
FPS							
STAIT	−0.062	−0.201	0.442	[−1.16, 0.76]	−0.114		
Orienting_ Benefits	0.074	0.632	0.322	[−0.06, 1.32]	0.496		0.165
						$F(2,12) = 2.10$	
Extinction learning gradient							
SCR							
STAIT	0.124	61.03	113.99	[−180.64, 302.69]	0.177		
Executive control	−0.003	32.99	33.91	[−38.89, 104.89]	0.321		0.138
						$F(2,16) = 2.24$	
FPS							
STAIT	0.041	−93.53	107.94	[−323.61, 136.54]	−0.209		
Orienting	0.059	−64.48	44.97	[−160.32, 31.37]	−0.346		0.177
						$F(2,15) = 1.95$	
STAIT	0.041	−176.90	90.94	[−370.73, 16.94]	−0.395		
Orienting_Costs	**0.274***	−100.15	36.82	[−178.63, −21.66]	−0.552		0.023
						$F(2,15) = 4.91$	
STAIT	0.041	−136.52	98.17	[−345.76, 72.72]	−0.305		
Alerting	0.142	67.43	34.63	[−6.39, 141.24]	0.427		0.086
						$F(2,15) = 2.91$	
Extinction recall gradient							
US expectancies							
STAIT	−0.038	0.96	3.23	[−5.76, 7.67]	0.055		
Orienting	0.024	−2.66	1.37	[−5.48, 0.16]	−0.364		0.171
						$F(2,25) = 1.90$	
STAIT	−0.038	3.75	3.33	[−3.12, 10.61]	0.215		
Orienting_Benefits	**0.118****	−4.50	1.70	[−8.00, −0.99]	−0.505		0.046
						$F(2,25) = 3.50$	
FPS							
STAIT	−0.111	30.07	35.57	[−51.95, 112.08]	0.257		
Executive control	0.106	−21.54	9.86	[−44.28, 1.20]	−0.664		0.154
						$F(2,8) = 2.39$	

*US, unconditioned stimulus; SCR, skin conductance response; FPS, fear-potentiated startle; STAIT, State-Trait Anxiety Inventory, trait version. Significant values in bold. *$p = 0.016$; **$p = 0.014$.*

DISCUSSION

In this paper, we found that individual differences in self-reported non-emotional AC are not significantly associated with fear extinction learning and recall. However, we did find that the two components of orienting network functioning are significantly negatively associated with fear extinction learning and recall beyond that accounted for by trait anxiety. Specifically, participants with enhanced orienting costs (i.e., difficulties in disengaging attention from cues not relevant for the task) showed faster extinction learning, while those with enhanced orienting benefits (i.e., facilitated orientation by valid cues) exhibited faster extinction recall as measured by FPS and US expectancies, respectively.

The lack of a significant association between self-reported non-emotional AC and fear extinction is at odds with the findings of Barry et al. (2016a), who reported that higher self-reported emotional AC was associated with faster fear extinction learning. In our calculation of the extinction gradients, we considered the difference between CS+ and CS− in each trial; however, when we used the same criteria as Barry and colleagues (Barry et al., 2016a,b) (i.e., considering only the response to the CS+) the

results did not change (see Supplementary Table S3). The main difference between Barry's studies and ours is that we measured AC in non-emotional conditions whereas Barry et al. (2016a, 2017) measured emotional AC. This underlines the importance of the distinction between emotional and non-emotional AC.

Our results on orienting network functioning are not easily comparable to previous research because, to our knowledge, this is first study to analyze how individual differences in the functioning of attentional networks under non-emotional conditions are associated with individual differences in fear extinction learning and recall. Our results on orienting costs resemble those reported of Waters and Kershaw (2015) using threat-related stimuli. While Waters and Kershaw (2015) found that higher *allocation to threat* was a predictor of *higher* extinction learning, we found that lower *capacity for disengaging attention from irrelevant cues* was a predictor of faster extinction learning. It may be that both processes tap into a similar construct that becomes apparent using both threat-related and non-emotional conditions. Consistent with this, Heeren et al. (2015b) stated that specific impairment of the orienting network, such as difficulty in disengaging attention from task-irrelevant distractors, may be a mechanism underlying attentional bias. Then, during fear extinction learning we could assume that people with greater orienting costs with non-emotional stimuli also display higher attentional allocation to the CS+ that speeds up the extinction learning process.

However, this interpretation conflicts with data showing that higher self-reported emotional AC is positively associated with faster extinction learning, as shown by Barry et al. (2016a). Nevertheless, in the study by Barry et al. (2017), a different stimulus was presented during extinction learning and during conditioning. The authors interpreted that participants with high AC were better able to shift attention from the common, threatening features of the original CS+ to the distinct features of a different but similar CS+, therefore "speeding up" the extinction learning process.

The fact that orienting costs and orienting benefits showed a different association with extinction learning and recall also suggests that distinct attentional capabilities may have different relationships with various fear learning processes. This is also consistent with previous studies showing that extinction learning and extinction recall are independent processes (Phelps et al., 2004; Milad et al., 2007; Quirk and Mueller, 2008).

In a previous study, Morillas-Romero et al. (2015) reported that, under non-emotional conditions, orienting network functioning was not related to spontaneous emotion regulation, but with explicit emotion regulation styles. To our knowledge, ours is the first report showing that individual differences in orienting network functioning under non-emotional conditions are related to a form of spontaneous emotion regulation (i.e., fear extinction). Our results underline the potential prominence of the orienting component of attention in anxiety and related processes, as shown recently by Heeren et al. (2015b), Heeren and McNally (2016) in adults with social anxiety disorder.

We also explored the contribution of the alerting network to fear extinction, and found that enhanced alerting was associated with faster fear extinction recall. Previous studies (Tortella-Feliu et al., 2014) have shown that the alerting network is related to self-reported emotion regulation strategies (i.e., enhanced alerting predicts a higher probability of suppressing distressing cognitions). Therefore, there seems to be a positive relationship between alertness and emotional regulation, and future research will need to investigate this relationship further.

Our results could have several methodological and clinical implications. From a methodological perspective, our data indicate that fear extinction gradients can provide a better understanding of individual differences in fear learning (and, more generally, a broader view of fear learning processes) than those offered by "static" fear indices, as previously observed by Barry et al. (2016a, 2017). They support that the empirical exploration of individual differences in non-emotional AC can be relevant for several clinical phenomena, as recently emphasized by Heeren et al. (2015b), and shown here for extinction learning and recall. Furthermore, our results highlight the utility of performance-based measures of attentional network functioning beyond general and self-reported AC.

Taken together with previous studies on the association between both fear extinction (e.g., Waters and Pine, 2016; Ball et al., 2017) and attentional functioning (e.g., Barry et al., 2015a) and exposure-based interventions, our results suggest that differences in the orienting network functioning may explain differences in exposure therapy outcomes, a question that deserves to be explored in future studies.

Our result may also have implications for other forms of psychological interventions, especially attention training. Attention training is a generic term that refers to repetitive "*practice in conflict-related tasks, working memory tasks or others tasks involving executive control mechanisms*" (Tang and Posner, 2009, p. 222) that requires directed effortful attention control. Importantly, most of these interventions train attention using non-emotional materials, as is the case of the attention training technique for anxiety disorders (Fergus and Bardeen, 2016; Knowles et al., 2016). However, in the field of anxiety disorders the most common attention intervention is attention bias modification (ABM) training (Bar-Haim, 2010). Positive results on the use of ABM, mainly as an add-on to cognitive behavior therapy, have been reported in several anxiety disorders (Linetzky et al., 2015). However, results on the efficacy of these interventions are inconsistent (Mogoaşe et al., 2014; Kuckertz and Amir, 2015), and some authors have called for ABM procedures to be improved (Mogg and Bradley, 2016). Notably, although these procedures are intended to train participants to disengage attention from threatening information, several studies have found that any active attentional training procedure will reduce anxiety symptoms, including procedures that use only neutral stimuli (Klumpp and Amir, 2010; Heeren et al., 2015c). Heeren et al. (2015c) also reported that several attention training procedures improve the executive control and alerting components of AC, but not the orienting one, in socially anxious patients. Therefore we propose that attentional training with neutral stimuli should be further explored as a way to improve AC, especially by directly manipulating the orienting network, as proposed by Heeren et al. (2015b). This in turn could be related to increased effectiveness of exposure.

Our study has several strengths. It is the first to explore the association between non-emotional AC and fear learning. Moreover, we measured fear learning using three different fear measures, controlled for some variables that are known to affect fear learning (menstrual cycle, time of the day), and used both magnitude and gradient-based measures. Also, our AC variables included self-reported and performance-based measures. We included analyses and results for the whole sample and only for those participants with successful conditioning and extinction learning. Finally, while previous studies focused on extinction learning, we also studied extinction recall.

We also note some limitations. Participants in our study were individuals with moderate to strong fear of spiders, which also involves disgust, not only fear (Cisler et al., 2009), and this may affect some of the processes investigated. Second, in the paradigm employed here conditioning and extinction learning occurred consecutively with no time for longer consolidation of fear conditioning. Third, some of our analyses including only participants with successful conditioning and extinction learning (those involving SCR and FPS measures and magnitude-based indices) were based on relatively small samples (less than a half of the whole sample for some analyses). However, the main findings from these analyses are fully consistent with those obtained using the whole sample ($n = 50$), which is a relatively large one for fear learning psychophysiological experiments using a 2-day procedure, compared to many previous studies (e.g., Milad et al., 2005; Rabinak et al., 2013, 2014; Garfinkel et al., 2014; Pineles et al., 2016). We computed post-hoc power (two-tailed) for our significant bivariate correlations using sample size, the effect size, and the alpha error (0.05). We had 53–63% (moderate) power to detect a significant correlation between the orienting network functioning and extinction learning and recall. This indicates that Type II error probability was still relatively high in our study, and therefore a replication with larger samples is warranted to ensure the generalizability of our findings. Finally, most significant findings could not be replicated across different fear measures, although this is consistent with many previous fear-learning studies (e.g., Sevenster et al., 2014).

Despite these limitations, we consider that these results contribute to a better understanding of how non-emotional AC is related to fear extinction learning and recall. The most important theoretical contribution is that attentional biases to threat in anxiety could reflect a much broader dysregulation of AC observed in face of non-emotional material.

In summary, in this exploratory study we showed that orienting network functioning is related to fear extinction learning and recall over and above trait anxiety. To the best of our knowledge, this is the first study that links non-emotional AC to fear extinction. An important avenue for future research is to explore the association between AC and anxiety treatments (i.e., exposure therapy).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Clinical Research Ethics Committee of Institut Hospital del Mar d'Investigacions Mèdiques, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Clinical Research Ethics Committee.

AUTHOR CONTRIBUTIONS

EF, DT-R, MF, and MT-F contributed to the development of the study hypothesis, and to the contribution of the study and experiment designs. EF, DT-R, and DT prepared the stimuli, and prepared data and software for analysis. EF, DT-R, and MT-F performed the data analysis. All authors drafted the manuscript, discussed the results, implications, and literature, and approved the final version of the manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2017.01654/full#supplementary-material

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IV. Discussió general

Aquest treball tenia la finalitat d'estudiar la relació entre les diferències individuals en l'extinció de la por al laboratori i la reducció de la por durant la teràpia d'exposició (estudi 1), així com estudiar la relació entre les diferències individuals en l'extinció de la por i la capacitat de control atencional (estudi 2).

Pel que fa a l'estudi 1, la nostra hipòtesi predeia una relació significativa entre l'extinció de la por al laboratori i la reducció de la por durant la teràpia d'exposició. En concret, esperàvem que una millor capacitat en extinció dins la sessió i en el record de l'extinció estaria associada a una major reducció de la por durant la teràpia. Com s'indica a la introducció, la literatura prèvia sempre ha considerat aquests processos com a equivalents. Tot i que els nostres resultats indiquen que aquesta relació existeix (quan tenim en compte la fase d'extinció dins la sessió), l'associació no és tan robusta com s'esperava. Així doncs, de les tres mesures emprades en el nostre estudi, la relació que esperàvem (a més capacitat d'extinció dins la sessió més reducció de la por durant la teràpia) només apareixia utilitzant mesures subjectives per les anàlisis principals (en anàlisis addicionals l'associació apareixia, a més, amb una mesura psicofisiològica).

Aquests resultats són parcialment consistents amb els dos únics treballs, comentats a la introducció, que han estudiat la qüestió. L'estudi de Waters i Pine (2016) va trobar que les diferències individuals en l'extinció dins la sessió es relacionaven amb la resposta a la TCC en grup. Mentre que el nostre estudi estava format per participants adults amb ansietat subclínica que feien una teràpia d'exposició breu, l'estudi de Waters i Pine (2016) avaluava nens amb trastorns d'ansietat que realitzaven un tractament grupal de 10 sessions. L'estudi de Ball et al. (2016) també va trobar que aquells participants (adults amb por de parlar en públic)

que tenien una millor capacitat d'extinció dins la sessió, mostraven una major reducció durant la teràpia d'exposició.

Un dels aspectes diferencials respecte els estudis previs és que el nostre treball avaluava també el paper del record de l'extinció. Tot i que la nostra hipòtesi era que també hi hauria una relació positiva entre major capacitat en record de l'extinció i major reducció de la por durant la teràpia, la relació obtinguda va anar en la direcció contrària (a millor capacitat en el record de l'extinció, menor reducció de la por durant la teràpia). Aquests resultats són poc esperats ja que van en contra dels pocs estudis que s'aproximen a la qüestió. L'únic estudi, segons ens consta, que podria donar un suport parcial a aquests resultats és el treball de Milad et al. (2013) en el que es va trobar que aquells pacients amb trastorn obsessivocompulsiu amb més gravetat mostraven millor capacitat en el record de l'extinció en un paradigma d'aprenentatge de la por similar al que hem utilitzat.

Tenint en compte el que s'ha exposat anteriorment, els nostres resultats serien parcialment consistents amb l'escassa literatura prèvia (en relació a l'extinció dins la sessió) que tradicionalment ha considerat l'extinció i la teràpia d'exposició com a processos equivalents. Això tindria importants repercussions en diferents àmbits. Des d'un punt de vista teòric, el nostre estudi dóna suport a la teoria de l'aprenentatge inhibitori que relaciona dificultats en la reducció de la por durant la teràpia amb dèficits en l'extinció de la por (Craske, Liao, Brown, i Vervliet, 2012). Es tracta doncs, d'una aportació important per a l'argument central de la teoria de l'aprenentatge inhibitori: l'estudi de l'extinció de la por al laboratori com un model de la teràpia d'exposició.

El fet de que els models de l'aprenentatge inhibitori es basin directament en la recerca de l'extinció de la por, i que els nostres resultats donin suport a la relació entre teràpia i extinció dins la sessió, té conseqüències en l'àmbit de la investigació translacional. En aquest sentit, una de les aplicacions més immediates que es pot extreure de les nostres conclusions

és l'ús de l'aprenentatge de la por al laboratori (principalment la fase d'extinció dins la sessió) com un model "pre-clínic" dels trastorns d'ansietat i el seu tractament. Un dels aspectes més interessants consistiria en identificar al laboratori aquells pacients que es podrien beneficiar (o no) d'una teràpia d'exposició, i poder investigar aquells factors i estratègies per millorar-ne l'eficàcia i (possiblement) prevenir les recaigudes. Tot i que les aplicacions a nivell translacional són prometedores, també és cert que l'estudi a nivell de laboratori és molt laboriós. Així, caldrà seguir investigant sobre els models de laboratori amb l'objectiu d'augmentar encara més la seva similitud amb les teràpies emprades en l'àmbit clínic (i per tant també el seu paper predictiu), així com intentar simplificar-ne els procediments (per exemple en relació al nombre d'assajos, o a l'ús de mesures psicofisiològiques que són difícils d'obtenir i processar).

Pel que fa a l'estudi 2, l'objectiu era estudiar la relació entre diferències individuals en l'extinció de la por al laboratori i el control atencional (CA) (definit com un constructe ampli que inclouria les xarxes de control executiu, orientació i alerta) en condicions no emocionals. Malgrat hi ha alguns estudis que apuntarien cap a una relació entre ambdós processos, la literatura és escassa i centrada en el CA en condicions emocionals, raó per la qual el nostre estudi era de caràcter exploratori.

El nostres resultats indiquen que existiria una relació entre l'extinció de la por i el CA. En concret, els dos components de la xarxa d'orientació (costos i beneficis) mostraven un caràcter predictiu sobre l'extinció de la por. És a dir, aquells participants amb majors costos d'orientació (i.e. dificultats per retirar l'atenció de senyals no vàlids) mostraven una extinció dins la sessió més ràpida, mentre que aquells amb majors beneficis d'orientació (i.e. orientació facilitada per senyals vàlids) exhibien un record de l'extinció més ràpid. Aquesta seria la primera evidència de que la relació entre CA en condicions emocionals i l'extinció de la por també apareixeria quan el CA s'avalua en condicions neutres, recolzant així l'argument

que els biaixos atencionals cap a l'amenaça propis de les persones ansioses podrien estar reflectint una desregulació més general de la capacitat de CA que pogués ser observable fins i tot en absència de càrrega emocional.

L'escassa literatura que hi ha fa que els resultats siguin difícils de comparar amb estudis previs. Els nostres resultats sobre CA autoinformat en condicions neutres no coincideixen amb els de Barry, Griffith et al. (2016) i Barry et al. (2017) sobre CA autoinformat en condicions emocionals, atès que nosaltres no hem trobat cap relació entre el procés d'extinció de la por i aquesta variable atencional autoinformada. En canvi, sí podríem trobar algunes similituds entre els nostres resultats amb els costos d'orientació i el treball de Waters i Kershaw (2015). Mentre que els nostres resultats indicarien que una baixa capacitat per retirar l'atenció de senyals irrellevants prediria una extinció dins la sessió més ràpida, Waters i Kershaw (2015) van trobar que aquells que exhibien més atenció cap a l'amenaça tindrien una major capacitat d'extinció dins la sessió. El punt en comú entre aquests dos factors predictors el podem trobar en el treball de Heeren et al. (2015) que argumenta que els dèficits en la xarxa d'orientació podrien ser el mecanisme subjacent als biaixos atencionals.

Els nostres estudis aporten un primer cos de coneixement en un àmbit que encara necessita futures investigacions que repliquin els resultats. No obstant això, el nostre treball és el primer en aportar coneixement sobre la relació entre CA no emocional i extinció de la por. Malgrat el caràcter preliminar d'aquests resultats, una de les aplicacions que se'n podrien derivar és el d'optimitzar les intervencions basades en l'entrenament atencional pels trastorns d'ansietat. Es tracta d'intervencions encara amb una baixa eficàcia (Mogoase, David i Koster, 2014), algunes de les quals empren material emocional en la intervenció. La necessitat de millorar els resultats d'aquestes intervencions fan necessari replantejar-ne alguns supòsits. En aquest sentit, seria interessant explorar les intervencions d'entrenament atencional utilitzant estímuls neutres com una via per millorar el control atencional (sense haver d'incorporar

estímuls emocionalment significatius pel pacient), el que podria estar també relacionat amb millores en els processos d'extinció de la por.

A nivell metodològic, una de les aportacions del segon estudi seria l'avantatge d'utilitzar els índexs d'extinció de la por basats en el gradient comparat amb els índexs de magnitud (que són els que s'utilitzen habitualment). Tal i com s'explica a l'article, el gradient defineix la pendent (i per tant, la velocitat) dels processos d'extinció, mentre que els índexs de magnitud aportarien una informació més "estàtica". El fet de realitzar totes les anàlisis amb els dos tipus d'índexs ens permet afirmar que els gradients podrien explicar millor les diferències en l'aprenentatge de la por, i per tant, ajudarien a comprendre millor aquests processos en comparació amb aquelles mesures basades en la magnitud.

En el futur les línies de treball en aquest àmbit s'haurien de dirigir, en un primer moment, a replicar i consolidar les troballes que s'han presentat en el present treball. Posteriorment, podria ser interessant realitzar alguns estudis que comparessin el caràcter predictiu del CA sobre l'extinció de la por utilitzant proves amb i sense contingut emocional. Això ens permetria valorar d'una manera objectiva si aquests processos s'expliquen millor a través de capacitats atencionals bàsiques o mitjançant processos més complexos amb contingut emocional.

Altres futures investigacions es podrien derivar combinant l'evidència obtinguda a través dels dos estudis que conformen aquesta tesi doctoral. Si tenim en compte que la capacitat per extingir la por i la reducció de la por durant la teràpia d'exposició són processos relacionats, de la mateixa manera que ho són l'extinció de la por i el CA, podem pensar també que la teràpia d'exposició i el CA (en concret la xarxa d'orientació) estarien associats d'alguna manera. En aquest sentit, futurs estudis podrien investigar intervencions que maximitzessin els resultats de la teràpia a través de millores en les variables atencionals (com es comentava abans en relació a les intervencions d'entrenament atencional), o identificar

aquelles persones, a través de la seva capacitat de CA, que poguessin beneficiar-se més de la teràpia d'exposició o, per contra, identificar aquelles que tindrien més dificultats en reduir la por amb una intervenció "estàndard" per tal de poder oferir tractaments més intensius. Així, en primer lloc els estudis haurien d'investigar la relació entre CA i la reducció de la por durant la teràpia d'exposició, i posteriorment estudiar si l'entrenament en aquestes variables atencionals aporta algun benefici de cara a la reducció de la por.

En definitiva, els nostres resultats amplien l'evidència prèvia en la relació extinció de la por-teràpia d'exposició, i fan una primera aportació a la relació entre l'extinció de la por i el CA en condicions no emocionals. Creiem que ambdues línies d'investigació s'haurien d'intensificar per poder millorar els resultats de la teràpia d'exposició.

V. Conclusions

Basant-nos en els nostres resultats, podem concloure que:

- una major capacitat per extingir la por al laboratori (dins la sessió) estaria relacionada amb una major reducció de la por durant la teràpia d'exposició, tot i que de manera menys sòlida a com s'ha considerat tradicionalment.
- La relació amb la fase de record de l'extinció és oposada (més record de l'extinció es relaciona amb menor reducció durant la teràpia) i contrària a la literatura prèvia.
- L'extinció dins la sessió podria ser un model pre-clínic vàlid de la teràpia d'exposició. Aclarir l'associació entre el record de l'extinció i la teràpia d'exposició és un aspecte important per a futur estudis.
- El control atencional en condicions no emocionals (neutres) estaria relacionat amb la capacitat d'extingir la por dins la sessió i el record de l'extinció. En concret, una major capacitat de les xarxes de costos i beneficis d'orientació prediu una extinció dins la sessió i un record de l'extinció més ràpids, respectivament.
- Futures investigacions hauran de replicar aquestes troballes i explorar la relació entre el control atencional i els tractaments dels trastorns d'ansietat, com la teràpia d'exposició.

VI: Referències de la introducció i la discussió general

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VII: Apèndix: Material suplementari dels estudis 1 i 2

DOES FEAR EXTINCTION IN THE LABORATORY PREDICT OUTCOMES OF EXPOSURE THERAPY? A TREATMENT ANALOG STUDY

Forcadell et al.

SUPPLEMENTARY MATERIALS

Methods and Results

METHODS

Fear learning paradigm

We adapted the 2-day fear learning paradigm developed by Milad, Orr, Pitman, & Rauch (2005).

The US (electric shock) had a duration of 100 ms and was generated by a Grass S48 stimulator, transmitted via a constant current unit, and delivered to the volar surface of the non-dominant forearm using a bipolar bar electrode. It was adjusted for each participant to be 'definitely annoying but not painful'. Participants were told that they would see images of two different rooms during the experimental task and that they may or may not be shocked. They were also told that, in case they were shocked, it would be at the end of the presentation of the images.

Before the experimental task, participants received four practice trials (in which the two CSs and the two contexts were combined). Then six startle probes were presented in order to further habituate responding.

The procedure on the first part of day 2 was the same as on day 1, with the following exceptions: participants were told that the shock intensity selected the day before would be used; they were reminded of the instructions; and they were told that they had to use their memory of what they had learned the previous day to predict the occurrence of the US (shock). They did not receive any practice trials, and 10 habituation startle probes were presented before the extinction recall phase.

Trial order was randomized across participants in blocks of nine trials (three of each type), with the restriction that no more than two trials of the same type occurred consecutively. Assignment of the rooms to the conditioning and the extinction contexts, and of the CS+ and the CS–, was counterbalanced across participants.

Recording and quantification (fear learning paradigm)

Skin conductance response (SCR)

Physiological measures were recorded using a Biopac 150 polygraph (BiopacSystems, Inc). SCR was recorded at the distal phalanges of the index and the middle fingers of the non-dominant hand using two Ag-AgCl electrodes filled with electrolyte.

Fear-potentiated startle (FPS)

The startle blink was measured by recording the electromyographic activity (EMG) of the orbicularis oculi, using two 0.5 cm Ag-AgCl surface electrodes. The raw EMG signal was sampled at a rate of 2000 Hz, filtered (analogue 50-Hz notch filter; and digital infinite-impulse-response, 28 to 500 Hz, band-pass filter), and rectified and smoothed offline (10-ms moving window average).

Fear extinction indices

The calculation of the fear extinction indices is shown in Table S1.

Table S1. Calculation of fear extinction indices.

	EXTINCTION LEARNING	Reference
US expectancies **SCR** **FPS**	100 – ([mean[(CS+) - (CS-)] during the last two trials of early extinction learning] / [mean[(CS+) - (CS-)] during first two trials of early extinction learning] * 100).	Based on Pineles et al. (2016)
	EXTINCTION RECALL	
US expectancies **SCR** **FPS**	Mean [(CS+) - (CS-)] during first two trials.	Based on Rabinak et al. (2013)

CS+: Conditioned stimulus associated with the unconditioned stimulus during conditioning; CS-, Conditioned stimulus not associated with the unconditioned stimulus; US, Unconditioned stimulus; SCR, Skin Conductance Response; FPS, Fear-Potentiated startle.

Exposure therapy analog

During exposure therapy analog (ETA), interleaved phobic and neutral images were displayed on a computer monitor in front of the participant. Selection of the phobic and neutral images was made by two pilot participants who were shown a pre-selected set of 30 pictures of spiders, which rated on a scale from 0 (no fear or anxiety) to 10 (severe fear or anxiety). In this study we used fifteen phobic images eliciting medium/strong fear/anxiety (i.e. scores between 5 and 8) and two neutral images (of a pen and a fork) eliciting no fear/anxiety (scores between 0 and 2).

The VAS ratings (ranging from 0 (no fear/anxiety) to 10 (high fear/anxiety)) were averaged for each picture, yielding a total of 20 VAS scores for the phobic and 20 VAS scores for the neutral stimuli.

RESULTS EXCLUDING PARTICIPANTS WITHOUT SUCCESSFUL FEAR CONDITIONING AND EXTINCTION LEARNING

Our criteria for establishing successful fear conditioning were based on the work of Schiller, Raio, & Phelps (2012): the differential SCR to the CS+ and CS– by the end of the conditioning phase (mean of second half of the conditioning trials) had to be in the right direction (i.e. CS+ > CS–) and >0.1 μs for SCR, >1 μV for FPS or >1 point for US expectancies. Similarly, the criteria for establishing successful extinction learning were: differential SCR to the CS+ and CS– by the end of the late extinction learning phase (last trial) had to be ≤0.1 μs for SCR, ≤1 μV for FPS or ≤1 for US expectancies. For indices calculated as a percentage, extreme values (i.e. >150% or <-150%) were excluded.

Fear learning paradigm results

Extinction learning

For SCR and FPS and for the whole sample, we found evidence of successful extinction learning (i.e. similar response to the CS+ and CS- in the last block of extinction), as shown by a non-significant CS type main effect and a non-significant CS type × Block interaction (*p*s > .284). Analyses of US expectancies for the whole sample revealed a main effect of CS type ($F(1, 47) = 7.16$, $p = .010$, $\eta_p^2 = .132$) but a non-significant CS type × Block interaction ($p = .096$).

Extinction recall

For FPS and for the whole sample, we found evidence of successful extinction recall (i.e. similar response to the CS+ and CS- in the extinction context during the first block of extinction recall), as shown by a non-significant CS type main effect and a non-significant CS type × Block interaction (*ps* > .372). For US expectancies and SCR, we found no evidence of extinction recall for the whole sample [significant CS type × Block interaction

for US expectancies: $F(2, 86) = 13.90$, $p < .001$, $\eta_p^2 = .24$; and for SCR: $F(2, 32) = 5.31$, $p < .001$, $\eta_p^2 = .25$].

Table S2. Alternative fear extinction indices.

Extinction learning	Reference
Mean SCR [(CS+) - (CS-)] of first two trials - mean [(CS+) - (CS-)] of last two trials during extinction learning	Soeter & Kindt, 2010
100 – ([mean SCR during the last four CS+ trials of extinction learning / largest SCR of a CS+ trial during conditioning] * 100)	Rabinak et al., 2014
Mean SCR [(CS+) - (CS-)] of early extinction learning - mean SCR [(CS+) - (CS-)] of last two trials of conditioning	Pineles et al., 2016
Mean SCR [(CS+) - (CS-)] of late extinction learning - mean SCR [(CS+) - (CS-)] of early extinction learning	Pineles et al., 2016
Extinction recall	
100 – ([SCR of first CS+ trial during extinction recall / largest SCR of a CS+ trial during conditioning] * 100)	Milad et al., 2005
100 – ([mean SCR [(CS+) - (CS-)] of first two trials of extinction recall / largest SCR [(CS+) - (CS-)] during conditioning] * 100)	Milad et al., 2006
100 – (mean SCR of first two CS+ trials of extinction recall / largest SCR of a CS+ trial during conditioning] * 100)	Milad et al., 2007
100 – (mean SCR of first four CS+ trials of extinction recall / largest SCR of a CS+ trial during conditioning] * 100)	Milad et al., 2009
100 – ([mean SCR of first two CS+ trials of extinction recall / mean SCR of the two largest CS+ responses during conditioning] * 100)	Hartley et al., 2011
Mean SCR [(CS+) - (CS-)] of first five trials during extinction recall	Pineles et al., 2016
Mean SCR [(CS+) - (CS-)] of first five trials during extinction recall - mean SCR [(CS+) - (CS-)] of early extinction learning.	Pineles et al., 2016
Mean SCR [(CS+) - (CS-)] of first five trials during extinction recall - mean SCR [(CS+) - (CS-)] of late extinction learning.	Pineles et al., 2016

CS+, Conditioned stimulus associated with the unconditioned stimulus during the conditioning phase; CS+, Conditioned stimulus never associated with the unconditioned stimulus; US, Unconditioned stimulus; SCR, Skin Conductance Response; FPS, Fear-Potentiated startle.

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Attentional Control and Fear Extinction in Subclinical Fear: an Exploratory Study

Forcadell et al.

SUPPLEMENTARY MATERIALS

Methods and Results

Methods

Attentional Network Functioning

Following standard criteria (Callejas, Lupiáñez, & Tudela, 2004; Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010; Pacheco-Unguetti, Acosta, Marqués, & Lupiáñez, 2011), we computed an efficiency index for each attentional network: executive control = incongruent–congruent trials; orienting = invalid–valid trials; alerting = no alerting–alerting tone (restricted to the uncued condition). Orienting was also divided into costs (i.e. difficulties in disengaging attention from invalid cues) = invalid–uncued trials, and benefits (i.e. facilitated orientation) = uncued–valid trials.

Fear learning paradigm

We adapted the 2-day fear learning paradigm developed by Milad, Orr, Pitman, & Rauch (2005).

The US (electric shock) had a duration of 100 ms and was generated by a Grass S48 stimulator, transmitted via a constant current unit, and delivered to the volar surface of the non-dominant forearm using a bipolar bar electrode. It was adjusted for each participant to be 'definitely annoying but not painful'. Participants were told that they would see images of two different rooms during the experimental task and that they may or may not be shocked. They were also told that, in case they were shocked, it would be at the end of the presentation of the images.

Before the experimental task, participants received four practice trials (in which the two CSs and the two contexts were combined). Then six startle probes were presented, in order to further habituate responding.

The procedure on the first part of day 2 was the same as on day 1, with the following exceptions: participants were told that the shock intensity would be the same as that selected

the day before, they were reminded of the instructions, and were told that they had to use their memory of what they had learned the previous day to predict the occurrence of the US (shock). They did not receive any practice trials, and 10 habituation startle probes were presented before the extinction recall.

Recording and quantification

Skin conductance response (SCR)

Physiological measures were recorded using a Biopac 150 polygraph (Biopac Systems, Inc). SCR was recorded at the distal phalanges of the index and middle fingers of the non-dominant hand using two Ag-AgCl electrodes filled with electrolyte. The signal was sampled at a rate of 125 Hz.

Fear-potentiated startle (FPS)

The startle blink was measured by recording the electromyographic activity (EMG) of the orbicularis oculi, using two 0.5 cm Ag-AgCl surface electrodes. The raw EMG signal was sampled at a rate of 2000 Hz, filtered (analogue 50-Hz notch filter; and digital infinite-impulse-response, 28 to 500 Hz, band-pass filter), and rectified and smoothed offline (10-ms moving window average).

Results

Preliminary analyses:

ANT-I reaction time analysis

We examined reaction time in the ANT-I using a factorial mixed ANOVA for overall intra-subject effects. In line with previous studies (e.g. Pacheco-Unguetti et al., 2011), extreme values (faster than 200 and slower than 1200 ms) were eliminated to avoid

anticipation and very long response latencies, respectively. Each of the 50 participants performed a total of 192 trials in the ANT-I task, for a total of 9600 trials (50 × 192). Reaction time for response trials as a dependent variable was introduced into a 2 (executive control: congruent, incongruent) x 3 (orienting: valid, invalid, uncued) x 2 (alerting: no alerting, alerting tone) factorial mixed ANOVA to explore overall attentional effects. After eliminating extreme values, mean reaction time per experimental condition and error rates are depicted in Table S1.

Consistent with previous studies (Callejas et al., 2004; Pacheco-Unguetti et al., 2010, 2011), we observed significant main effects for executive control (F[1, 49]=488.7, p< .001, η^2 = .909, mean square error (*MSE*) = *1167.56,*= 1961.8), orienting (F[2, 98] = 157.4, p< .001, η^2 = .763, *MSE* = 697.6) and alerting (F[1, 49] = 101.9, p< .001, η^2= .675, *MSE* = 1182,8). Specifically, responses were significantly faster in trials where distracters pointed in the same direction as the arrow target (i.e. congruent trials) compared to those where distracters pointed in the opposite direction, in trials with an orienting signal compared to those without, and in trials with an alerting tone compared to those without.

We also observed significant interactions between attentional networks. The interaction between executive control and orienting (F[2, 98] = 12.87, p< .001, η^2= .208, *MSE* = 546.6) showed a reduction in the congruency effect in valid trials. In the interaction between executive control and alerting (F[1, 49] = 26.9, p< .001, η^2 = .355, *MSE* = 484.5), we observed a larger congruency effect when the alerting tone was presented. Finally, in the orienting and alerting interaction (F[2, 98] = 47.43, p< .001, η^2 = .492, *MSE* = 436.8), we found longer reaction time differences between cued and uncued trials with the alerting tone. All these main effects and interactions were consistent with the pattern usually observed for this task (e.g.Callejas et al., 2004; Pacheco-Unguetti et al., 2010, 2011).

Evidence of conditioning and fear extinction

We found evidence of successful conditioning (i.e. higher response to the CS+ than to the CS- in the last block of conditioning) for all measures (US expectancies, SCR, and FPS). We also found evidence of successful extinction learning (i.e. similar response to the CS+ and CS- in the last block of extinction) for all measures (US expectancies, SCR, and FPS). Finally, we only observed successful extinction recall (i.e. similar response to the CS+ and CS- in the extinction context during the first block of extinction recall) for FPS. See Forcadell et al., 2017 for further information.

Additional analyses:

Relationships between trait anxiety and attentional variables

Since trait anxiety has been widely reported to be related to lower attentional control, we also examined the relationships between these variables. We found that trait anxiety was negatively associated with self-reported attentional control (r = -.404, p =.004 for the overall scale; r = -.393, p = .005 for the focusing subscale, and r = -.303, p = .032 for the shifting subscale) and performance-based attentional control (i.e. greater interference in the executive control network, r = .279, p = .049). No significant associations were found for the orienting (p = .415) and alerting (p = .961) networks.

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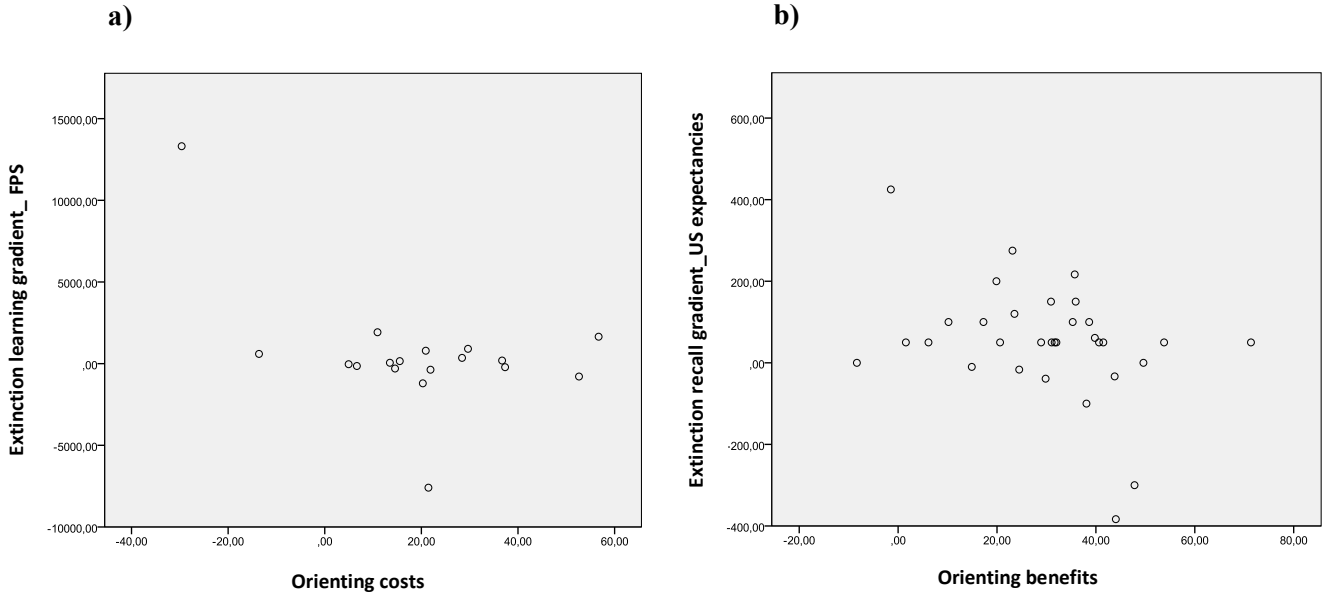

*Figure S1.*Scatter plots for the main significant correlations.

a) Scatter plot for the correlation between extinction learning gradient (as measured by FPS) and orienting costs (when only those participants with successful conditioning and extinction learning were included). Results remained unchanged when one possible outlier was excluded (a participant with a score 3 standard deviations above the mean).
b) Scatter plot for the correlation between extinction recall gradient (as measured by US expectancies) and orienting benefits (results for the whole sample). Results remained unchanged when one possible outlier was excluded (a participant with a score 3 standard deviations below the mean).

FPS: Fear-Potentiated startle; US: Unconditioned stimulus.

Table S1.
Mean reaction times (in milliseconds) and error rates (in parentheses) for each condition of the Attentional Network Test for Interactions.

	Without alerting tone			With alerting tone		
	Neutral	Valid	Invalid	Neutral	Valid	Invalid
Congruent	565(.01)	519(.00)	552(.01)	502(.00)	491(.00)	530(.00)
Incongruent	626(.02)	590(.03)	632(.04)	590(.02)	565(.02)	637(.06)

Table S2.
Bivariate correlation between self-reported attentional control and attentional network functioning in the Attentional Network Test for Interaction (n = 50)

	ACS total	ACS focusing	ACS shifting
Executive control	**-.438** (p = .001)	**.323** (p = .022)	.106 (p = .464)
Orienting	-.136 (p =.345)	.124 (p =.391)	.160 (p =.268)
Orienting-costs	.085 (p =.556)	-.087 (p =.549)	.069 (p =.633)
Orienting-benefits	-.243 (p =.088)	.230 (p =.108)	.122 (p =.401)
Alerting	-.057 (p =.694)	-.162 (p=.260)	-.245 (p=.087)

ACS: Attentional Control Scale. Significant values in bold.

Table S3.

Bivariate correlation between attentional control and fear extinction gradient-based indices (considering responses to CS+).

	AC TOTAL	AC focusing	AC shifting	Executive control	Orienting	Orienting-costs	Orienting-benefits	Alerting
EXTINCTION LEARNING GRADIENT								
US expectancies n=46	.073 (*p*=.631)	.059 (*p*=.695)	.035 (*p*=.815)	.015 (*p*=.919)	.010 (*p*=.946)	-.113 (*p*=.456)	.119 (*p*=.413)	.001 (*p*=.994)
SCR n=18	-.297 (*p*=.232)	-.307 (*p*=.216)	-.219 (*p*=.383)	.100 (*p*=.693)	-.004 (*p*=.987)	.199 (*p*=.428)	-.176 (*p*=.484)	-.169 (*p*=.504)
FPS n=22	.212 (*p*=.344)	.003 (*p*=.990)	.295 (*p*=.183)	.003 (*p*=.988)	.050 (*p*=.824)	.141 (*p*=.533)	-.085 (*p*=.708)	.277 (*p*=.213)
EXTINCTION RECALL GRADIENT								
US expectancies n=32	-.037 (*p*=.839)	.007 (*p*=.971)	-.076 (*p*=.679)	.092 (*p*=.617)	.001 (*p*=.997)	-.131 (*p*=.473)	.121 (*p*=.510)	.163 (*p*=.373)
SCR n=17	.246 (*p*=.342)	.002 (*p*=.994)	.310 (*p*=.226)	-.305 (*p*=.233)	.404 (*p*=.107)	.389 (*p*=.122)	.178 (*p*=.494)	-.281 (*p*=.274)
FPS n=13	.017 (*p*=.955)	.115 (*p*=.708)	-.156 (*p*=.610)	-.078 (*p*=.801)	-.030 (*p*=.921)	.180 (*p*=.556)	-.365 (*p*=.220)	**-.695 (*p*=.008)**

CS+, conditioned stimulus associated with the unconditioned stimulus during conditioning; US, unconditioned stimulus; SCR, skin conductance response; FPS, fear-potentiated startle. Significant values in bold.