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FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES

DOCTORAL SCHOOL ‘‘EVIDENCE BASED PSYCHOLOGICAL ASSESSMENT AND INTERVENTIONS”

PH.D. THESIS SUMMARY

ASSOCIATIVE LEARNING INTERVENTIONS WITHIN AN INTEGRATED AND CLINICALLY ORIENTED FRAMEWORK. AN EVIDENCE-BASED FOCUS ON EXPOSURE AND ATTENTION BIAS MODIFICATION

AUTHOR: PH.D. CANDIDATE PODINĂ IOANA ROXANA

SCIENTIFIC ADVISOR: PROF. DAVID DANIEL, PH.D.

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Notes: _____

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CHAPTER I

THEORETICAL BACKGROUND

1. What is associative learning?

The scientific research of associative learning (also called conditioning) debuted more than 100 years ago with the groundbreaking studies of Thorndike and Pavlov. In the United States, Thorndike (1911) arranged a *response-stimulus* (R-S; e.g., key-press and food) pairing where the stimulus was administered to strengthen or weaken a behavior (i.e., instrumental conditioning). In Russia, Pavlov (1927, 1928) repeatedly trained a *stimulus-stimulus* (S-S; tone-food) pairing, independent of behavior (i.e., classical conditioning).

With regard to the definition, associative learning (i.e., conditioning) has two meanings. The *first* meaning makes reference to the capacity owned by a broad range of organisms (e.g., animals and humans) to learn the information that two or more events are related to each other. The *second* meaning is more restrictive and refers, predominantly, to cognitive process, where connections are made between mental representations of associated stimuli (Mitchell, De Houwer, & Lovibond, 2009). These cognitive updates allowed for conditioning modalities (i.e., fear acquisition, fear extinction, and fear return) to be incorporated in state of the art treatments for anxiety disorders, as described below.

2. Associative learning in a clinical setting: introducing exposure therapy in anxiety

Cognitive-behavior therapy (CBT) for anxiety disorders is among the indubitable success stories in psychological interventions (Barlow, 2002). Restricting the view to anxiety disorders, todays CBT treatments for anxiety embody the principle of exposure stating, among others, that the conquest of fear responses necessitates confrontation with the feared object/situation. Therefore, in the following we will focus on one type of CBT technique, exposure therapy.

Exposure therapy is defined as an intervention that encourages the systematic confrontation with feared stimuli, which can be done either in an external (e.g., feared objects, activities, situations) or internal manner (e.g., feared thoughts, physical sensations), depending on the problem. The purpose of exposure therapy is to diminish (i.e., habituate) to normal levels fearful reactions to the threatening stimulus. Its efficacy has been documented in several studies and meta-analyses (e.g., Tolin, 2010).

3. Attention bias modification: a new form of associative learning

Though in exposure therapy visual and cognitive attention is important, it is not central to the efficacy of exposure as it is for attention bias modification (ABM). Unlike exposure, ABM targets attention processing tendencies, visual attention in particular. ABM is a new intervention, within the CBT framework, developed to correct exaggerated attention to threat (attention bias; AB), which is an important risk factor for anxiety (e.g., Amir, Beard, Burns, & Bomyea, 2009). The literature on this topic is relevant as it supports the involvement of attention bias in the etiology of emotional responses (i.e., anxiety, distress, etc.) and it provides a pathway to correct and modify these biases.

In a standard ABM task, two stimuli (one negative and one positive or neutral) are displayed in parallel on the screen. When training attention away from threat, the target (e.g., a letter) follows only on the location of the nonthreatening stimulus. This way, the participant, which is instructed to detect the target, is learning an association between benign stimuli and target, association which should change his/hers attention pattern. This basic manner of repeatedly associating stimulus to response, reminds of associative learning, therefore, we raise the hypothesis that ABM is a paradigm within an associative learning framework. We enlist several arguments below.

1) In line with the basic tenets of associative learning theories, ABM manipulates associability at an automatic level, facilitating learning in tasks where participants are not explicitly instructed to learn contingencies (Beesley & Le Pelley, 2011).
2) Relying on principles of spatiotemporal contiguity (i.e., a cue predicts the location of a target) and repetitive pairing between cue (i.e., stimulus) and target (i.e., response), it modifies the associative strength between stimulus and response so that an individual can detect and respond faster to the stimulus to which it has been trained to.
3) In order to make the idea of ABM as a new technique of associative learning more intuitive we can depict some of the similarities to exposure. First, both interventions rely on learning of new non-aversive contingencies (i.e., ABM reinforces contingencies between benign stimuli and response; exposure reinforces stimulus-stimulus contingencies) which compete for retrieval with older aversive contingencies. Second, in each case, a new contingency is learned and reinforced repeatedly without making the patient explicitly aware of the new rule, both interventions relying on uninstructed contingency learning.

In support of our arguments, other authors seem to agree that ABM resembles an associative learning technique (e.g., Hertel and Mathews, 2011) drawing parallels between ABM and conditioning, reinforcing the idea that ABM is, indeed, associative learning intervention.

4. New perspectives on ABM and exposure: an interplay

Though few, there are recent studies which bridge the gap between attention training and exposure therapy. First, there are studies which reconcile major theoretical discrepancies between ABM and exposure. Namely, ABM literature sees threat avoidance as an anxiety alleviator and exposure literature conceptualizes threat avoidance as an enhancer of anxiety, especially on the long-term. However, several recent studies indicate that attentional avoidance during exposure might not be detrimental to symptom reduction, contrary to theoretical assumptions (e.g., Oliver & Page, 2007). Therefore, these results bring closer two different viewpoints, in that to some extent avoidance of threat leads to clinical benefits in ABM, as well as in exposure.

Second, there are studies which suggest that ABM could enhance the efficacy of exposure based interventions (Najmi & Amir, 2010). The conjoint action of ABM and exposure is plausible for vigilant-avoidant individuals whose early vigilance may serve to heighten anxiety, whereas their later avoidance may maintain fear. Attention training may be a means of modifying the initial vigilant response, whereas exposure therapy might target the component of avoidance. In this way, the two treatment strategies could become complementary, rather than opposite (Reese, McNally, Najmi, & Amir, 2010). Ultimately, both strategies aim to alleviate fear and

anxiety by teaching an individual about alternative pathways of responding to threatening cues and situations.

5. Relevance and impact of the research topic

We highlight the relevance of the research topic in two complementary lines of investigation that is (1) mechanisms of change and (2) clinical efficacy.

The first line of investigation targets efficacy with respect to anxiety/fear symptoms. Though investigated on a large scale in cognitive and cognitive-behavioral frameworks for anxiety disorders, there is much debate around the factors that facilitate or impede symptom reduction in exposure and ABM, as well as their efficacy on the whole. We, therefore, turned to basic research and inspected each line of investigation in congruence with its specific gaps in terms of clinical efficacy.

The second direction targets mainly mechanisms of change. Since we tailored the current paper to address gaps in the literature, we focused on concerns regarding the mechanisms of change in ABM. In this respect, it is relevant to understand why ABM works and for whom it works, especially in a context where there are publications contradicting its efficacy (e.g., Julian, Beard, Schmidt, Powers, & Smits, 2012).

The relevance of our research theme lies in its potential to contribute with empirical research to the explanation of ABM's and exposure's clinical utility and underlying mechanisms of change, all approached from an integrated and clinically oriented framework.

CHAPTER II

RESEARCH OBJECTIVES AND OVERALL METHODOLOGY

The general goal of this research project was to approach interdisciplinary the gap between separate lines of research (e.g., between attention allocation and exposure) and provide an integrated framework. We plan to reach this objective by tapping into the mechanisms of change and by running efficacy investigations in exposure and ABM, as detailed in the specific objectives section.

The **1st** specific objective was to quantitatively review the data available in the literature regarding the efficacy of attentionally focused exposure against distracted exposure, one of the most important theoretical and clinical debates in the field of exposure. Given the focus on both attention and exposure, this objective provides the impetus for the current project (see the **1st study**).

The **2nd** specific objective was dedicated to replicating and extending previously reported results on the laboratory counterpart of exposure (i.e., fear extinction) with emphasis on its clinical utility in relapse prevention. To be specific, this objective is fueled by recent findings which render exposure, in general, and extinction, in particular, liable to fear relapse. Therefore, in a fear reinstatement paradigm, we contrasted standard extinction to a new form of extinction, called blockade of fear reconsolidation (see the **2nd study)**. it has important clinical implications.

The **3rd** objective investigates mechanisms of change involved in responsiveness to ABM. This aim is reached via two main studies (**study 3** and **5**). In this respect, the 3rd study focuses exclusively on the mechanism of change underlying an ABM intervention (i.e., attention bias), mainly its malleability to genotype and cognitive influences. The fifth study expands the view on ABM, this time considering not only mechanisms of change, but also change in anxiety following an ABM intervention. The novelty of this objective is that it taps into clinical efficacy research, as well as into underlying potential novel mechanisms of change in ABM.

The **4th objective** expands the focus to concepts originating from CBT within a study of genetic correlates of irrationality. Therefore, starting from an interdisciplinary view, we aimed at investigating the relationship between genetic and cognitive vulnerabilities to psychopathology, two concepts which we analyzed previously only in parallel (in the 3rd study). It was intended to provide a theoretical and empirical fundament for the relationship between these two concepts relevant for therapy (**study 4**).

The structure of the Ph.D project is closely molded on these objectives. Most of the conducted investigations are basic research studies aimed to advance the current understanding of associative learning techniques in fear relapse (study 2) and mechanisms of change involved in ABM's efficacy (study 3 and 5) or expand on the relationship between concepts relevant in therapy and psychopathology (study 4). However, three of the conducted studies (Study 1, 2, 5) have important proximal clinical and translational relevance, detailed in the following: a) study one documented on the optimal attentional focus during exposure and its impact on anxious symptomatology, b) study two investigated the efficacy of a new potential form of exposure in preventing fear relapse (Study 2), and c) study five explored potential novel mechanisms of involved in ABM's efficacy in anxiety reduction.

CHAPTER III

ORIGINAL RESEARCH

Study 1. Optimal Attentional Focus during Exposure in Specific Phobia: A Meta-analysis[1]

Exposure therapy is a widely used and effective treatment for anxiety disorders (McNally, 2007). In many treatment packages for anxiety, exposure is considered a crucial component, which involves confronting the feared stimulus or situation until fear related to that stimulus subsides. Though exposure is used on a large scale in cognitive and behavioral therapies for anxiety disorders, there is much debate around the factors that facilitate or impede symptom reduction in exposure (McNally, 2007). One factor that has been subjected to a wealth of research is *optimal attentional focus* during exposure therapy, which according to some views plays a major role in exposure efficacy (Craske et al., 2008). However, as results of studies have been inconsistent, this research has diminished with negative implications in terms of providing answers to questions about optimal attentional focus during exposure. Up to date, only narrative reviews of the literature have been published (Ellis, 2012). More systematic attempts to examine the available data are lacking.

In an attempt to investigate attentional focus as a mechanism of change for evidence based-exposure interventions, we sought to examine the influence of attentional focus on the efficacy of exposure therapy through systematic review of the literature and meta-analysis. Given that most available data on this precise question addressed specific phobia, in order to draw clear cut conclusions, we specifically targeted this disorder.

Overview of the Present Study

The present investigation sought to establish the relative efficacy of different attention allocation instructions during exposure on distress, physiological and behavioral symptoms manifestations of anxiety. The purpose of the present study is twofold.

First, the goal is to investigate differences in efficacy between focused exposure (i.e., allocated attention to threat during exposure), distracted exposure (i.e., diverted attention from threat during exposure), and uninstructed exposure (i.e., without any instruction about attention allocation) with respect to distress, behavior, and physiology by means of two by two comparisons at post exposure and follow-up.

Second, the goal is to investigate potential moderators of the difference in efficacy between focused and distracted exposure with respect to distress, behavior, and physiology. Selected moderators are discussed in the method section.

[1] This study was published: Podină, I.R., Koster, E., Philippot, P., Dethier, V., & David, D. (2013). Optimal Attentional Focus during Exposure in Anxiety Disorders: A Meta-analysis. Clinical Psychology Review, 33 (8), 1172–1183. Doi.10.1016/j.cpr.2013.10.002. Impact factor 6.696.

Method

Literature search

Potentially relevant studies were identified following a systematic search of the PsychInfo and Medline databases through September 2012, using the following keywords: "exposure-only'', "exposure alone", "attentional focus'', "distraction'', paired with "exposure", "anxiety", and "fear". We also systematically searched the references within the most recent articles (Schmid-Leuz et al., 2007), and reviews on the topic of attention allocation during exposure (McNally, 2007).

Selection of studies

The search procedure led to the identification of 37 records. Following the exclusion of irrelevant publications, a total of 29 potentially relevant articles were inspected for relevance based on their full-text. Only studies fulfilling the following criteria were included into the meta-analysis: (a) assessed distress (i.e., fear, anxiety, subjective units of distress) and/or behavioral, physiological symptoms at post exposure and/or follow-up; (b) were English-language publications; (c) included samples with high anxiety or clinically diagnosed anxiety; (d) had sufficient data to compute between-group effect sizes; (e) participants were randomly assigned to at least two out of the three targeted experimental groups (i.e., focused, distracted, and/or uninstructed exposure) and (f) focus and distraction tasks were performed during exposure; (g) dealt with specific phobia. Fifteen articles satisfied the inclusion criteria.

Procedure

Outcome measures were classified into one of the following three clusters:

Distress. Following Powers and Emmelkamp (2008), distress includes anxiety related-specific distress and general distress. This outcome includes self-reports of anxiety, fear related questionnaires, as well as situational and general distress estimates.

Behavior. The behavioral outcome included the level of behavioral approach (e.g., number of steps completed during the behavioral approach test, BAT).

Physiology. Measures assessing physiological responding include: heart rate, skin conductance, systolic and diastolic blood pressure, self-reported blushing responses, and so on.

Moderators were classified into one of the following four clusters:

Clinical status of the sample. Since all the included studies had participants who experienced diagnosed or undiagnosed anxiety, we split this moderator into *clinical samples* (i.e., participants diagnosed with an anxiety disorder) and *analogue samples* (i.e., undiagnosed participants with elevated symptoms of anxiety).

Level of interaction within distraction tasks. We split this moderator into *interactive distraction* and *non-interactive distraction*. Interactive distraction involves patient-therapist communication on topics unrelated to the feared stimulus. In contrast, non-interactive distraction does not involve patient-therapist communication (e.g., listening to a documentary recording and counting key words).

Number of exposure sessions. Following Wolitzky-Taylor, Horowitz, Powers, and Telch (2008), we split the number of exposure sessions into *single exposure session* and *multiple exposure sessions* (i.e., two or more sessions).

Follow-up length. In the targeted distraction-focus studies, follow-up intervals ranged from 1 to 4 weeks. We split the follow-up interval into *less than one month* (i.e., varying from 1 to 3 weeks) and *one month,* which was based on inspection of the typical length of follow-up duration in the included studies. This decision is in line with other meta-analyses (e.g., Covin, Ouimet, Seeds, & Dozois, 2008), which also split the follow-up interval depending on the available follow-up range.

Data anaysis

For effect size estimates we chose Hedges's *g*, a coefficient which controls for variations in sample size among studies (Hedges & Olkin, 1985). Its values can be interpreted just like Cohen's *d* (Cohen, 1988). The effect sizes were coded so that in an uninstructed-distracted and uninstructed-focused exposure pair a positive value points to a result in favor of uninstructed exposure, while in a distracted-focused exposure pair a positive value indicates results in favor of distraction. To examine the degree to which effect sizes differ among studies, we tested for heterogeneity of effect sizes using the Q statistic and the I^2 statistic. A statistically significant Q pin points to a true heterogeneity in effect sizes beyond random error. I^2 but indicates the proportion of observed heterogeneity. These analyses, along with the rest of the examinations, were run using Comprehensive Meta-Analysis (Version 2.2.046; Borenstein, Hedges, Higgins, & Rothstein, 2005).

Results

Between-group analysis for distress

Distraction-focus. At both post ($g = .242$, $p = .177$, 95% CI = [-.110; .594]; $Q(8) = 17.241$, $p = .028$, $I^2 = 53.599$) and follow-up ($g = .101$, $p = .721$, 95% CI = [-.454; .656]; $Q(6) = 21.693$, $p = .001$, $I^2 = 72.342$) pooled effect sizes for distress indicated no differences between conditions.

Uninstructed-distraction. Results showed no significant difference in terms of distress between distraction and uninstructed condition at post exposure ($g = -.088$, $p = .818$, 95% CI = [-.831; .656]; $Q(5) = 28.405$, $p < .001$, $I^2 = 82.398$) and follow-up ($g = -.747$, $p = .248$, 95% CI = [-2.016; .521; $Q(2) = 15.065$, $p < .001$, $I^2 = 86.724$].

Uninstructed-focus. Pooled effect sizes indicated no significant differences between uninstructed and focused exposure with respect to distress at post exposure ($g = .033$, $p = .894$, 95% CI = [-.451; .517]; $Q(3) = 5.573$, $p = .134$, $I^2 = 46.166$) or follow-up ($g = -.032$, $p = .875$, 95% CI = [-.426; .363]; $Q(2) = 1.218$, $p = .544$, $I^2 = .000$).

Between-group analysis for behavioral outcomes

Distraction-focus. At post exposure ($g = .672$, $p = .080$, 95% CI = [-.080; 1.425]; $Q(4) = 17.678$, $p = .001$, $I^2 = 77.373$) the average effect size was near significance and in favor of distraction, where participants in the distraction group tended to display better behavioral

outcomes (i.e., less avoidance and more approach behavior) than 76% of those in the focus group. At follow-up (g = 1.490, p = .008, 95% CI = [.394; 2.586]; Q (2) = 6.610, p = .037, I^2 = 69.742), the average effect size was significant and in favor of distraction, where participants in the distraction group demonstrated better behavioral outcomes relative to 92% of those in the focus group.

Uninstructed-distraction. We could not compute an average effect size at follow-up because of lack of studies and data for this contrast pair. At post exposure, the resulting medium effect size indicated a significant difference between uninstructed exposure and distraction in favor of uninstructed exposure, g = .664, p = .017, 95% CI = [.120; 1.206] ;Q (1) = .001, p = .970, I^2 = 0.000, meaning that participants in the uninstructed group had better behavioral outcomes than 73% of those in the distraction group.

Uninstructed-focus pair. We could not compute an average effect size at follow-up because of lack of studies and data for this contrast pair. However, the resulting small effect size at post-exposure (g = .289, p =.231, 95% CI = [-.184; 0.761]; Q (2) = .967, p =.326, I^2 = .000.) was not significant.

Between-group analysis for physiological outcomes

Distraction-focus. At both post (g = -.276, p = .282, 95% CI = [-0.781; 0.228]; Q (6) = 20.509, p = .002, I^2 = 70.745) and follow-up (g = -.520, p = .168, 95% CI = [-1.259; 0.219]; Q (5) = 25.993, p =. 000, I^2 = 80.764) pooled effect sizes for physiology indicated no differences between conditions.

Uninstructed-distraction. We could contrast uninstructed-distraction pair at post exposure considering data reported in only 2 studies. Results showed no significant difference in terms of physiology between distraction and uninstructed exposure, *g* = .074, p = .772, 95% CI = [-0.428; 0.577]; Q (1) = .906, p = .341, I^2 = .000).

Uninstructed-focus. We could not compute an average effect size for the uninstructed-focus pair at post exposure or follow-up on account of lack of physiological measurements for this contrast.

Moderators of distress outcome

As our primary focus was on the distraction-focus pair, we investigated potential moderated responses with respect to this contrast.

Clinical status of the sample. In the distraction-focus pair, the clinical status did not moderate the effect size for distress, post exposure or follow-up (Table 3)

Number of exposure sessions moderated post exposure and follow up effect size for distress in the distraction-focus pair. At post exposure, in the multiple sessions' condition, participants in the distraction group had lower levels of distress than 92% of those in the focus group. In the single session, distraction and focused exposure did not differ significantly. At follow-up, in the multiple sessions' condition, participants in the distraction group reported lower levels of distress relative to 92% of those in the focus group. This was not the case for the single session condition, where there was no significant difference between both groups (Table 3).

Level of interaction within distraction tasks. This variable significantly moderated post exposure effect size for distress. Distraction was significantly superior to focus in terms of distress in the interactive condition, while in the non-interactive condition; there were no significant differences between both conditions. In the interactive condition, participants in the distraction group had lower distress levels than 84% of the individuals in the focus group (Table 3).

Follow-up interval length. Follow-up length did not moderate effect sizes for distress in the distraction-focus pair (Table 3).

Moderators of behavioral outcome

Clinical status of the sample. The clinical status did not moderate the effect size for behavior in either dataset, post exposure or follow-up (Table 4).

Number of exposure sessions. Distraction significantly outperformed focused exposure in the multiple sessions' condition, where individuals from the distraction group had better behavioral outcomes (i.e., less avoidance and more approach behavior) than 95% of the individuals in the focus group. In the single session condition, the difference between distracted versus focused exposure did not reach significance. The analysis could not be extended to follow-up on account of lack of diversity between studies with respect to number of exposure sessions, meaning that the majority of studies had multiple exposure sessions (Table 4).

Level of interaction within distraction tasks. This variable significantly moderated post exposure effect size for behavioral outcome. That is, distraction was significantly superior to focus in terms of behavior for interactive tasks, while for non-interactive tasks there was no difference between distraction and focus. Furthermore, with interactive tasks, distracted exposure had better behavioral outcomes than 84% of the individuals in the focused exposure group (Table 4).

Follow-up interval length. The analysis could not be extended to follow-up time interval or follow-up length moderator since there were too few studies.

Moderators of physiological outcome

Irrespective of the time of measurement, post exposure or follow-up, none of the investigated variables was a significant moderator of the physiological outcome.

Publication bias

To investigate the presence of publication bias we computed Duval and Tweedie's (2000) trim-and-fill procedure using a random effects model.

For distress, in the distraction-focus pair, trim-and-fill procedure estimated no study with effects higher or lower than the mean which could modify the results at post-exposure. At follow-up, trim and fill estimated one study with an effect size higher than the mean which did not change significantly the results, g = .280, 95% CI = [-.313; .874], Q = 30.419.

For behavior, in the distraction-focus contrast, trim-and-fill procedure estimated one study, at post exposure, with an effect size lower than the mean which did not change

significantly the results, g = .443 95% CI = [-.326; 1.213], Q = 25.502. For the remaining contrasts, the presence of only two studies per condition implied that publication bias could not be investigated.

For physiology, at post exposure, the trim and fill procedure estimated one study with effect sizes above the mean, which did not change significantly the results, g = -.096, 95% CI = [-.645; .452], Q = 30.902. At follow-up, two studies with effect sizes below the mean were estimated to reduce the effect size, g = -.925, 95% CI = [-1.693; -.157], Q = 48.677. As was the case for behavior, the other two exposure contrasts cannot be investigated for publication bias because of lack of studies.

Table 3. Moderation analysis with categorical variables for distress at post exposure and follow-up (FU)

Outcome	Time of measurement	Moderator	Condition	N	g	p	Q w	p	CI	Q b	p
Distress	Post	Analogue/ Clinical Sample	D-F	4	0.434	0.322	12.127	0.007	[-0.426;1.294]	0.001	0.989
				6	0.427	0.170	23.881	0.000	[-0.183;1.037]		
	FU		D-F	3	0.342	0.637	14.479	0.001	[-1.081;1.756]	0.000	0.991
				5	0.351	0.402	23.373	0.000	[-0.471;1.173]		
	Post	Single/ Multiple Sessions	D-F	7	0.057	0.684	6.869	0.333	[-0.218;0.333]	8.099	0.004
				3	1.527	0.002	7.594	0.022	[0.553;2.501]		
	FU		D-F	5	-0.237	0.175	4.367	0.359	[-0.579;0.105]	15.124	0.000
				3	1.519	0.000	5.395	0.067	[0.703;2.335]		
	Post	Interactive/ Non-Interactive	D-F	5	1.010	0.010	21.524	0.000	[0.242;1.778]	6.147	0.013
				5	-0.062	0.736	4.741	0.315	[-0.420;0.297]		
	FU		D-F[a]	3	0.647	0.205	12.301	0.002	[-0.349;1.624]	2.688	0.101
				4	-0.296	0.266	4.316	0.229	[-0.817;0.225]		
	FU	Less than one month/One Month F.U.	D-F[a]	2	-0.665	0.259	3.397	0.065	[-1.820;0.490]	2.528	0.112
				5	0.394	0.205	11.624	0.020	[-0.215;1.003]		

Table 4. Moderation analysis with categorical variables for behavior and physiology at post exposure and follow-up (FU)

Outcome	Time of measurement	Moderator	Condition	N	g	p	Q w	p	CI	Q b	p
Behavior	Post	Analogue/ Clinical Sample	D-F	3	0.647	0.135	4.876	0.087	[-0.201;1.495]	0.011	0.916
				2	0.750	0.396	12.202	0.000	[-0.981;2.481]		
	Post	One session/ Multiple sessions	D-F	3	0.032	0.873	0.716	0.699	[-0.359; 0.423]	16.913	0.000
				2	1.606	0.000	0.048	0.826	[0.965; 2.246]		
	Post	Interactive/ Non Interactive	D-F	3	1.128	0.016	6.995	0.030	[0.208;2.049]	5.142	0.023
				2	-0.061	0.792	0.130	0.718	[-0.520;0.397]		
Physiology	Post	Interactive/ Non Interactive	D-F	2	-0.759	0.315	8.057	0.005	[-2.240;0.722]	0.677	0.411
				5	-0.094	0.741	10.659	0.031	[0.653;0.465]		
	FU		D-F	2	-0.703	0.366	9.548	0.002	[-2.227;0.299]	0.322	0.570
				4	-0.233	0.408	5.028	0.170	[-0.554;0.821]		
	FU	Less than one month/One Month F.U.	D-F	2	0.072	0.750	0.130	0.719	[-0.785; 0.319]	2.478	0.115
				4	-0.877	0.117	19.219	0.000	[-1.973; 0.219]		

Notes. D-F = distraction-focus.

Discussion

The current meta-analysis aimed at investigating the efficacy of focused vs. distracted and uninstructed exposure on distress, behavioral, and physiological outcomes. In the following, we discuss several main results derived from the current met-analysis.

Main effects. First, there were no differences in efficacy between focused, distracted and uninstructed exposure regarding distress and physiology at post-exposure or follow-up. The lack of significant differences between interventions indicates that distracted exposure is comparable to focused and uninstructed exposure in terms of distress and physiology.

Second, there were significant and marginally significant differences between exposure pairs regarding behavioral outcomes. An explanation for these results might have to do with perceived control during exposure. Therefore, distracted exposure might enhance perceived control and thus the approach towards threat. Noteworthy, in the uninstructed-distraction pair,

results for behavioral outcomes were in favor of the uninstructed group at post-exposure. Perhaps, in terms of approach behavior, it is important for the patients to be able to choose how to direct their attention.

Moderator effects. First, the number of exposure sessions was a significant moderator of distress and behavioral outcomes, with results in favor of distraction. The results are in line with a dose-response relationship, indicating that a larger number of sessions is related to larger symptom improvement (Kopta, Howard, Lowry, & Beutler, 1994).

Second, with reference to the level of interaction within distraction, our results indicate that this variable was a significant moderator of the efficacy of distress and behavioral outcomes. Distracted exposure significantly outperformed focused exposure, in terms of behavior and distress. It may be that interactive distraction triggered pleasant emotions. In turn, the positive emotions, experienced during stressful conditions, might have created the premises for counterconditioning.

None of the moderation analyses were significant for physiology. This may have to do with the nature of the outcome. Previous reports indicate that physiological measures do not always follow trends in other anxiety related outcomes (Alpers & Sell, 2008).

Theoretical and clinical implications. From a *theoretical point of view*, our results may pose a challenge to current views on exposure where it is thought that distraction during exposure may prevent fear reduction. From a *clinical point of view*, our results indicate that as long as the exposure sessions are extended over multiple sessions and the distracter is interactive, distraction does not impede symptom reduction.

The present meta-analysis has several limitations related to the current state-of-affairs in this literature, as detailed in the following: 1) there were a limited number of studies contrasting attentionally instructed exposure against uninstructed exposure; 2) we had no objective information regarding the amount of load imposed by the distracter on cognitive resources; 3) lack of cognitive assessments within studies limits our meta-analysis to emotional, physiological and behavioral findings; 4) because the manipulation check for compliance with instructions is missing in most studies, the degree of attention allocation to and from threat couldn't be controlled for; 5) the current evidences are generalizable to specific phobias only.

In addition to extending research to other anxiety disorders, future studies could: (a) endeavor to further refine distraction tasks to assess the amount of distraction that takes place during exposure; (b) investigate to what extent different types of distraction, like visual or cognitive, impede or not exposure mechanisms; (c) investigate whether distraction is present in some tasks of focused exposure, like patient-therapist conversation on threat related topics; (d) measure symptom reduction from a multilevel perspective; or (e) examine whether distraction per se or attribution of recovery to distraction instead of exposure is counterproductive to therapy.

On the basis of these findings, the present meta-analysis suggests that distraction in contrast to focused exposure could be less counterproductive and even useful to exposure when distraction task is interactive and exposure is spread over the course of multiple sessions.

Study 2. Preventing the return of fear: Reconsiderations of standard exposure in the context of the blockade of fear reconsolidation technique

Phobic disorders are the most common categories of psychiatric disorders and much effort has been put into the development of treatments. Despite money and time investment, decades of psychological studies have shown that extinguished fear responses return with the passage of time (Pavlov, 1927).

An alternative to standard extinction and therefore standard exposure is a new intervention called *extinction through reconsolidation blockade* (Schiller et al., 2010). This technique shows that in a brief window of opportunity following threat reminders, fear can be updated with non-fearful information (e.g., extinction training) after a 10 min to 1 hour window, when memories become unstable. As a consequence of this procedure, "fear responses were no longer expressed, an effect that lasted at least a year and was selective only to reactivated memories without affecting others" (Schiller et al., 2010, pp. 49).

Overview of the present study

However, along with the encouraging results, in the reconsolidation background, come along a series of questions.

One question would be: Are the results, regarding behavioral reconsolidation blockade, replicable? So far, various studies have replicated Schiller et al.'s (2010) results via a within group design (e.g., Bellander, 2010). However, the whole benefit of this intervention is the superiority regarding fear return or reinstatement (i.e., that is triggered return of fear) in contrast to standard extinction. Therefore, the current study was designed to replicate, on a larger sample size, the initial study on behavioral reconsolidation blockade (Schiller et al., 2010). We focused on contrasting standard exposure to reconsolidation blockade with respect to physiological responses (i.e., skin conductance responses, SCR).

Another question would be: Does the reconsolidation blockade prevent fear reinstatement on other fear assessments, aside from SCR? The current study was designed to extend the research findings of Schiller et al. (2010) to other conditioned responses relevant to the etiology of anxiety disorders and treatment relapse. In this respect, we selected attention bias and evaluative conditioning. *Attention bias* was a fit selection, as previous studies have shown that it is conditionable and it varies according to the conditioning modalities (fear acquisition, extinction, and fear reinstatement) (Van Damme et al. 2006). *Evaluative conditioning* or the acquirement of likes and dislikes (De Houwer, Baeyens, & Field, 2005), was chosen in light of studies indicating that the valence component may be more resilient to extinction interventions (De Houwer et al., 2005) than the fear component, predisposing to symptom return.

In light of the previously stated arguments and given the focus on fear reinstatement differences between standard extinction and fear reconsolidation blockade, we expect that:

(1) The extinction group will have a higher physiological reinstatement than the reconsolidation group.

(2) The extinction group will have a higher negative attention bias to threat relative to the reconsolidation group.

(3) The extinction group will have higher negative evaluative estimates than the reconsolidation group.

(4) The extinction group will have lower positive evaluative estimates than the reconsolidation group.

To test these hypotheses, we designed an experiment to examine whether the new extinction training (Schiller et al., 2010) would block, as opposed to standard extinction, the reinstatement of extinguished fear related responses (i.e., SCR, attention bias to threat, and evaluative conditioning). Additionally, we investigated pre-intervention differences regarding trait anxiety and beliefs about the feared consequences of anxiety (i.e., anxiety sensitivity), which could account for variability in response to fear extinction manipulations.

Method

Participants

Ninety healthy participants were recruited by email advertisements. Two participants were eliminated from statistical analysis, as these participants failed to arrive on all three experimental days. Thus, the final sample included 88 participants (M age = 22.573, SD = 4.171; 77.272% women), randomized to standard extinction (N = 42) and reconsolidation conditions (N = 46). Volunteers signed an informed consent and received credits for participation.

Instruments

Questionnaires. For the purposes of this study, we used (a) the Anxiety Sensitivity Index-3 (ASI 3)(Taylor et al., 2007; Miclea, Albu, & Ciucă, 2009) to assess beliefs about the feared consequences of anxiety related symptoms and (b) the Endler Multidimensional Anxiety Scale-Trait Version (EMAS-T) (Endler & Kocovski, 2001) to assess four dimensions of trait anxiety, that is anxiety in social evaluation situations, anxiety regarding physical danger, anxiety in ambiguous situations, and anxiety regarding daily routines.

Bias Assessment Task. In order to measure attention bias, we employed an adapted version of the Spatial Cueing Task from Koster, Crombez, Verschuere, Van Damme, and Wiersema (2006). Two neutral faces were used as cues and were labeled as CS+ (the conditioned stimulus which was paired with an aversive white noise, called US) and CS- (the conditioned stimulus which was never paired with the US). Each trial started with a fixation cross flanked by two white rectangles. One of the selected cues filled one of the white rectangles. Directly after the cue offset, the target, a small black square appeared either in the same location as the cue (i.e., valid cued targets; VC) or in the opposite location (i.e., invalidly cued targets; IC). The target persisted on the screen until response. The trials were randomized with respect to the type of stimulus (i.e., CS+ vs. CS-) and validity (i.e., VC vs. IC). The spatial cueing task was built in E-Prime (Version 2; Psychology Software Tools, Pittsburgh, PA).

Evaluative Conditioning Assessment Task. Evaluative conditioning was measured via a priming task adapted from Fazio, Jackson, Dunton, and Williams (1995). The task was split

into baseline and the priming task per se. In baseline, participants had to respond as fast as possible to negative or positive adjectives which followed a neutral cue, i.e. an asterisk. In the priming phase, participants had the same task, but instead of an asterisk, the cue was one of the CSs.

Procedure

The experimental paradigm involved three consecutive stages, conducted 24 hours apart: Day 1 - Acquisition, Day 2 - Reactivation and Extinction, and Day 3 – Reinstatement and Re-extinction (Fig. 1).

First day. Before fear acquisition, participants filled in potential covariate measures, namely ASI-3 and EMAS-T, followed by a baseline assessment of (a) skin conductance response (SCR), (b) bias assessments, and (c) evaluative conditioning. Both groups underwent fear conditioning in the same manner (Figure 1). The CS+ was associated with the US (i.e., a 200 ms burst of 95 dB) on 38% of the trials and the CS- was never paired with the US. After the acquisition phase, during which we measured only SCR, followed the bias and evaluative conditioning assessment.

Second day. The 2nd day was different for the two groups. The reconsolidation group received a reminder from the previous day, the CS+, followed by a 10 min break. Immediately after the 10 min break, participants in the reconsolidation group were assigned to extinction trials, which consisted of non-reinforced presentations of CS+ and CS-. In contrast, the extinction group was not reactivated, but was directly assigned to the 10 min break, followed by extinction trials. After the extinction phase, during which we measured only SCR, we performed bias and evaluative conditioning assessments (see Figure 1).

Third day. Day 3rd day consisted of reinstatement and re-extinction and it was identical for both groups. In the reinstatement stage, subjects were administered 4 unsignalled, aversive, sounds. Directly after reinstatement, a re-extinction session was initiated, where participants were displayed the non-reinforced CS+ and CS- stimuli (see Figure 1. Following the re-extinction phase, during which we measured only SCR, was the bias and evaluative conditioning assessment.

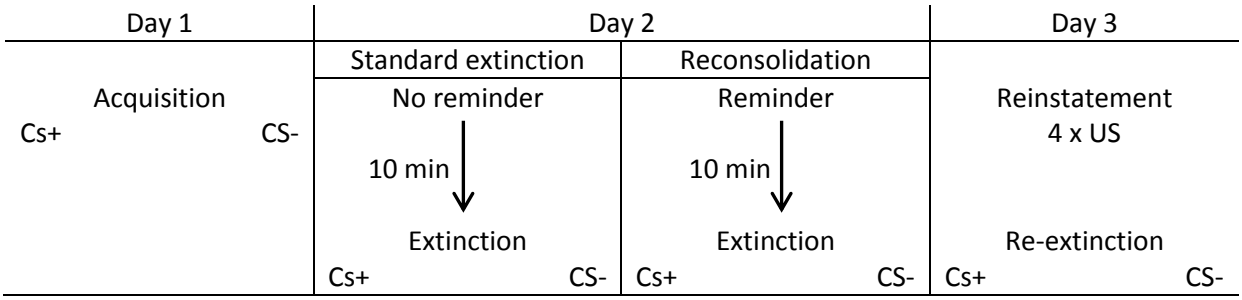

Figure 1. Overview of the three day routine (acquisition, reactivation and extinction, reinstatement and re-extinction)

Data analysis per outcome

Attention Bias Score. We computed a cue validity index (CVI) for CS+ and CS-trials, in all experimental phases (RT IC minus RT VC) (Van Damme, Crombez, Hermans, Koster, &

Eccleston, 2006). A larger CVI in CS+ trials relative to CS trials shows that more attention is allocated to the CS+ than to the CS. In order to examine the difference in attentional bias between groups we performed a differential score (i.e., CVI CS+ minus CVI CS). Positive values indicate an attention bias for CVI CS+ relative to CVI CS-.

Evaluative Conditioning Estimates. Evaluative conditioning was expressed in terms of speed of response, called facilitation score. The facilitation scores for positive and negative adjectives was computed for each CS by subtracting the mean latency of the baseline adjective from the mean latency of the priming adjectives (RT CS+ minus RT baseline; RT CS- minus RT baseline). Hence, we had four facilitation scores, two negative evaluations for CS+ and CS- and two positive evaluations for CS+ and CS-.

Skin Conductance Response. Fear acquisition was assessed by comparing CS+ to the CS- during the second half of the acquisition session (last 4 trials). Extinction was assessed by comparing CS+ to the CS- during the last trials of extinction. The change in fear response from acquisition to extinction was assessed by comparing the mean second half of acquisition (last 4 trials) with the last trial of extinction for each stimulus (CS+ and CS-). To test for fear reinstatement, the response to each stimulus in the first re-extinction trial was compared with that of the last extinction trial. At each stage, the differential fear response was calculated by subtracting responses to the CS- from responses to the CS+.

Results

Baseline assessment

Baseline assessments revealed no group-related differences with respect to self-report measures of anxiety sensitivity or trait anxiety, $p > .05$.

Manipulation check with respect to the SCR

In congruence with previous studies (Schiller et al., 2010), there were no between-group differences regarding baseline ($t(86) = .041$, $p = .968$/p corrected = 1.936), acquisition ($t(86) = -.720$, $p = .473$/p corrected = 1.419), or extinction ($t(86) = -.270$, $p = .788$).

Given that there were no between group differences, we investigated for successful acquisition and extinction across the two groups (i.e., extinction and reconsolidation). As such, there was a difference between CS+ and CS- in the acquisition phase, $t(87) = 7.008$, $p < .001$, $d = 1.502$, difference which was in favor of the CS+ ($M = .418$, $SD = .300$), as opposed to the CS- ($M = .3477$, $SD = .297$). This cues to a successful fear acquisition. As expected, with regard to extinction, there was no significant difference between the CS's ($t(87) = -.585$, $p = .560$, $d = -.125$) cueing that, in the second day, the CS+ extinguished its negative valence.

These results allow for further investigations of change in time from day one to day two. The decrease in differential SCR from acquisition to extinction for each group was assessed using a two-way ANOVA with main effects of group (standard extinction vs. reconsolidation) and time (acquisition, extinction). This showed a significant main effect of time ($F(1,86) = 15.866$, $p < .001$, $\eta p2 = .162$), but no interaction ($F(1,86) = .012$, $p = .913$, $\eta p2 = .000$) or group effect ($F(1, 86) = .127$, $p = .723$, $\eta p2 = .002$), therefore there was no

difference in the level of fear reduction between the groups. The manipulation check is in line with Schiller et al., (2010).

Main results with respect to the SCR

With regard to reinstatement, there was a between group difference, t (86) = 4.610, p < .001, d = .994, favoring the reconsolidation group (i.e., less differential SCR values; M = .043, SD = .202) relative to the extinction group (M = .284; SD =. 281). This is an important result, as our primary between-group difference is expected only in the reinstatement phase. Spontaneous reinstatement of fear was assessed using a two-way ANOVA with main effects of group (extinction vs. reconsolidation) and time (extinction and reinstatement). The results showed a significant main effect of time (F (1, 85) = 25.955, p < .001, ηp2= .243), a group-time interaction (F (1, 85) = 13.745, p < .001, ηp2= .145), and a between-group difference, F (1, 85) = 4.166, p = .045, ηp2= .058. Follow-up t-tests contrasted the differential responses between the last trial of extinction and the first trial of re-extinction.

Significant spontaneous reinstatement was found in participants in the standard extinction group, t (40) = - 4.606, p < .001, d = -.719 (see Figure 1), but not in the reconsolidation group (t (45) = -1.496, p = .142, d = -.220). These results point out that the spontaneous reinstatement of fear can be prevented if extinction training is performed during the reconsolidation window for fear memory.

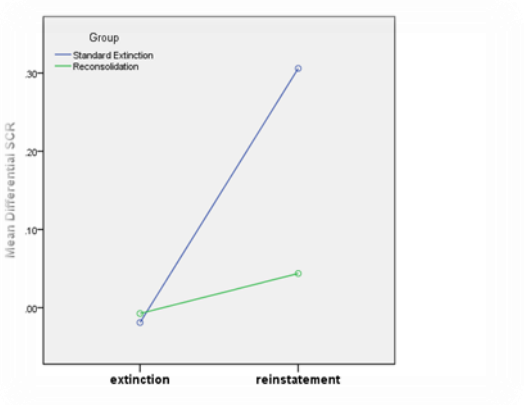

Figure 1. Graphical view of the difference between standard extinction and blockade of fear reconsolidation with respect to reinstatement (i.e., the mean differential SCR from day 2 to day 3).

Extended results

There were no baseline group differences regarding bias (t (86) = -.236, p = .814) or negative (t (86) = -.297, p = .767, p corrected = 1.534) and positive evaluative conditioning (t (86) = .580, p = .564, p corrected = 1.692). Given that there were no between group differences, we investigated for successful acquisition and extinction across the two groups (i.e., extinction and reconsolidation).

Noteworthy, there was no evidence of fear acquisition with respect to the attentional and evaluative outcomes. To be specific there was no difference between CVI CS+ and CVI CS- (t (87) = -.219, p = .827) or between CS+ and CS- in terms of positive (t (87) = -.515, p =

.608, p corrected = 1.216) and negative evaluative conditioning (t (87) = 1.420, p = .159, p corrected = .477). Given these results, we could not perform any further analysis regarding bias/evaluative conditioning in extinction and/or reinstatement stages. Therefore, fear acquisition of the physiological outcome was not paralleled by conditioning of the attentional and attitudinal measurements.

Discussion

The present study was designed to examine whether the extinction training conducted during an approximately half an hour reconsolidation window (Schiller et al., 2010) would block, as opposed to standard extinction, the reinstatement of extinguished fear related responses (i.e., SCR, attention bias to threat, and evaluative conditioning). The following paragraphs provide a summary of the study's results and broader implications.

Main results. The results of the Pavlovian fear conditioning paradigm replicated previous research (Schiller et al., 2010). It indicated that the differential SCR depended on the experimental condition, with the reconsolidation group revealing more fear reinstatement relative to the standard extinction group. These results are in line with separate replications of Schiller et al (2010), cueing to a robust result in favor of reconsolidation in terms of differential SCR. However, we couldn't extend our results to attention bias and evaluative responses, as these responses were not conditioned. In this respect, it may be argued that the number of trials in the current conditioning paradigm may not have been sufficient to cause changes in the cognitive processing of the CS+/CS- , as measured by the visual search task and priming task. This is plausible as our conditioning paradigm was built especially following the guidelines from studies focused solely on physiological outcomes, while we know that for attention bias, for instance, far more trials are required in order to establish an association.

In light of this limitation, future studies should use attention bias and evaluative responses during conditioning procedures. One way to do this would be via eye tracking devices. This would be a more reliable way of measuring attention bias and evaluative conditioning, as previous research has that conditioned responses might not always be accessible in post-acquisition measures relying on reaction times (Onnis, Dadds, & Bryant, 2012).

Despite successful replication of Schiller et al (2010), the research regarding the blockade of fear reconsolidation is still in its infancy. Issues, like the mechanisms of change involved in the efficacy of this intervention, remain unsolved. Namely, it is unclear whether the reconsolidation blockade intervention weakens the original fear memory or whether a new extinction occurs and future studies should direct their efforts in this direction.

Study 3. The impact of irrational cognitions and COMT Val^{158}Met in response to attention bias modification. An integrated perspective

Attention bias modification (ABM) is an emerging intervention developed to correct exaggerated attention to threat (attention bias; AB), which is an important risk factor for anxiety (e.g., Amir, Beard, Burns, & Bomyea, 2009). Earlier experimental manipulations of AB indicated that ABM can be effective in reducing emotional reactivity and anxiety levels, revealing a promising therapeutic potential for this intervention (e.g., Amir et al., 2009).

Recently, genetic factors have been shown to contribute to change in bias following ABM (Fox, Zougkou, Ridgewell, & Garner, 2011). Search for genetic moderators of ABM is still in its infancy. However, Catechol-O-Methyltransferase (COMT) gene, coding for a dopamine degrading enzyme, stirred special interest in therapy and attention bias research. One of its variants, a G to A substitution (rs4680) that results in an amino acid change (Val158Met) (Mannisto & Kaakkola, 1999), has been investigated as a biomarker for response to psychological interventions.

COMT Val^{158}Met could be a candidate genotype for differential response to ABM based two main reasons. First, previous research points to a differential response to psychological interventions (e.g., exposure, Lonsdorf et al., 2010; extinction, Lonsdorf et al., 2009) with Met homozygotes benefiting less from interventions. Second, Met allele, in particular, was linked to psychopathology markers relevant for the efficacy of ABM, like increased attention to threat (Williams et al., 2010) and poor cognitive flexibility (Bilder, Volavka, Lachman, & Grace, 2004).

CBT research might provide several other candidates, which may alter the response to ABM. Factors like irrational cognitions (e.g., It is dreadful if I have no control) have been proven to alter the sensitivity to therapy (e.g., for a review, see Driessen & Hollon, 2010). Irrational cognitions (i.e., referred to as appraisals) are illogical, inconsistent with reality, and impede individuals from attaining their goals (Ellis, 1994).

Cognitive rigidity is considered a hallmark of irrationality (Dryden, 2003), so a pre-existent high-level of irrational beliefs could negatively impact on cognitive/attentional functioning. This is plausible from a theoretical standpoint, since general irrational beliefs are organized as schemas (David, 2003), which are thought to disturb every level of information processing, including selective attention to threat (e.g., irrational beliefs regarding a potential plane crash contribute to a person's attention to flight related stimuli).

Overview of the present study

In the present study, the ABM training aimed to decrease attention for negative stimuli, as well as to increase attention to positive stimuli (i.e., a resilience factor against psychopathology; Johnson, 2009), as described below.

Irrationality related. In light of studies viewing irrationality as a cognitive rigidity marker, we expected the low irrationality group to develop less negative AB on the ABM

task as opposed to the high irrationality group. Moreover, we expected the low irrationality group to develop stronger positive AB in contrast to the high irrationality group.

COMT Val^{158}Met genotype related. In view of findings indicating that Met allele is associated with resistance to psychological interventions, we expect larger negative AB reduction following ABM in Val carriers (i.e., Val/Met + Val/Val genotypes) relative to Met/Met. The Met/Met and Val carrier comparison follows a recessive genetics effect of the Met allele. This genotype grouping matches previous studies (e.g., Lonsdorf et al., 2009, 2010).

For these aims, we used an ABM procedure (Dandeneau & Baldwin, 2009), that trained attention to positive stimuli and was delivered online. The online format was intended to increase ABM's accessibility and ecological validity. Additionally, we investigated pre-training differences in trait anxiety and depression, which could account for variability in response to ABM (Eldar & Bar-Haim, 2010).

Method

Participants

We recruited 66 healthy volunteers (age: *M* = 23.318 years, *SD* = 4.517; 87.87% women). Participants had the following genotype frequencies: 0.44, Met/Met (*n* = 29); 0.30, Val/Met (*n* = 20); 0.26, Val/Val (*n* = 17). The study was approved by the University's Board of Review. Volunteers signed an informed consent and received credits for participation.

Instruments

Questionnaires. We used the following instruments: (a) the *Attitudes and Beliefs Scale-Second Edition* (ABS-II; DiGiuseppe et al., 1988; Macavei, 2002) for general core irrational cognitions; (b) the *Trait Anxiety Inventory* (STAI-X_2; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983; Pitariu, Miclea, & Munteanu, 1987) for anxiety assessments and (c) the *Beck Depression Inventory – Second edition* (BDI-II; Beck, Steer, & Brown, 1996; David & Dobrean, 2012) for assessing depression levels.

Visual Search Training Task (VSTT). VSTT was adapted from Dandeneau & Baldwin (2009) and was used for ABM training. Participants were instructed to find the randomly presented happy face among 15 angry faces and click on it, as quickly as possible.

Dot Probe Task (DBT). DBT was adapted from Bradley, Mogg, Falla, and Hamilton (1998), and used for AB assessment. A trial consisted of a fixation cross, flanked by a picture pair, followed by a target (":" or "..") replacing one of the pictures. Trials were congruent to angry or happy (i.e., the target replaced the angry face or the happy face) or incongruent to angry or happy (i.e., the target replaced a neutral face). Participants had to press with their dominant hand, as fast as possible, "1" for ": "or "3"for "..".

Genotyping

Following peripheral blood extraction, genomic DNA was extracted from leukocytes using a 300µl blood sample DNA isolation protocol (Wizzard Genomic DNA Purification

Kit, Promega, Milan, Italy). Genotyping was performed via polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) based on Albaugh et al.'s (2010) protocol. A 109-base-pair (bp) fragment was amplified via PCR in a gradient thermocycler (Mastercycler Gradient, Eppendorf, Hamburg, Germany) using *COMT*forward, 5'-CTCA TCACCATCGAGATCAA-3' and *COMT*reverse 5'-CCAGGTCTGACAACGGGTCA-3' primers. Val and Met alleles were determined using RFLP with restriction endonuclease NlaIII. Resulting fragments were visualized on a UV trans-illuminator. The fragment lengths for each genotype were: Val/Val (86 and 23 bp), Val/Met (86, 68, 23, and 18 bp), and Met/Met (68, 23 and 18 bp).

Procedure

First, volunteers gave their informed consent, were genotyped, and filled in trait related measures: STAI-X_2, BDI-II and ABS-II. Second, participants underwent the three steps of the online delivered study: (a) pre-training assessment of AB via DBT, (b) followed by ABM and (c) post-training AB assessment.

Data analysis

AB scores were computed separately for negative and positive biases and extracted from negative-neutral face pairs and positive-neutral pairs. Negative bias scores were computed by subtracting the average reaction time (RT) on negative-congruent trials from the average RT on negative-incongruent trials. Bias scores were similarly computed for happy faces. Positive scores stand for attention to negative (or happy) as opposed to neutral faces.

A sample of healthy volunteers was divided according to initial levels of core irrationality, such that individuals scoring less than the median were grouped into the low irrationality group (N = 33) and individuals scoring equal to the median or higher were grouped into the high irrationality group (N = 33).

Results

Preliminary analyses

Pre-training and post-training bias scores correlated positively and significantly for the negative bias, r (64) = .329, p = .003 and near significance for the positive bias, r (64) = .186, p = .068, cueing to a reliable estimate of attention bias via dot probe. The genotype distribution did not follow the Hardy-Weinberg equilibrium, $x_1^2 = 10.613$, $p = .001$.

In terms of *irrationality*, results revealed differences regarding baseline anxiety (t (64) = 2.553, p = .013, d = .638) and baseline depression level (t (64) = 2.468, p = .016, d = .617). With respect to the pre-training attention bias, there were no irrationality related differences in terms of negative, t (64) = 1.078, p = .285, d = .269, or positive bias, t (64) = -1.009, p = .317, d = -.252.

In terms of *genotype*, there were no differences regarding baseline anxiety (t (64) = -1.470, p = .147, d = -.367), baseline depression level (t (64) = -.852, p = .397, d = -.213) or pre-training positive bias, t (64) = .199, p = .843, d = .049. Interestingly, there were near significance genotype differences in terms of pre-training negative bias, t (64) = -1.913, p = .060, d = -.478. Noteworthy, there were significant genotype differences in terms of baseline irrationality levels, t (64) = 2.304, p = .024, d = .576, with Met/Met scoring higher than Val carriers.

Negative bias

Irrationality. Results indicated no significant main effect of time across groups, F (1, 62) = 2.114, p = .151, η_p^2 = .033, or a main effect of irrationality on bias change, F (1, 62) = .058, p = .810, η_p^2 = 001. Importantly, there was a significant 2 (time: pre–training and post-training) by 2 (irrationality: lower and higher irrationality) mixed ANCOVA interaction effect on AB, *F* (1, 62) = 6.927, *p* = .011, η_p^2 = .100 (see Figure 1).

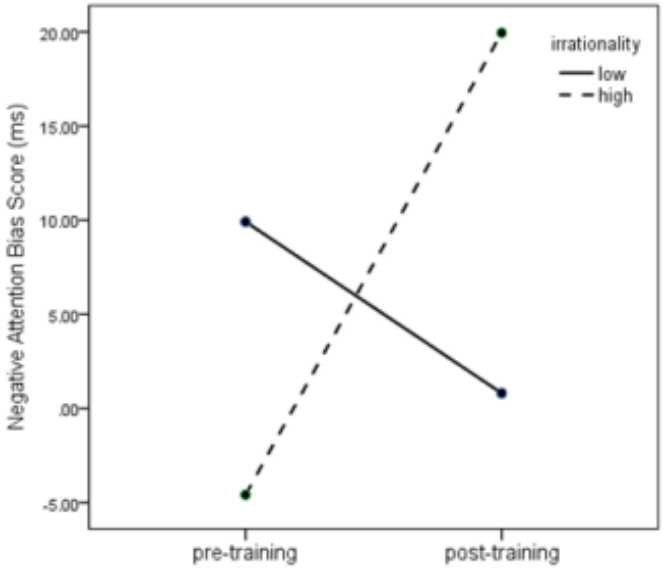

Figure 1. Graphic plot of the interaction between the level of irrationality and time of training with respect to negative attention bias. Higher scores on the ordinate represent higher attention bias to negative stimuli.

Follow-up paired samples t-tests revealed that the AB change (pre-to-post) was significant for the high irrationality group, t (32) = -2.421, p = .021, d = - .421, but not for the low irrationality group, t (32) = .759, p = .453, d = .142. The two irrationality related groups differed significantly at post-training with regard to the level of negative bias, F (1, 61) = 5.886, p = .018, η_p^2 = .088. As a result, after training, the high irrationality group was more negatively biased than the low irrationality group. In other words, the individuals in the high irrationality group had higher negative bias than 69 % of the individuals in the low irrationality group (for a conversion of effect size to percentage, see McGough & Faraone, 2009).

Genotype. On account of marginally significant pre-training genotype differences, we analyzed change in negative bias for each genotype separately. As such, as opposed to Val carriers, F (1, 36) = .305, p = .584, η_p^2=.008, there was a significant change in negative bias in the Met/Met group, F (1, 28) = 4.924, p = .035, η_p^2 =.150, who developed negative bias following ABM. Interestingly, when controlling for covariance with irrationality, there were no longer significant bias changes in the Met/Met group, F (1, 27) = .346, p = .561, η_p^2 = .013, despite an initially large effect size in results.

Positive bias

Irrationality. Results indicated no significant main effect of time across groups, F(1,62) = 1.120, p = .294, η_p^2 = . 018, or a main effect of irrationality on bias change, F (1, 62) = .688, p = .410, η_p^2 = 011. There was no significant 2 (time: pre–training and post-training) by 2 (irrationality: lower and higher irrationality) mixed ANCOVA interaction effect on AB, *F* (1, 62) = .612, *p* =. 437, η_p^2 = .010.

Genotype. Results indicated no significant main effect of time across groups, F (1, 63) = 2.044, p = .158, η_p^2 = .031, or a main effect of genotype groups on bias change, F (1, 63) = .004, p = .953, η_p^2 = 0. There was no significant 2 (time: pre–training and post-training) by 2 (genotype: Met/Met and Val carriers) mixed ANCOVA interaction effect on AB, *F* (1, 63) = .334, *p* =. 565, η_p^2 = .005.

Discussion

This study aimed at investigating the role of genetic (i.e., COMT Val^{158}Met) and general cognitive (i.e., core irrational beliefs) psychopathology markers in differential response to ABM. The results partially supported our hypotheses, revealing some interesting results, detailed below.

Main results regarding irrationality. Concerning change in negative bias, the low irrationality group was less negatively biased following ABM as opposed to the high irrationality group. However, this result is mainly a consequence of the significant change in negative bias experienced by the high irrationality group, which developed a negative bias following the ABM intervention. This finding is in line with recent research in ABM. Though few, there are studies indicating that ABM can be detrimental for some individuals, such as students with moderate to severe depression, which experienced an increase in depressive symptoms after training (Baert et al., 2010).

Concerning change in positive bias, the training of selective attention to positive stimuli was ineffective. There was no significant increase in attention to happy faces across groups or in comparison to each other. One reason why the training was ineffective in changing positive attention bias could have to do with the nature of the task. Though we adapted the task according to previous work (Dandeneau & Baldwin, 2009), standard task requirements may have interfered with the learning process. Given that, while searching for the happy face, the participant was concomitantly exposed to a series of angry faces, to which he/she has to pay attention to in order to find the location of the happy face, it is possible that it took place a priming for negative faces instead of happy faces. This could also explain the detrimental effect of ABM on the high irrationality group.

Main results regarding COMT *Val^{158}Met.* Though in terms of hypotheses we have null findings, there are some interesting patterns in results, detailed in the following.

One interesting result was that, when controlling for the irrationality effect, the initial significant change in negative bias for the Met/Met group turned non-significant. In other words, the significant Met/Met effect on negative bias change was explained only by its covariance with irrationality. It is highly improbable for this genotype-irrationality relationship to be a random result, as there are theoretical frameworks cueing to a biological predisposition to irrational beliefs (Ellis, 1976) and empirical evidences supporting the role of COMT Val^{158}Met as a biological correlate of irrational thinking (see study 4). Therefore, this result signals the importance of considering core irrational cognitions in investigations regarding a differential effect of COMT Val^{158}Met in response to psychological interventions, all the more in interventions where irrational cognitions are a known mechanism of change (e.g., rational emotive behavior therapy; REBT).

This study is not without limitations. *First*, the correlational nature of the design implies a lack of control over environmental distracters, though outlier exclusion should prevent against external influences. *Second*, the participants in our study were unselected healthy volunteers. To strengthen our results, future studies should aim to replicate our findings on clinical samples of socially anxious individuals, for instance, to which interventions with positive and rejecting faces are highly relevant social cues (Straube, Mentzel, & Miltner, 2005). *Third*, we did not include clinical outcomes relating dysfunctional feelings and/or maladaptive behaviors to differential response to ABM; as it was important, before doing so, to explore and to understand the relationships between etiopathogenic mechanisms, and thus to avoid burdening clinical patients. However, future studies should also take into account the whole etiopathogenic chain, thus also including clinical outcomes relating dysfunctional feelings (e.g., anxiety) and/or maladaptive behaviors to differential response to ABM.

Although some of the results are null-findings and, therefore, need to be interpreted with caution, our findings are of relevance to the emergent field of ABM. These results support the idea that trying to change only pathogenic mechanisms (i.e., attention biases), rather than etiologic factors (i.e., irrational beliefs) and/or both etiologic and pathogenic mechanisms, might be inefficient (and/or of short time duration) for people with strong cognitive vulnerabilities (i.e., a high level of irrational beliefs). Based on these findings, future controlled studies should replicate and further investigate the importance of irrationality in the efficacy of ABM.

Study 4. Genetic correlates of irrationality: COMT Val^{158}Met and irrational beliefs[2]

A key mechanism of change underlying response to CBT, in general, and Rational Emotive Behavior Therapy (REBT), in particular, is related to irrational beliefs. Irrational cognitions (i.e., appraisals) are *illogical*, *inconsistent with reality*, and *hinder* the person from achieving his/her goals (Ellis, 1994). Four categories of irrational beliefs are evidenced: (a) *demandingness* (i.e., absolutistic requirements that a person/situation must be in a certain way; DEM), (b) *self-downing* (i.e., global negative evaluations about oneself; SD), (c) *awfulizing* (i.e., beliefs which conceptualize people or events as terrible or the worst thing that could happen; AWF), and (d) *low frustration tolerance* (i.e., beliefs that one cannot tolerate an event/situation; LFT). Unlike irrational beliefs, rational thoughts are logical, empirically based, flexible (e.g., "I prefer not to be laughed at, but I can tolerate it" instead of "I must not be laughed at") and are considered protective factors against psychopathology (Caserta, Dowd, David, & Ellis, 2010).

Core irrational beliefs (B) are relevant for psychopathology because they reflect a general dysfunctional style of thinking (e.g., "It is awful if I have no control") which biases the processing of activating events (A) (e.g., plane flight), generating specific irrational beliefs (e.g., "It is awful that I have no control of the plane flight") that lead to negative consequences (C) (e.g., agitation, anxiety) (see the ABC model - Ellis, 1994). Both core/general and specific irrational beliefs have been linked to several psychopathological disorders, both in an associative and causal manner (for a review, see Browne, Dowd, & Freeman, 2010). They are seen, particularly the core/general irrational beliefs, as cognitive vulnerability factors for psychopathology

While there is preliminary evidence regarding the neural mechanisms underlying specific irrational beliefs (Cristea et al., 2011), little is known about the biological (i.e., genetic) correlates of irrational thinking. There are speculations, dating back to 1976 (Ellis, 1976), regarding biological predispositions to irrational beliefs, but no research has been performed so far.

To further investigate this issue, we chose as a candidate gene for irrational beliefs the catechol-o-methyltransferase (*COMT*) gene, which codes for a dopamine degrading enzyme. One of its variants, a G to A substitution (rs4680) that results in an amino acid change (Val^{158}Met), stirred special interest in psychopathology research. Individuals with 2 copies of the Met allele (Met/Met) have 25–75% reduction in COMT enzyme activity relative to individuals with 2 copies of the Val allele (Val/Val) (Chen *et al.* 2004). This difference has an effect on the regulation of dopamine (Meyer-Lindenberg & Weinberger, 2006), with impact on disorders like anxiety and depression.

In this study, COMT Val^{158}Met was chosen as a candidate gene for irrationality for a number of reasons. *First,* COMT Val^{158}Met was investigated as a biomarker for response to psychological interventions. Research indicates differential response to exposure therapy (Lonsdorf et al., 2010) and fear extinction (Lonsdorf et al., 2009), with Met homozygotes benefiting less from either intervention. *Second*, like irrational beliefs, COMT Val^{158}Met and Met allele, in particular, was linked to a wide range of psychopathology (e.g., anxiety, depression, and schizophrenia). *Third,* recent research indicates a gene-environment interaction, where Met homozygotes display higher anxiety (Lonsdorf et al., 2010) in stressful conditions, as

[2] This study is under review at the Journal of Clinical Psychology. Impact factor 1.668

well as a higher risk to develop post-traumatic stress disorder under low traumatic load. Similar interactions exist between stress and irrational beliefs (David, Freeman, & DiGiuseppe, 2010).

The present study

Considered together, genetic (i.e., COMT Val^{158}Met) and cognitive (i.e., irrational beliefs) psychopathology markers could extend our knowledge regarding the genetic correlates of core/general irrationality. In view of studies which regard the Met/Met genotype as a risk factor for psychopathology, we hypothesized that: Met/Met homozygotes would display more general irrationality than Val carriers (i.e., Val/Val and Val/Met). The Met/Met and Val carriers (Val/Met + Val/Val genotypes) contrast corresponds to a recessive genetics effect of the Met allele. This genotype grouping is in congruence with previous studies (Lonsdorf et al., 2009, 2010).

A-posteriori (i.e., post-hoc), we analyzed genotype differences with respect to core categories of irrational beliefs, that is (a) *DEM (i.e., rigid thinking), (b) SD,* (c) *AWF*, and (d) *LFT*. A second, a-posteriori analysis, regarded COMTVal^{158}Met genotype differences with respect to rationality. All irrationality and rationality related concepts were extracted from the Attitudes and Belief Scale II (ABS-II; DiGiuseppe, Leaf, Exner, & Robin, 1988).

Method

Participants

We recruited 78 healthy Caucasian volunteers (age: M = 23.575 years, SD = 4.983, 85.897% women). Participants had the following genotype frequencies: 0.44, Met/Met (n = 34); 0.29, Val/Met (n = 23); 0.27, Val/Val (n = 21). The study was approved by the Babeș Bolyai University's Review Board. Volunteers signed an informed consent and received credits for participation.

Instruments

Questionnaire. We used the ABS-II (DiGiuseppe et al., 1988; Macavei, 2002) to measure general core irrational cognitions. ABS-II is grouped into the following subscales: *overall irrationality*, *overall rationality*, *DEM* (e.g., "I must be liked by people I want to like me, and I do not accept their not liking me"), *SD* (e.g., "If important people dislike me, it is because I am an unlikable, bad person"), *AWF* (e.g., "It is awful to do poorly at important things, and I think it is a catastrophe if I do poorly"), and *LFT* (e.g., "It is unbearable to fail at important things, and I cannot stand failing at them"). For the purposes of this study, we were interest in all the subscales.

Genotyping. The genotyping protocol is identical to the one present in the third study.

Procedure

Given the correlational nature of the design, volunteers gave their informed consent, were genotyped and then filled in the ABS-II scale, which assessed their general, core rational and irrational beliefs.

Results

The genotype distribution did not follow Hardy-Weinberg equilibrium (HWE), $x_1^2 =$ 12.071, $p < .001$.

A-priori analysis. Between-group t-test analysis revealed significant differences between Met/Met and Val carriers, $t(76) = 2.627$, p = .010, Cohen's d = .602, with Met/Met having higher mean irrationality scores than Val carriers (see Figure 1). In other words, Met/Met individuals had higher irrationality than 73% of the Val carriers (for a conversion of effect size to percentage, see McGough & Faraone, 2009).

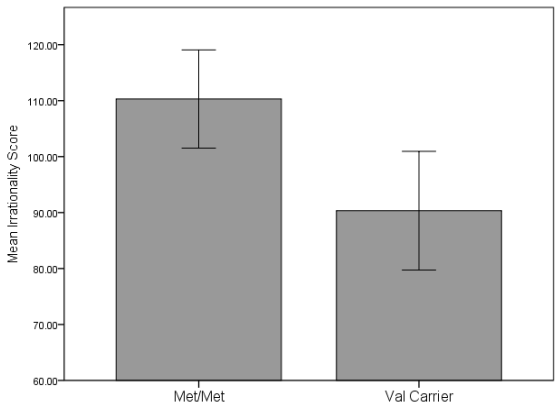

Figure1. Graphic plot of *COMT* Val^{158}Met genotype differences regarding overall irrationality. Higher scores on the ordinate represent higher irrationality values.

A-posteriori analysis. There were initial significant genotype differences with respect to (a) SD(t(76)= 2.544, p = .013), AWF(t(76)= 2.359, p = .021), and LFT (t(76)= 2.952, p = .004), as well as marginal significant differences in terms of DEM (t(76)= 1.851, p = .068). After performing the Holm–Bonferroni correction, genotype differences regarding SD (p = 0.039), AWF (p = 0.042), and LFT (p = 0.016) remained significant. In all categories of irrationality, Met/Met individuals scored higher than Val carriers. With respect to rational beliefs, a-posteriori analysis revealed no significant differences between genotypes, $t(76) = 1.518$, p = .133, d = 0.348.

Discussion

This study aimed at investigating COMT Val^{158}Met genotype differences with respect to core general irrational beliefs. Results supported our hypotheses, showing that Met/Met genotype carriers were more irrational compared to Val carriers. This result is in line with speculations, dating back to 1976, regarding biological predispositions to irrational beliefs (Ellis, 1976).

Furthermore, the biological predispositions to irrationality seem to be distinct from the biological predispositions to rational beliefs (Ellis, 1994). Namely, while irrational beliefs are conceptualized as having biological influences, rational cognitions are believed to depend on

learning and socio-cultural influences. Indeed, the a-posteriori analysis revealed no significant COMTVal^{158}Met genotype differences with respect to rational beliefs.

Additionally, after correcting for multiple testing, there were significant genotype differences with respect to almost all categories of irrationality, except for DEM. Several studies highlight the mechanistic role played by SD in depression, AWF in anxiety, and LFT in self-control problems (e.g., addictions, binge eating, self-harm). Furthermore, there are studies indicating that COMT Val^{158}Met, and Met allele in particular, is related to the same psychopathology spectrum as SD, AWF, and LFT (Albaugh et al., 2010). Thus, these separate lines of research pinpoint to a joint vulnerability to psychopathology. With respect to the marginally significant result, considering that DEM is seen as the core irrational belief from which other irrational beliefs stem from (Ellis, 1994), it may be that it was harder for participants to be aware of the demandingness cognitions. Also, it may be possible that our sample was not powered enough to identify small effect sizes, as in the case of DEM.

To sum up, our findings have important (1) theoretical and (2) research implications. *First*, they contribute with empirical data to theoretical assumptions about biological predispositions to irrational thinking. *Second*, the knowledge that there are genetic differences with respect to irrational thinking provides insights for studies interested in testing the joint influence of these variables in stressful situations. Namely, it would be interesting to measure the distress responses of irrational individuals with Met/Met in contrast to irrational Val carriers in stressful situations. *Third*, although, irrationality is an intermediate endophenotype for psychopathology (i.e., cognitive vulnerability factor), it is a complex concept. Therefore, multifactorial genetic influences are to be expected and tested.

Several limitations should be further addressed. First, the current sample was not within HWE equilibrium. However, we used a genotyping protocol which has been successfully used in previous studies (Albaugh et al., 2010) and all the genotypes were determined in duplicates. As genotyping error seems unlikely, lack of HWE could be very well due to the fact that Met/Met genotype seems to be overrepresented among our participants. Second, we had a rather small sample size for a genetic association study. However, considering that we had a clear main hypothesis and our study was powered enough to identify a medium effect size, it provides some reassurance about the robustness of our findings. Nevertheless, results should be further tested in larger samples, especially to replicate our findings regarding the a-posteriori analyses, where Bonferroni-Holm correction canceled some previously significant results.

Based on these preliminary findings, future studies should replicate and further investigate the importance of COMT Val^{158}Met in irrational thinking. Nevertheless, this study provides the first preview of the genetic correlates of irrationality.

Study 5. Can expectancies provide a mechanistic understanding of ABM's efficacy in social anxiety?

Social anxiety is a highly prevalent and debilitating disorder, accompanying social and occupational impairments and being comorbid to other psychiatric disorders (e.g., Stein & Kean, 2000). Even though there are a number of empirically validated psychotherapies (e.g., Clark et al., 2006; Heimberg et al., 1998), many individuals with social anxiety do not have access to these treatments for a variety of reasons (Olfson et al., 2000). In this respect, one accessible intervention, with promising therapeutic potential, is attention bias modification (ABM). Earlier experimental manipulations of AB indicated that ABM can be effective in reducing emotional reactivity and anxiety levels (e.g., Amir et al., 2009).

One of the hypothesized mechanisms behind successful anxiety reduction following ABM is the reduction of attention bias to threat (AB), the tenet of ABM. Indeed, there are studies reporting on reductions in negative AB, reductions which predicted diminished distress and anxiety in stressful situations (e.g., Amir et al., 2008; See, MacLeod, & Bridle, 2009). However, there are also publications separating change in AB from change in emotional distress (Reese, McNally, Najmi, & Amir, 2010; Baert, De Raedt, Schacht, & Koster, 2010). These mixed findings could be accounted by other explanatory mechanisms of change. One such mechanism is related to expectancies, detailed in the following.

Along with classical conditioning, expectancies are considered to be the mechanism behind the placebo effect (Kirsch, 1997; Milling, 2009). In clinical research there are two types of expectancies which have received empirical attention; these are outcome expectancies and response expectancies.

Outcome expectancy (i.e., the degree to which individuals anticipate benefits from therapy) is considered to be an important predictor of treatment response (e.g., Price & Anderson, 2012). Some authors (DeFife & Hilsenroth, 2011) even argue that positive outcome expectancies are among the most highly relevant factors to influence the early psychotherapeutic process, treatment maintenance, and therapeutic outcome.

Concerning *response expectancies* (i.e., expectations regarding non-volitional responses, like pain or anxiety), Kirsch (1985; 1999) has theorized that response expectancies are self-sufficient to cause non-volitional responses (e.g., anxiety), unmediated by other variables. There is a robust literature supporting the impact of response expectancies on a broad area of non-volitional responses, like distress (Cristea et al., 2011) or public speaking anxiety (Schoenberger, Kirsch, Gearan, Montgomery, & Pastyrnak, 1997).

Overview of the present study

Considering the involvement of expectancy in the efficacy of various therapeutic modalities and considering its relation to anxiety, the present study aimed at investigating outcome and response expectancies as possible mechanisms of change in anxiety reduction following an ABM intervention. We performed this investigation by manipulating the participants' expectancies into positive, negative, or no information about ABM's efficacy. We especially targeted expectancies regarding state anxiety in an impromptu speech task.

Expectancy related differences regarding anxiety in the impromptu speech situation are described below.

Outcome expectancies. We expected the positive expectancy group to experience lower anxiety, in response to the impromptu speech, than the control group (i.e., no expectancy manipulation). Similarly, we expected the negative expectancy group to experience higher anxiety relative to the control group.

Response expectancies. Given that the manipulation of expectancies targets mainly outcome expectancies, we believe that the paper's focus on response expectancies and anxiety has an exploratory nature.

For these aims, we selected a sample of socially anxious individuals (i.e., individuals scoring higher than 30 on the Liebowitz Social Anxiety Scale, LSAS) to whom ABM has been shown to be successful in reducing anxiety. Additionally, we investigated pre-training differences in depression and optimism traits, which could account for variability in response to expectancy manipulations. The results are discussed in terms of *a-priori* and *a-posteriori* analyses, the latter focusing on the overall group of socially anxious individuals.

Method

Participants

Eighty six participants were enrolled in the study (M = 24.09 years, SD = 6.868; 81.385 % women). Out of an initial sample of 250 volunteers, we selected those scoring over 30 on the LSAS scale. Selected participants were randomly distributed in three groups: positive expectancies (N = 28), neutral expectancies (N = 29), negative expectancies (N = 29). Participants signed an informed consent and received credits for participation.

Instruments

Questionnaires. For the purposes of this study, we selected the following questionnaires instruments:

(a) The Liebowitz Social Anxiety Scale, the Self-Report Version (LSAS–SR; Fresco et al., 2001; Liebowitz, 1987) was employed to assess social anxiety via reported fear and avoidance estimates in social interaction and performance situations.

(b) The visual analogue scale (VAS) was used to assess response expectancies and outcome expectancies. VAS regarding response expectancies was formulated in the following manner: "*How anxious to you expect to feel during the speech*". VAS regarding outcome expectancies stated the following: "*How effective do you expect the training to be in reducing the anxiety felt during the speech*".

(b) The short form pertaining to the State version of the State-Trait Anxiety Inventory (mSTAI; Marteau & Bekker, 1992) for state anxiety assessment.

(c) The Beck Depression Inventory – Second edition (BDI-II, Beck, Steer, & Brown, 1996; David & Dobrean, 2012) to assess the severity of depressive symptoms over a two-week time interval.

(d) The Life Orientation Test–Revised Form (LOT-R; Scheier, Carver, & Bridges, 1994) to measure dispositional optimism (i.e., generalized positive outcome expectancies).

Attention bias Modification (ABM). The ABM task used to train attention away from threat (i.e., disgust faces) and it was a variation of the dot probe used by Van Bockstaele et al. (2012). A trial consisted of a cross, on the center of the screen, followed by a pair of faces (neutral - neutral or disgust – neutral). During incongruent trials (i.e., disgust - neutral face pairs) the target appeared on the location of the neutral picture. During neutral trials (i.e., neutral-neutral face pairs) the target (i.e., E or F) could appear on the location of either one of the faces. Participants were instructed to identify, as fast as possible, the target and press the corresponding button. The ABM task was developed in in E-Prime (Version 2; Psychology Software Tools, Pittsburgh, PA).

Procedure

First, LSAS was administered to an unselected sample of volunteers. Based on scores of 30 or higher on the LSAS, we selected a sample of socially anxious volunteers. Selected participants were randomized into three groups: negative expectations, positive expectations, and control. Prior to any expectancy manipulation, participants filled in baseline measures, that is mSTAI, BDI-II, and LOT. Following, participants received expectancy manipulations according to their assigned group, as detailed below.

a) **Negative expectancy**: Numerous scientific studies show that attention training is ineffective in reducing the anxiety experienced by a person during speech.
b) **Positive expectancy**: Numerous scientific studies show that attention training is effective in reducing the anxiety experienced by a person during speech.
c) **Control**: No manipulation of expectancies

In the T1 time point (i.e., immediately after manipulation, but still before training) participants were measured their outcome and response expectancies regarding the anxiety anticipated during the impromptu speech. Then followed the ABM training away from threat (i.e., disgust faces).

In the T2 time point (i.e., immediately before speech), participants were assessed, once again, their outcome and response expectancy levels, having in mind that the speech will follow soon. Also, in this phase, they were given a topic to which they had to express their agreement or disagreement (e.g., "Are you pro or against the legalization of death punishment"). After expressing their opinion on the topic, during speech, participants had to provide arguments in opposition of their initial opinion. Participants were not given time to prepare the speech. Immediately after expressing their opinion regarding the topic, they had to hold a 3 minute speech in front of a video camera. Participants were informed that there would be no interaction with the experimenter and that the recording would last precisely 3 minutes. They were also informed that their performance during speech will be evaluated by a board of experts. Immediately after the speech, participants rated on the mSTAI scale how anxious they felt while performing the speech.

Results

A-priori analyses

Preliminary analyses. There was no significant difference between experimental groups regarding the following potential covariates: baseline LSAS, F (2, 83) = .804, p = .451, η_p^2 = .019; baseline BDI-II, F (2, 83) = 1.527, p = .223, η_p^2 = .037; baseline LOT, F (2, 83) = .122, p =. 885, η_p^2 = .003. Similarly, there was no between group difference regarding baseline levels of state anxiety, F (2, 83) = .053, p = .948, η_p^2 = .001. The impromptu speech task induced, successfully, anxiety across groups from baseline to the anxiety reported during speech, t (83) = -8.475, p < .001, d = -0. 924.

Manipulation check. In terms of expectancy regarding the anxiety during speech, there was no difference between the experimental groups in T1, F (2, 83) = .216, p =.806, η_p^2 = .005, or T2, F (2, 82) =1.953, p = .148, η_p^2 = .045. Similarly, in terms of expectancy of therapeutic gain, there was no difference between conditions in T1, F (2, 83) = .763, p =. 469, η_p^2 = .018, or in T2, F (2, 83) = 2.157, p = .122, η_p^2 = .051. Therefore, the manipulation of expectancies seems to be unsuccessful, despite following an expectancy induction protocol from previous studies (adapted from Bonner & Everett, 1982).

Post-hoc analyses

Part 1

Given the focus on expectancies and given that there was no significant difference between experimental groups; we extended the analyses to the relationship between expectancies and state anxiety in the impromptu speech task. These investigations were performed on the overall group. We investigated, in T1 and T2, whether outcome and response expectancies predicted reported anxiety during the speech task.

Main results

Given the lack of correlation between outcome expectancies and state anxiety during the impromptu speech task, we performed regression analyses for response expectancy only (see Table 1). Accordingly, response expectancy predicted anxiety levels in the speech situation at both time frames (T1, b = .094, t (84) = 6.162, p < .001; T2, b = .103, t (84) = 7.144, p < .001). In other words, in T1 response expectancy for anxiety predicted around 30% from the variance in anxiety during speech (R change = .308), while in T2 it predicted around 40% from the variance in anxiety during speech (R change = .376).

Table 1. Correlations between variables

	1	2	3	4	5	6
1. Response expectancy for anxiety T1	1	.781**	-.078	-.026	.563**	.469**
2. Response expectancy for anxiety T2		1	-.100	-.083	.619**	.505**
3. Outcome expectancy T1			1	.657**	-.155	-.088
4. Outcome expectancy T2				1	-.122	-.034
5. State anxiety during speech					1	.395**
6. Social Anxiety Symptoms						1

Note. **$p < 0.01$; **p < .015 Bonferonni-Holm corrected

Discussion

A-priori results. The present study aimed at investigating the role of expectancies (i.e., outcome and response expectancies) as potential explanatory mechanisms for the reduction in anxiety following an ABM intervention.

Contrary to our assumptions, there were no differences between experimental groups regarding response or outcome expectancies, making it impossible to test discrepancies between expectancies and how they reflect on anxiety during a speech task. Despite using a standard manipulation procedure (Bonner & Everett, 1982), the lack of differences among experimental groups is most probably a result of unsuccessful manipulation of expectancies. One would be that the induction of expectancies was not ecological enough. In every-day life, expectancies are rarely guided by scientific facts or studies, but rather by personal or another person's experience.

Post-hoc results. Given the focus on expectancies, we investigated whether expectancies (i.e., outcome and response expectancies) predicted anxiety in social evaluative situations, like the impromptu speech task. A few interesting outcomes resulted, detailed in the following.

First, response expectancy in T2 (i.e., after training and immediately before speech) was a more accurate predictor of anxiety during speech than response expectancy in T1 (i.e., before training and immediately after manipulations). To be specific, response expectancy in T2 predicted 40% from the variance in anxiety during speech, while response expectancy in T1 predicted around 30% in reported anxiety variance. In both cases, the association was positive; the higher the response expectancy, the higher the anxiety in a social evaluative situation. These findings are in line with previous studies. Though, expectancies have rarely been investigated in anticipation of the stressful event, it is somewhat plausible for the prediction to be more accurate

before the actual stressor since fight-flight responses have already been activated. Similar situations were reported for other predictors, like social anxiety, where increased levels of trait social anxiety predicted stronger anxiety manifestations when a socially threatening situation was present (McNeil, 2001). Moreover, our results are in line with previous results regarding the positive association between response expectancy and anxiety (Vîslă et al., 2013), contributing to the extant literature.

Second, there was no was no significant association between outcome expectancies and anxiety during speech. These null-findings are probably due to (a) a low power to detect small effect sizes and due to (b) a relatively wider range in social anxiety levels (ranging from 30 to 100, with scores over 60 signaling generalized social anxiety disorder). In support of the first argument are the G*Power (3rd version, Faul, Erdfelder, Lang, & Buchner, 2007) analyses which indicate that our sample size was powered to reveal medium to high significant effect sizes and not small effect sizes.

Interestingly, there was no significant association between outcome expectancies and response expectancies. Evidence for the relationship between these two types of expectancies is weak at best. Given the lack of correlation between them and given the different trend in results, one could speculate that these are independent constructs. Therefore, a higher expected level of anxiety might not entail a lower expectancy regarding intervention efficacy. Though this result is a null finding and needs to be treated with caution, it also cues to the importance of assessing both types of expectancies when trying to lower post intervention anxiety.

Several limitations should be further addressed. First, there is the manipulation issue. There are several reasons for which the manipulation was unsuccessful. One would be the method of instruction delivery (displayed on a computer). This is a less ecological manner of delivering information, unlike patient-experimenter interaction, and it could lead to less treatment credibility across all groups. Outcome expectancies are thought to develop from treatment credibility (i.e., how logical and plausible is the treatment) (Hardy et al., 1995). Another reason could be the instruction itself. Though based on a standard procedure, the instructions lacked emotional and personal relevance, namely referring to scientific facts and general facts regarding ABM. Alternatively, presenting the manipulation instruction in a more treatment rationale format could have made the instructions more persuasive. Data indicate that treatment rationale is especially helpful for individuals unsure of their anxiety management skills in stressful situations (Ahmed & Westra, 2009).

Second, the study would have probably benefited from a more restricted selection of socially anxious individuals. Though the selection of socially anxious individuals with scores of 30 or higher on the LSAS is common (e.g., Vîslă et al., 2013) it is still a broad spectrum of anxiety levels which brings diversity amongst individuals and the way they manage their anxiety in stressful situations.

Third, anxiety measurements relied exclusively on self-reports. Since multimodal anxiety assessments provide a more reliable estimate of anxiety (Schwerdtfeger, 2004) further studies should consider using multiple indexes to measure anxiety during speech (e.g., self-report, behavioral, and physiological indexes). Also, a drawback of our self-report anxiety assessment was that it made impossible to measure anxiety levels during speech. Therefore, the anxiety experienced during speech was measured immediately after the speech. However, the significant

difference between baseline state anxiety and state anxiety regarding the impromptu speech task provides reassurance that the anxiety did change, increasing significantly from baseline levels.

Though we were unable to successfully manipulate expectancies, this result does not rule out the influence of these variables on anxiety following an ABM intervention. This argument is grounded on a positive significant association between response expectancies and anxiety in evaluative situations, indicating that the expectations a persons has before training (T1) and after training (T2) are relevant in predicting the actual anxiety in a social evaluative situation.

Post-hoc analyses

Part 2

On a parallel note, (1) considering that there are no differences between experimental groups and (2) considering the relationship between response expectancy for anxiety and state anxiety, we were interested in investigating whether response expectancy for anxiety could mediate the relationship between social anxiety symptomatology and state anxiety in a social evaluative situation. For a better estimate of the relationship between these concepts and for ecological reasons we used response expectancy for anxiety in T2 as a mediator.

Our a-posteriori investigation was performed in light of cognitive (Clark & Wells, 1995) and cognitive-behavioral (e.g., Rapee & Heimberg, 1997) models of social anxiety, in that cognitive processes account for the relationship between social anxiety and state anxiety in evaluative situations. There are several studies in this respect; however, neither study included measures of response expectancy. Therefore, in the current investigation, we sought to extend the research regarding cognitive mediators of the relation between social anxiety and state anxiety in social evaluative situations, hinting to potential a mechanistic approach. The research would be a pertinent scientific contribution, given that in the last decade response expectancy has been less investigated with reference to anxiety.

Data analysis and Main results

To examine the data we used correlational and mediational analysis. Mediational analysis was achieved by means of the Preacher and Hayes (2008) mediation script for SPSS. We ran bootstrapping tests with 5000 re-samples and the bias corrected confidence interval (Preacher & Hayes, 2008). Concerning the effect size, we used the kappa-square (i.e., κ^2; Preacher & Kelley, 2011) as an effect size index. The values suggested for this index should be interpreted in the same fashion as the Cohen's r^2. Correlations between the investigated variables are displayed in Table 1.

The results (see Figure 1) showed that response expectancy significantly mediated the relationship between social anxiety symptoms and speech anxiety, indirect effect = .068, SE = .016, 95% CI = [.039; .104]. The effect size was high, k^2 =. 279, 95% CI = [.165; .403]. Interestingly, when controlling for response expectancy, there was no longer a relation between social anxiety symptoms and speech anxiety, B = .253, SE = .024, p = .294, CI = [-.022; .073].

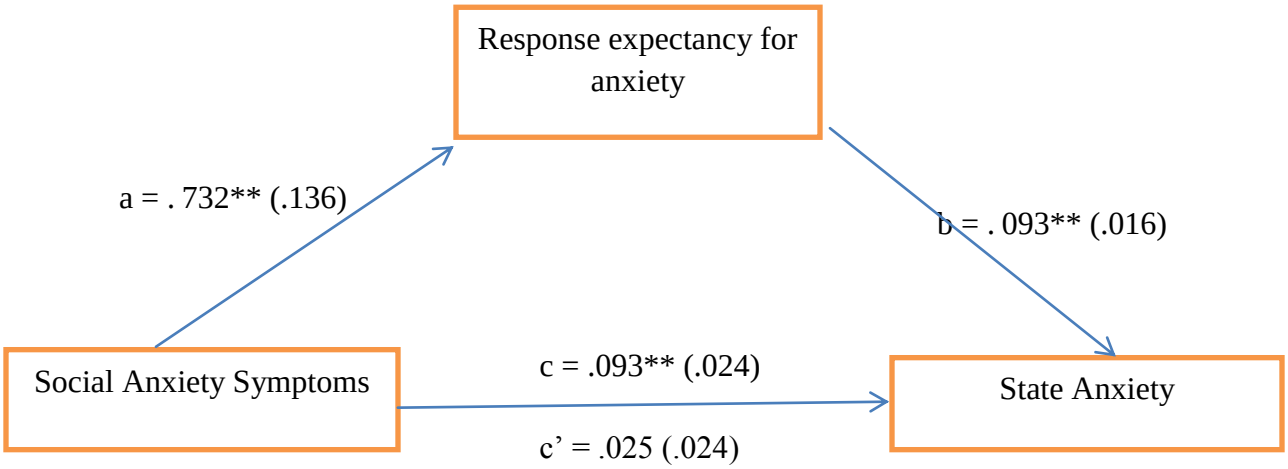

Figure 1. Simple mediation diagram: a, b, c and c' are path coefficients representing unstandardized regression weights and standard errors (in parentheses). The c path coefficient represents the total effect of social anxiety on state anxiety. The c-prime path coefficient refers to the direct effect of social anxiety on state anxiety. All significant paths were marked with **, meaning that $p < 0.001$.

Discussion

This study aimed at investigating cognitive explanatory mechanisms (i.e., response expectancies) regarding the relationship between social anxiety symptomatology and elicited state anxiety, in evaluative situations (i.e., during an impromptu speech task). The results are discussed in the following.

First, the relationship between social anxiety and state anxiety was driven by response expectancies. These findings provide support for researches which argue that in a stressful situation social anxiety is a risk factor, but it is not directly linked to the anxiety experienced in a stressful situation, but rather mediated by another cognitive mechanism (Beard & Amir, 2010; Schulz, Alpers, & Hofmann, 2008). Alternatively, these findings provide an integrative approach to previous results which link response expectancies to anxiety in general and social anxiety in particular, but haven't attempted an explanatory understanding of this relationship in a mediational manner.

Our findings have both theoretical and practical clinical implications. From a *theoretical point of view*, the study is in congruence with cognitive models and cognitive-behavioral models of social anxiety which state that cognitions mediate the relationship between social anxiety and anxious response to stressful situations (Clark & Wells, 1995; Rapee & Heimberg, 1997). Moreover, this result expands the importance of response expectancies in social anxiety, a field of research less investigated in expectancy focused studies. It further reinforces CBT frameworks which aim to alleviate distress in social anxiety, and not only, by targeting/modifying cognitive content and processes.

From a *clinical point of view*, it points to the importance of assessing response expectancies when addressing emotional distress in socially anxious individuals, as modifying response expectancies might lead to alterations in how social anxiety expresses in key situations, like holding a speech. This is especially relevant in the context in which expectancy modification

is proposed as a therapeutic tool by itself (Kirsch, 1990). Furthermore, it validates current clinical practices which adjust expectancies via treatment rationale.

A few limitations should be further addressed. *First*, our approach relied exclusively on self-reports of anxious symptoms. Since multimodal anxiety assessments provide a more reliable estimate of anxiety (Schwerdtfeger, 2004) further studies should consider using multiple indexes to measure anxiety in impromptu speech situations. *Second*, the study, part of a larger research, had a cross-sectional design (see Part 1). Nonetheless, since we did not produce or assess actual changes in our mediator, we cannot draw any causal conclusions. Future studies should address this limitation by using longitudinal designs and by manipulating mediators.

Nevertheless, the current investigation extended research regarding cognitive mediators of the relation between social anxiety and state anxiety in social evaluative situations, hinting to a mechanistic role of response expectancies. The research is a pertinent scientific contribution, given that in the last decade response expectancy has been less investigated with reference to anxiety, leaving this field under investigated.

General discussion

We attempted, on a sample of socially anxious individuals, to investigate the role of expectancies (i.e., outcome and response expectancies) as potential explanatory mechanisms for the reduction in anxiety following an ABM intervention. Contrary to our assumptions, there were no differences between experimental groups regarding response or outcome expectancies, making it impossible to test discrepancies between expectancies and how they reflect on anxiety during a speech task.

Given our focus on the triad social anxiety – expectancies - state anxiety, we reconsidered the relationship between these concepts in the context of an overall group approach. Building on a significant relationship between response expectancies and state anxiety, we analyzed whether response expectancy could have a mediating role between social anxiety symptoms and state anxiety in response to evaluative situations. As such, the relationship between social anxiety and state anxiety was fully driven by response expectancies, providing support for assumptions that anxious vulnerabilities manifest in anxious responses via cognitive mechanisms (Beard & Amir, 2010; Schulz, Alpers, & Hofmann, 2008).

Overall limitations include the lack of a successful manipulation of expectancies in the a-priori section of the study with impact on the a-posteriori analyses, the latter having a cross-sectional nature. Therefore, we cannot draw any causal conclusions from our analyses. Nonetheless, restricting the focus to the mediational investigation, the results hint to a mechanistic role of response expectancies in the relationship between social anxiety and state anxiety in response to distressing situations. Furthermore, it validates current CBT practices which aim to alleviate distress in social anxiety by targeting/modifying cognitive content and processes.

CHAPTER IV

GENERAL CONCLUSIONS AND IMPLICATIONS

The present thesis aimed to approach interdisciplinary the gap between separate lines of research (ABM and exposure) and to inspect each line of research in congruence with its specific gaps in knowledge. We managed to do this by providing an integrative overview of the interplay between attention and exposure, in study 1, and then by investigating each line of research in the following studies. In this respect, several theoretical and clinical advances deserve to be mentioned here.

4.1. Theoretical and clinical advances

Theoretical advances. From a theoretical viewpoint, we enlist the main contributions in this respect.

Study 1 was a meta-analysis which assessed the efficacy of attentionally focused exposure against distracted and attentionally uninstructed exposure regarding distress, behavioral, and physiological outcomes. Some interesting results were that a) distracted exposure was comparable to focused and uninstructed exposure in terms of distress and physiology and b) that distraction outperformed focus in terms of behavioral approach. These results might urge the reconsideration of distraction's role in the efficacy of exposure, at least in comparison to focused exposure.

The 2nd study was designed to examine whether the extinction training conducted during an approximately one hour reconsolidation window (Schiller et al., 2010) would block, as opposed to standard extinction, the reinstatement of extinguished fear related responses (i.e., SCR, attention bias to threat, and evaluative conditioning). The results replicated previous research (Schiller et al., 2010), where the reconsolidation group revealed less fear reinstatement relative to the standard extinction group. These findings further advance the theoretical views that fear memory can be updated and altered.

The 3rd study aimed at investigating the role of genetic (i.e., COMT Val^{158}Met) and general cognitive (i.e., core irrational beliefs) psychopathology markers in differential response to ABM. Main results show that individuals with high irrationality run the risk of becoming more negatively biased than at the beginning of the training, as opposed to low irrationality individuals. In particular, this result bridges a gap between cognitive and cognitive-behavioral lines of research, highlighting the complexity of the relationship between distal (i.e., irrational thoughts) and proximal (i.e., attention biases) cognitive factors involved in psychopathology.

The 4th study investigated COMT Val^{158}Met genotype differences with respect to core general irrational beliefs. The main finding was that Met homozygotes were more irrational compared to Val carriers. The result provides support for theoretical assumptions about biological predispositions to irrational thinking.

The 5th study contributes to theoretical advancements via post-hoc findings. Namely, response expectancies accounted fully for the relation between social anxiety and state anxiety in response to a stressful task following an ABM intervention. From a theoretical point of view, the

study is in congruence with cognitive models and cognitive-behavioral models of social anxiety (Clark & Wells, 1995; Rapee & Heimberg, 1997).

Clinical advances. We name several of the most important clinical advances we found along this project.

In the 1st study, our results indicated that as long as the exposure is extended over multiple sessions and the distracter is interactive, distraction does not impede symptom reduction. These results could lead to a reexamination of the role played by distraction in exposure therapy applied in a clinical setting, at least in terms of specific phobia.

The 2nd study provides clinical advancements, in the field of fear relapse, mainly via its translational potential. Given that it is a successful replication of previous results in terms of physiological reinstatement, like any new potential treatment, fear reconsolidation blockade needs to be tested against established phobic treatments if its clinical utility is to be established.

The 5th study points to the importance of assessing response expectancies when addressing emotional distress in socially anxious individuals. This is especially relevant in the context in which expectancy modification is proposed as a therapeutic tool by itself (Kirsch, 1990).

4.2. General conclusions

To sum up, the following main conclusions may be pointed out in the following:

1) Distraction in contrast to focused exposure could be less counterproductive and even useful to exposure when the distraction task is interactive and exposure is spread over the course of multiple sessions. From an empirical perspective, based on the current evidence, there are no indications that distraction would predispose to symptom return, challenging models of exposure.

2) The blockade of fear reconsolidation paradigm seems to provide robust findings, as we managed to replicate previous research (Schiller et al., 2010). As such, the reconsolidation group revealed less fear reinstatement relative to the standard extinction group. However, the attention bias measurement and evaluative conditioning did not parallel the physiological changes, mainly due to the fact that there was no differential response to the CS's in the acquisition phase. Therefore, we need to modify the conditioning tasks in order to be able to expand results on reconsolidation to other measurements.

3) Individuals with high irrationality run the risk of becoming more negatively biased than at the beginning of the training, as opposed to low irrational individuals. Therefore, knowing who might benefit the most from ABM could spare time, money, and could help to provide focused interventions to those who are likely to benefit from them.

4) The relationship between social anxiety and state anxiety was found to be driven by response expectancies regarding anxiety. This result stresses on the importance of cognitive variables in psychopathology.

5) We found the first cue regarding genetic correlates of irrationality, showing that Met/Met individuals were more irrational compared to Val carriers. This result is in line with speculations, dating back to 1976, regarding biological predispositions to irrational beliefs (Ellis, 1976).

4.3. Limitations and future directions

Methodological limitations. One essential limitation refers to the unsuccessful manipulation of outcome expectancies in the 5th study. This manipulation was ineffective despite adapting a standard procedure from the literature. As previously noted, there are several reasons why the manipulation was unsuccessful. One would be the manner in which we delivered the instructions (displayed on a computer), which is a less ecological way of delivering information. Another reason could be the instruction itself. Though based on a standard procedure, the instructions lacked emotional and personal relevance.

Another general limitation derives from the correlational nature of the 3rd and 4th study. Though these investigations were not designated for an experimental format, their correlational nature limits the conclusions of the current paper. Also, with respect to the methodological limitations, our associative genetics studies had a relatively low number of participants for a genetics paper. However, considering that we had a clear main hypothesis and the results were powered enough to identify a medium effect size (i.e., study 4), it provides some reassurance about the robustness of our findings. Nevertheless, null findings regarding the genetic component (i.e. study 3) should be interpreted with caution and results should be further tested on larger samples before drawing any final conclusions.

Furthermore, with respect to our null findings, we restrict the focus to the 2nd study where we found no fear acquisitions for attention bias and evaluative conditioning. This finding could very well be the consequence of a task particularly focused on targeting fear at a physiological level. Therefore, a basic research study would be required on how to mold the conditioning task to assess fear in a multidimensional manner.

Limitations inherent to the selected samples. An additional general limitation has to do with unequal gender distributions. In all studies there were preponderantly more women than men, which might have obscured some of the potential effects. Moreover, on the subject of sample representativeness, we stress on the fact that we recruited participants mainly from the student community, limiting the generalizability of the findings. To overcome this general limitation, the clear-cut solution is to expand the study to individuals from the community.

Further stressing on the sample characteristics, our second study could have benefitted more from a clinical or subclinical population. A more ecological version, closer to clinical practice and translational applications, would have been to bypass the acquisition stage by selecting already anxious individuals (e.g., spider phobics) who would have to undergo extinction and reinstatement trials specific to the extinction and reconsolidation groups. Future studies should endeavor to preselect their subjects based on anxiety levels, given that the next step is to test blockade of fear reconsolidation in the context of older fear memories.

In spite of its inherent limitations, we trust that the present paper provided answers and insights into some important research questions regarding two of the most investigated associative learning interventions, tapping into their clinical utility and mechanistic views. We also trust that especially via the introductory theoretical background and via the first study we managed to provide arguments that these two interventions could be perceived in an integrated and clinically oriented framework.

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