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Ph.D. THESIS SUMMARY

A MULTINIVELAR ANALYSIS OF VIRTUAL REALITY MEDIATED ATTENTIONAL CONTROL EVALUATION AND ATTENTIONAL BIAS MODIFICATION INTERVENTIONS IN ANXIETY AND DEPRESSION

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Notes._____

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the thesis

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CHAPTER 1. THEORETICAL BACKGROUND

1.1. Introduction and Research Problem

1.1.1. General Framework

The overall objective of the present thesis is represented by our endeavour to evaluate the effectiveness of novel, technologically-augmented interventions in evaluating attention and modifying attentional biases, with the scope to reduce anxious symptomatology. More specifically, through the present work we intended to take a step forward towards a better understanding of evidence-based virtual reality augmented attention bias modification interventions and how these interventions can be employed to alleviate anxious symptomatology.

In this sense, the present thesis was build around four chapters. In the first chapter, we described the theoretical basis and the research limitations that exist in the field. The second chapter describes the specific objectives of the doctoral thesis and the research methodology that was employed in order to meet those objectives. The third chapter details the original research that was conducted, as well the results that were obtained. The fourth chapter we presented the conclusions that were derived from the original research, as well as the theoretical and practical implications. Lastly, we detailed the inherent limitations of the original research and we suggested possible avenues for future research.

1.1.2. Understanding executive functioning and cognitive biases in general, with a focus on attentional control and attentional bias

Anxiety and depressive disorders represent the most prevalent mental health disorders, with 3.94% of the world population being affected by an anxiety disorder and 3.59% of the world population being affected by a depressive disorder (Dattani et al., 2021). More specifically, between 10% - 20% of adults will seek professional mental health services in any given 12 month period, in relation to a anxious or depressive disorder episode, with more than 50% of them being affected by comorbid second anxiety or depressive disorder episode (Hirschfeld, 2001). The effects of the high rate of comorbidity between anxiety and depression cannot be understated. In general, people that have comorbid anxiety and depressive disorders tend to have a greater illness severity, a higher chronicity, and significantly greater impairment in work functioning, psychosocial functioning, and quality of life (Olfson et al., 1997, Brown et al., 1996, Kessler et al., 1998, Sherbourne et al., 1996, apud Hirschfeld, 2001).

To survive, all individuals must be ready to adapt to ever-changing environments. The term “executive function” refers to the ability to adapt by regulating reflexive reactions to current stimuli, in order to achieve goals that require the manifestation of complex behaviours. Executive function is thought to be a set of higher order cognitive abilities that allow people to plan for the future, exercise self-control, and successfully complete goal-directed behaviour. Directly related to attention as an executive function, attentional control is defined as the ability of an individual to pick what they pay attention to and what they ignore and is mediated primarily by the anterior cingulate cortex. One of the most fundamental assumptions of attentional control theory is that knowing how anxiety affects attentional

performance requires understanding the effects of anxiety on attentional processes. One suggestion is that worry can impair attentional control via a process that alters the balance between the goal-directed and stimulus-directed attentional systems, with the stimulus-driven attentional system having a far greater effect (Eysenck et al., 2007). More precisely, deficits in neurocognitive functioning are associated with anxious/depressive symptomatology, with an abundance of evidence highlighting the role of impairments in attentional control (Eysenck et al., 2007; Pacheco-Unguetti et al., 2011; Rock et al., 2014). The evidence that supports this hypothesis comes from research focused on cognitive biases, more specifically from studies investigating attentional biases (Eysenck et al., 2007). Specifically, it has been shown that there is a strong association between attentional control and attentional biases in anxious adults (Derryberry & Reed, 2002). Moreover, attentional control acts as a moderator for the relationship between attentional biases and anxious symptomatology (Campbell & Kertz, 2019; Susa et al., 2012).

The most widely studied cognitive biases, which have been proposed to have causal and disorder-maintaining effects in anxious and depressive symptomatology are attention and interpretation biases.

Attention bias is defined as "the tendency to prioritize the processing of certain types of stimuli over others" (Azriel & Bar-Haim, 2020). More specifically, people can be perceptually confronted with potentially unlimited stimuli from the environment and, because the human cognitive system has limited resources, attention is directed towards certain types of stimuli, while discarding others. When this process takes place in relation to threatening stimuli, it is known as threat-related attention bias. The exact definition of threat-related attention bias has been proposed as "the tendency to prioritize the processing of potential threats over benign stimuli" (Azriel & Bar-Haim, 2020). In other words, when individuals are confronted with a threatening stimulus, they tend to prioritize it, even if other types of stimuli are present in the environment and competing for attention, such as neutral or positive stimuli.

The scientific evidence for the link between anxious symptomatology and attention bias to threat has largely been derived from research approaches involving the dot probe task (MacLeod et al., 1986). This computerised task consists of a large number of trial repetitions. In each trial, the participant observes a series of events, namely: 1) a fixation cross that has the role of directing the participant's gaze towards the computer screen; 2) after the fixation cross disappears from the screen, for a short duration (usually 500 milliseconds), a pair of stimuli are presented on the computer screen, one threatening and one neutral (or positive in some research areas); 3) after the stimuli disappear from the screen, a target probe is presented in the location in which one of the stimuli was presented. The participant has to react as fast as he/she can to the target probe, usually by pressing a key and the allocation of attention is determined as a function of the time needed to react to the target probe. The majority of the studies found that participants with anxious symptomatology respond faster when the probe replaces the threatening stimulus, than when the probe replaces the neutral stimulus (Mogg & Bradley, 1998).

While such a process (an attentional bias to threat) can have certain evolutionary advantages, it can also lead to an oversensitivisation to detecting threat. There is ample evidence for this phenomenon happening in individuals with anxious symptomatology (Williams et al., 1997). Attentional bias has been considered to have an active role in initiating and maintaining anxious symptomatology (Koster et al., 2004), while also being responsible for other changes such as increasing the frequency,

intensity and duration of anxious symptomatology (Azriel & Bar-Haim, 2020). Moreover, it has been demonstrated that having an attentional bias to threat leads to lesser improvements following cognitive-behavioural therapy (Campbell & Kertz, 2019).

Given the causal role of the attentional bias in anxiety disorders, a procedure called attention bias modification training has been developed in order to reduce attentional bias towards threat-related stimuli and, through this mechanism, to reduce anxious symptomatology. More precisely, by taking an alternative route to classical cognitive-behavioural therapies which aim at changing the automatic thoughts through cognitive restructuring and thus reducing anxious symptomatology, the attention bias modification training procedures aim at reducing anxious symptomatology by changing the attentional bias towards threat instead of changing the automatic thoughts (David et al., 2013). Thus, the underlying schema does not produce negative automatic thoughts and the anxious symptomatology is reduced (David et al., 2013). The attention bias modification training is a computerized intervention and makes use of the dot probe paradigm described above for bias modification, while aiming at automatically training alternative way of processing information.

The advantages of such an attention bias modification intervention are immediately obvious. Firstly, the intervention is very easy to deliver, the only equipment needed being a desktop computer or a laptop. The attention bias modification task is relatively easy to build and configure locally using a software such as PsychoPy, Inquisit or Pebl or it can be implemented online via the PsychoPy software or via classical web programming. Moreover, the procedure is wholly automated, with no need for the therapist to intervene during the procedure. These advantages also make attention bias modification procedures ideally suited for being used as an addition to classical therapeutic interventions or as therapeutic homework.

There are also a number of disadvantages that current attentional control evaluation methods and/or attention bias modification procedures are plagued with, among which the most relevant are the mixed results when it comes to therapeutic effectiveness for attention bias modification, and the fact that the procedures themselves are monotone, non-interactive. Firstly, there are mixed findings in the literature when discussing the effectiveness of attention bias modification procedures. With regard to attention bias modification interventions for anxiety disorders, a number of meta-analyses reported small, frequently non-significant, symptom reductions compared to control conditions (Cristea et al., 2015; Heeren et al., 2015), while others reported significant effects of larger magnitude (Linetzky et al., 2015; Price et al., 2016). Moreover, the interventions have only been compared in a pairwise manner, there being no investigation in which cognitive bias interventions for anxious symptomatology are compared simultaneously. Secondly, it has been suggested in previous research that the attentional control evaluation and/or attention bias modification procedures are monotone and can pe perceived as boring by the research participants, as the number of trials increases (Van Ryckeghem et al., 2018). To counter this, a number of solutions have been proposed. On one hand, one suggested solution would be to augment the interest towards the task by employing motivational elements such as a reward for appropriate performance or introducing gamification elements such as a points system (Dennis & O'Toole, 2014; Karoly & Crombez, 2018). On the other hand, an alternative solution would be to perform the attentional control and/or attention bias modification training by using a similar to real-life context. For example, in the case of attention bias modification for pain, it has been proposed to use cues of

actual pain stimuli, rather than semantic representation of pain (i.e., words that are often associated with the sensation of pain or images suggestive of pain) presented in a safe context (Karoly & Crombez, 2018; Van Ryckeghem & Crombez, 2014). In the case of anxiety disorders, an adaptation of the aforementioned proposal would not be very feasible. An alternative approach would be to change the medium primarily, rather than the stimuli, namely to implement the training in such a way that it can be performed in a augmented / virtual reality medium that can be built and customised to resemble real-life contexts and scenarios.

1.1.3. Understanding virtual reality interventions

Ivan Sutherland created the Ultimate display in 1965, which had the first computer-generated interface, allowing people to interact with VR in real time (Sutherland, 1965).

Since then, virtual reality interventions have been used in for a broad range of therapeutical targets, either as standalone interventions or as components of composite therapeutic plans. Empirical research was conducted to evaluate the efficacy of virtual reality interventions for mental health symptomatology such as fear of flying (Hodges et al., 1996; Wiederhold & Wiederhold, 1998; North & Rives, 2003), fear of driving (Kaussner et al., 2020), fear of heights (Rothbaum, Hodges, Kooper, et al., 1995; Rothbaum, Hodges, Opdyke, et al., 1995; North et al., 1996a), agoraphobia (North, North, & Coble, 1995b; North, North, & Coble, 1996b), claustrophobia (Booth & Rachman, 1992; Botella et al., 1998), fear of public speaking (Harris, Kemmerling, & North, 2002), autism spectrum disorder (Strickland, 1996), body experience in eating disorders (Riva, 1997), posttraumatic stress disorder (Rothbaum et al., 1999; Rizzo et al., 2010), obsessive-compulsive disorder (North & North, 2000), attention deficit hyperactivity disorder (Rizzo et al., 2000). Specifically, virtual reality therapy for anxiety disorders has primarily arisen as a practical alternative to imaginal and in vivo exposure, treatments that, despite their undeniable effectiveness, are not usually adopted due to being perceived by both patients' (Garcia-Palacios et al., 2007) and even therapists' (Schumacher et al., 2017) as invasive. Moreover, the research that was conducted until now to investigate the efficacy of virtual reality interventions has revealed promising results. One of the first meta-analysis conducted in this sense (Parsons & Rizzo, 2008) has indicated that the effect sizes in favour of virtual reality as compared to agglutinated control groups were very high, from 0.87 for post-traumatic stress disorder to 1.79 for panic disorder with agoraphobia. Another pioneer meta-analysis (Powers & Emmelkamp, 2008) has revealed that 1) therapies involving virtual reality were more efficient than control groups (all types mixed together), with a large effect size of $d = 1.11$, 2) therapies involving virtual reality were more efficient than control groups with regard to general distress measures ($g = 0.5$), cognitive measures ($g = 1.30$), behavioral measures ($g = 1.27$) and psychophysiology measures ($g = 0.68$). Finally a more recent and rigorous meta-analysis (Opriș et al., 2012) has identified 1) a large effect size in favour of virtual reality interventions as compared to wait-list ($d = 1.12$), a result that had stability in time (at follow-up) and 2) the fact that there is a direct connection between dosage and response, namely that the number of virtual reality sessions is a statistically significant moderator of the effect size, namely the effect size increases linearly with the increase of the number of sessions. In conclusion, it would seem that virtual reality interventions are effective compared to "passive" control conditions and at least as effective as "active" control conditions.

Virtual reality interventions come with a series of advantages and disadvantages however, that have to be weighted before being employed in a treatment scheme. Among the advantages, without being exhaustive, we can mention the fact that simpler virtual reality environments can be developed and implemented on smartphones, thus circumventing the need for very expensive computer configurations. Another advantage is represented by the fact that virtual reality therapy has the potential to have high ecological validity, be very immersive and immersion (i.e., quantity and quality of sensory data that is perceived from the virtual reality environment) directly determines user presence (Cummings & Bailenson, 2016). Presence has been defined as the patient's sense of "being there" in the virtual environment (Slater & Wilbur, 1997), a construct that has been shown to be associated to therapeutic effectiveness (Price, 2011). Moreover, virtual reality applications have the potential to give, as an output, objective metrics of treatment effectiveness, such as total scores, points, number of errors and so on, providing alternative avenues of treatment efficacy exploration, beyond the classical clinician-rated and/or self-report instruments. Among the disadvantages of virtual reality therapies, again, without being exhaustive, we can mention cyber sickness (i.e., nausea induced by the virtual environment, caused by motion in the virtual environment) and cost-effectiveness, in the sense that complex virtual reality environments (in terms of visual / auditory attributes and interactivity) can be run only on relatively expensive hardware configurations.

1.1.4. Virtual reality attentional control evaluation

Usually, attentional control has been evaluate using pen and paper methods such as the Trail Making Test (TMT) and computerized tasks such as the Continuous Performance Task (CPT). Having taken into consideration the limitations described above (i.e., the classical evaluation methods are considered to be monotone, non-interactive), new lines of research have pursued in order to investigate if virtual reality-based evaluation of attentional control can represent a feasible and efficacious alternative. For example, a meta-analysis investigating the convergent validity of virtual-reality-based neurocognitive assessment, indicated that there was a medium association between virtual reality measures and classical or computerized measures. (Neguț et al., 2015). However, it has been posited that virtual reality-based evaluation tools can be more difficult than pen and paper or computerized evaluation tools, because they require additional cognitive resources to cope with the virtual environment and associated peripherals (Neguț et al., 2016). Indeed, a meta-analysis that investigated the task difficulty of virtual reality-based evaluation tools as compared to classical methods of evaluation, found that the evaluation tasks that are embedded in a virtual environment are more difficult, requiring more cognitive resources than classical evaluation methods (Neguț et al., 2016). Some limitations are that both meta-analyses focused on executive functions in general, without distinguishing attentional control. Moreover, the studies that were included in these meta-analyses focused on healthy participants or a narrow clinical spectrum (i.e., attention deficit hyperactivity disorder, schizophrenia, traumatic brain injury), with healthy participants usually being the norm. Or as we know and mentioned above, deficits in neurocognitive functioning are associated with anxious/depressive symptomatology, with an abundance of evidence highlighting the role of impairments in attentional control. Nevertheless, to our knowledge, there are no studies that investigated the comparative discriminatory power of virtual reality-based attentional control evaluation, as compared with

classical, computerized and/or pen and paper methods, with regard to in anxious and/or depressive symptomatology.

1.1.5. Virtual reality attention bias modification

When speaking about attention bias modification procedures in virtual reality, the literature is extremely sparse. To date, there are only two studies that embedded attention bias modification procedures in virtual environments (Urech et al., 2015; Ma et al., 2019). While providing significant and very informative results with regard to virtual reality-based attention bias assessment and modification, these studies have a series of limitations, respectively 1) the first study was conducted as a proof-of-concept study, adopting a pre-post intervention design, without employing a control group (Urech et al., 2015) and 2) the second study employed no "classical" intervention control group, all groups experiencing VR immersion, the aim of the study being to discern the efficacy of different stimuli dimensionalities. This state of affairs illustrates clearly why more research is needed in the field of virtual reality-based attention bias assessment and modification.

1.1.6. Summary and Concluding Remarks

Anxiety and depression represent major global issues, with a profound clinical, economic and social impact, with more than 7% of the world population suffering of one of these mental health problems at any given time (Dattani et al., 2021). We know that deficits in neurocognitive functioning are associated with anxious/depressive symptomatology, especially impairments in attentional control (Eysenck et al., 2007; Pacheco-Unguetti et al., 2011; Rock et al., 2014), as evidenced by studies in the field of cognitive biases, more specifically from studies investigating attentional biases (Eysenck et al., 2007). We also know that the attentional bias has been considered to have an active role in initiating and maintaining anxious symptomatology (Koster et al., 2004), while also being responsible for other changes such as increasing the frequency, intensity and duration of anxious symptomatology (Azriel & Bar-Haim, 2020). Moreover, virtual reality-based assessment and interventions have matured enough, with a significant corpus of research being conducted in this direction. However, there still are some questions that remain and areas of research that merit further investigation.

Firstly, meta-research conducted until now on the efficacy of virtual reality interventions for anxiety has some limitations, one of the most important ones being that comorbidities were not taken into account when investigating treatment efficacy, or it well known that the presence of depressive symptoms is associated with worse treatment outcomes (Kalin, 2020).

Secondly, with regard to cognitive bias modification interventions for anxiety disorders, the findings of meta-research conducted in order to investigate their efficacy are mixed, some research reporting small or non-significant effects (Cristea et al., 2015; Heeren et al., 2015), while others reporting larger effect sizes (Linetzky et al., 2015; Price et al., 2016). As in the case of meta-research of virtual reality-based interventions, no study took comorbidities into account and the intervention were compared only in a pairwise manner, with some possible combinations or pairings of treatments never being investigated.

Thirdly, even if research regarding the use of virtual reality-based assessment of attentional control has matured and we have some results with regard to discriminatory power in the case of some mental health issues such as attention deficit hyperactivity disorder, we don't know if this type of assessment is effective at discriminating between anxious / depressed individuals and healthy controls and thus, being fit to be potentially employed in the diagnosis process.

Fourthly, the research literature on employing virtual reality in modifying attentional biases is extremely sparse, with only two studies breaching this avenue of research, none of which used a control group that would give more insight into the efficacy of virtual reality-based attention bias modification.

CHAPTER II. RESEARCH OBJECTIVES AND OVERALL METHODOLOGY

Through the present thesis, we aimed to test the efficacy of virtual reality-based procedures for attentional control evaluation and attentional biases modification.

The first major goal of the present research was to investigate the efficacy of virtual reality-based interventions, as compared to passive or active control conditions, for anxious symptomatology and comorbid depressive symptomatology. Given that the empirical evidence in this sense has some limitations and there have been no updates in this sense for a significant amount of time, there is a need for updated research in the form of a quantitative synthesis. For this objective, we conducted a updated meta-analysis of 39 studies, comprising 52 direct comparisons between virtual reality-based interventions and passive or active control conditions, while also investigating potential moderators of the effect size, study quality, publication bias and attrition rates **(Study 1).**

The second major goal of the present research was to investigate the comparative efficacy of cognitive bias modification interventions with regard to anxious symptomatology, depressive symptomatology, comorbid anxious symptomatology and comorbid depressive symptomatology. Given the fact that 1) the interventions have only been compared in a pairwise manner in individual studies, and there being no investigation in which cognitive bias interventions for anxious symptomatology are compared simultaneously in a meta-research framework, and 2) no intervention effects on comorbidities being previously investigated, there is a need for this literature gap to be filled. In this sense, we conducted a network meta-analysis of 85 trials, 65 on anxiety and 20 on depression. **(Study 2).**

Given the fact that the discriminatory power of virtual reality-based attentional control evaluation methods when compared to classical methods has not been investigated for anxious / depressive individuals and healthy controls, in Study 3 we aimed to pursue this **third research goal**. In order to achieve this, we conducted a study in which anxious / depressive individuals and healthy controls performed a virtual reality-based attentional control evaluation task, the computerized equivalent of the aforementioned task and a attentional bias measurement task. We aimed at comparing response times and error rates between these three evaluation methods, with the goal of establishing if the virtual reality evaluation method is better at discriminating between affected and healthy individuals than the classical computerized tasks. We also investigated possible adverse effects, virtual system usability, the level of presence induced by the virtual environment and stress/perceived mental load **(Study 3).**

The fourth major goal of the present research, given the scarcity of the literature in this sense, was to investigate the efficacy of a virtual reality-based attention bias modification procedure, as compared with the classical computerized version, in modifying attentional bias and reducing anxious symptomatology. In this sense, we conducted a pilot randomized controlled trial in which we randomized participants either to the virtual reality-based or computerized attention bias modification intervention. We also investigated possible adverse effects, virtual system usability, the level of presence induced by the virtual environment and stress/perceived mental load **(Study 4).**

CHAPTER III. ORIGINAL RESEARCH

3.1. Study 1: The effectiveness of virtual reality based interventions for symptoms of anxiety and depression: A meta-analysis[1]

3.1.1. Introduction

Virtual reality (VR) has garnered significant attention as a cost-effective tool for delivering psychological treatments (Freeman et al., 2017). Virtual reality exposure (VRE) in particular is considered an effective treatment for several anxiety disorders (David et al., 2013), on par with in vivo exposure/IVE (Gerardi et al., 2010; Opriș et al., 2012), though doubts were expressed about the quality of this evidence (Meyerbröker & Emmelkamp, 2010).

While many narrative reviews and commentaries focused on VR interventions, only three systematic reviews with meta-analyses examined their efficacy in randomized controlled trials/RCTs (McCann et al., 2014; Opriș et al., 2012; Turner & Casey, 2014) and they present certain shortcomings. Included trials were published through 2014 the latest, and many more trials have been conducted since, given VR technology has become more accessible. Outcomes other than anxiety were scarcely analyzed, though data on some of these has been accruing. The effects of VR interventions on treatment attrition remained unclear, with some speculation of possible superiority (Botella et al., 2015; Freeman et al., 2017; Meyerbröker & Emmelkamp, 2010), but no assessment in a meta-analysis.

Only one meta-analysis (Turner & Casey, 2014) considered heterogeneity between effect sizes (ESs), but did so only descriptively, without providing a quantification. Assessment of quality (McCann et al., 2014; Turner & Casey, 2014) relied on mixed and potentially inadequate tools that included items not linked to any type of trial bias (e.g., treatment fidelity) (Armijo-Olivo et al., 2013), thereby potentially confounding the relationship between study quality and treatment effects. Only one meta-analysis (Turner & Casey, 2014) considered publication bias, with conflicting results between the assessment methods used (Egger's test and fail-safe N). Moreover, many VR trials are conducted on a small number of participants, which exposes meta-analyses to "small study effects" (Sterne et al., 2000), the notion that smaller studies show different, often larger, treatment effects than large ones. Few potential moderators were examined, with generally contradictory results regarding treatment intensity, or the type of comparison group. One yet uninvestigated potential moderator regards the involvement of developers of VR tools and interventions in the trials, as these are often for-profit developments.

Consequently, we report a meta-analysis for the effectiveness of VR-enhanced interventions in RCTs, for symptoms of anxiety and depression, as well as treatment attrition, along with assessment of risk of bias, heterogeneity, and potential moderators.

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[1] This study has been published
Fodor, L. A., Coteț, C. D., Cuijpers, P., Szamoskozi, Ștefan, David, D., & Cristea, I. A. (2018). The effectiveness of virtual reality based interventions for symptoms of anxiety and depression: A meta-analysis. Scientific Reports, 8(1), 10323. https://doi.org/10.1038/s41598-018-28113-6

3.1.2. Methods

Identification and selection of studies

A literature search of PubMed, PsycInfo, EMBASE and Cochrane Central Register of Controlled Trials databases was conducted through May, 2015, updated in March, 2016 and subsequently August 2017, using the keywords "virtual reality", "therapy", "exposure", "intervention", "treatment" and a filter for randomized trials. We also searched the references from the most recent systematic reviews and meta-analyses.

Studies were included if they were a) RCTs comparing b) a VR-enhanced intervention to a control or an active psychological intervention for c) adults, d) measuring outcomes related to depression and anxiety, and e) published in peer-reviewed journals. We included studies comparing a VR-enhanced condition with controls (e.g., waitlist, placebo, treatment-as-usual) or active conditions not employing VR.

Risk of bias and data extraction

We used four criteria from the Risk of Bias (RoB) assessment tool, developed by the Cochrane Collaboration (J. P. T. Higgins et al., 2011), which assesses possible sources of bias in RCTs. The following domains were rated: a) the adequate generation of allocation sequence, b) the concealment of allocation to conditions, c) the prevention of knowledge of the allocated intervention (blinding of assessors) and d) the adequate addressment of incomplete outcome data. We also computed an overall RoB score for each study by awarding 1 point for each bias source rated as low risk.

We also extracted a series of variables from the included studies. Details about the interaction with the virtual environment were extracted from the methods sections describing the intervention or the technology used. For each trial, we noted (1) which elements the interaction with the VR environment relied upon (e.g., visual, sound, haptic) and (2) whether or not the authors had explicitly assessed sense of presence or immersion in the trial with validated or ad hoc instruments. We also quantified the first component by tabulating the number of interaction elements each study employed, as a very crude indicator of the degree of interaction.

The involvement of a developer was coded using the information available in each trial, at the section of the method that described the VR therapy package used. If authors of the VR package were not listed in the original article, we independently searched the web for the specific VR program or package used in order to identify its authors.

Meta-analyses

We computed and pooled the individual ESs with Comprehensive Meta-Analysis (CMA version 3.3.070) and Stata (Stata SE, version 15).

For anxiety and depression, we calculated the standardized mean difference (SMD) at post-test and follow-up, by subtracting the mean score of the comparison group (control or active treatment) from the mean score of the VR-enhanced group, and dividing the result by the pooled standard deviation of the two groups. We report the indicator corrected for small sample bias (Hedges et al., 1985), Hedges' g. We also

transformed the SMD into number needed to treat (NNT), using the formula of Kraemer & Kupfer (Kraemer & Kupfer, 2006). The NNT represents the number of patients that would have to be treated to generate one additional positive outcome (Laupacis et al., 1988).

Given the considerable variability among outcomes measures, we grouped them into anxiety and depressive symptoms. These included all such outcomes, whether measured by general or disorder-specific scales or subscales. As anxiety outcomes were sometimes measured for individuals without an anxiety disorder, we also conducted sensitivity analyses restricted to patients with one such disorder, diagnosed with a clinical interview or by use of a cut-off at a symptom scale. When a study used multiple measures from the same category, the average ES was computed using the CMA procedure (Borenstein et al., 2009) that assumes a correlation of 1 between outcomes. Since the correlation is probably less than 1, this approach is conservative (Scammacca et al., 2014). ITT (intent-to-treat) data were preferred where available. If means and standard deviations were not available, we calculated the SMD from other statistics available in the study, such as t-values or exact p-values, using the standard formulae in the program (Borenstein et al., 2009). If data was still insufficient for ES calculation, a request was sent to the study authors.

Drop-outs were defined as all randomized participants not finishing treatment, regardless of the reasons. Odds ratio (ORs) indicated the odds of participants dropping out from the VR versus the comparison group, with sub-unitary ORs indicating smaller odds for drop-out in the VR group.

We conducted sensitivity analyses excluding outliers and, respectively, excluding studies with a small number (N) of participants.

Heterogeneity was assessed with the I^2 statistic, with values of 25%, 50% and respectively 75% indicating low, moderate and high heterogeneity (J. P. T. Higgins et al., 2003). We calculated 95% confidence intervals (CI) around I2 (J. P. A. Ioannidis et al., 2007), using the non-central χ2-based approach (Orsini et al., 2006). For categorical moderators, we conducted subgroup analyses using the mixed effects model, which uses a random-effects model within subgroups and a fixed-effects one across subgroups (Borenstein et al., 2009). For continuous moderators, meta-regression analyses employed a restricted maximum likelihood model with the Knapp-Hartung method (Borenstein et al., 2009).

We investigated small study effects and publication bias using a variety of methods. We resorted to visual inspection of the funnel plot, and contour enhanced funnel plots (Peters et al., 2008), where contour lines indicate regions where a test of treatment effects was significant for various established levels for statistical significance. We also employed statistical tests for small study effects. In the case of continuous outcomes, we conducted Egger's test (Egger et al., 1997) for the asymmetry of the funnel plot and corresponding Galbraith plots (Galbraith, 1988) if the test indicated significant asymmetry. We also used the trim and fill procedure (Duval & Tweedie, 2000) as a complementary method to adjust for potential publication bias or small study effects. For drop-out rates, as these were binary outcomes pooled with the ORs, we used the Harbord test (Harbord et al., 2006).

3.1.3. Results

Selection and inclusion of studies

The search generated 1394 records (720 after duplicate removal). We excluded 374 records based on abstract inspection and examined the full-texts for 346 articles. Figure 1 reports the flowchart of the inclusion process following the PRISMA guidelines (Moher et al., 2009). Subsequently, 42 trials met our inclusion criteria, six of which had insufficient data for ES calculation. Following contact with the original authors, we obtained data for one study. For two others, the author confirmed the samples overlapped with those from larger included studies. For 3 remaining trials, authors did not provide data, thus leaving a total of 39 trials in the meta-analysis.

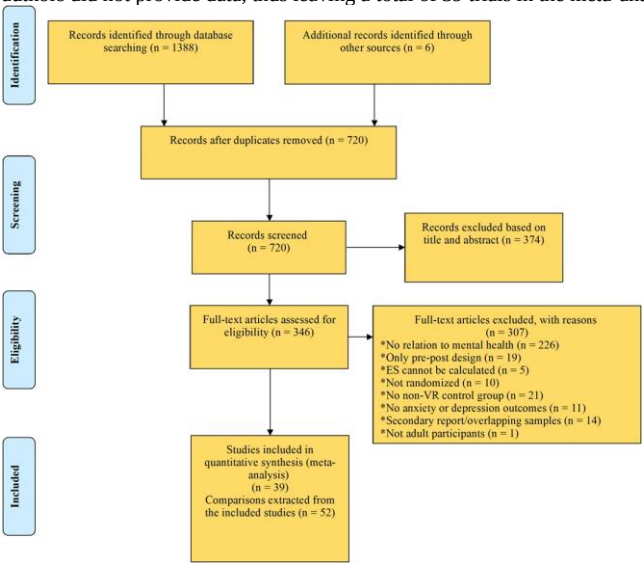

Figure 1. PRISMA flow-diagram of the study selection process

Characteristics of included studies

The 39 RCTs included 52 relevant comparisons, with 869 participants in the VR-enhanced condition, and 1122 in the control or active treatments ones. The most frequent conditions were anxiety and anxiety-related (e.g., PTSD) disorders (31 studies). The most frequently used VR therapy was VR exposure (VRE) (in 21 out of the 39 RCTs), followed by VRCBT (in 19 out of the 39 RCTs). The number of VR sessions ranged from 1 to 16. The most used VR device was the head-mounted display (HMD) (35 studies). Apart from visual feedback, the majority of studies included sound (27 studies) or some form of navigation (18 studies). Only 6 trials explicitly assessed presence or immersion in the virtual environment. In most cases, developers of the VR program used were also among the authors (27 studies).

Risk of bias of the included studies

Most trials had uncertain or high risk of bias for three domains. Four RCTs had low RoB on all four domains. Nineteen studies were rated low RoB in only one domain.

VR-enhanced therapy compared to a control condition

For anxiety outcomes, twenty-three RCTs were pooled, g = 0.79, 95% CI 0.57 to 1.02, NNT = 2.36, with substantial heterogeneity (I^2 = 59%, 95% CI 35 to 74). Analyses restricted to participants with an anxiety disorder (17 comparisons) led to slightly smaller estimates: g = 0.72, 95% CI 0.51 to 0.94, NNT = 2.56, with similarly substantial heterogeneity (I^2 = 58%, 95% CI 28 to 76). Exclusion of three potential outliers led to a small decrease, g = 0.73, 95% CI 0.55 to 0.92, and reduced heterogeneity (I^2 = 36%; 95% CI 0 to 63). Only 7 trials had at least 25 participants randomized in each arm. Their aggregate ES was g = 0.64, 95% CI 0.39 to 0.88, and heterogeneity was still present (I^2 = 42%; 95% CI 0 to 76).

For depression, ten RCTs were pooled, g = 0.73, 95% CI 0.25 to 1.21, NNT = 2.54, with high heterogeneity (I^2 = 71%, 95% CI 45 to 85). Exclusion of one outlier resulted in a sizable decrease, g = 0.60, 95% CI 0.19 to 1.01, I^2 = 62%. Only one trial had at least 25 participants randomized in each arm.

Follow-up outcomes were only reported in two RCTs for anxiety and in one for depression. Seventeen trials reported non-zero drop-outs in at least one group and nine trials reported zero drop-outs in both groups.

Drop-out rates did not significantly differ between the groups, with similar estimations for the Mantel-Haenszel (OR = 1.34, 95% CI 0.95 to 1.89, $\chi 2$ = 3.06, p = 0.08) and Peto methods (OR = 1.37, 95% CI 0.96 to 1.95, $\chi 2$ = 3.06, p = 0.08).

VR-enhanced therapy compared to an active condition

For anxiety, twenty-nine RCTs were pooled, g = −0.02, 95% CI −0.14 to 0.10, with low heterogeneity (I^2 = 20%, 95% CI 0 to 50). Analyses restricted to trials with participants with an anxiety disorder (23 comparisons) also resulted in non-significant effects (albeit slightly more favourable to the non-VR interventions), g = −0.10, 95% CI −0.24 to 0.04, with similar heterogeneity estimates, I^2 = 26%, 95% CI 0 to 55. Results remained comparable after excluding two potential outliers, g = −0.02, 95% CI −0.13 to 0.08, I^2 = 0%, and in analyses limited to trials with at least 25 participants randomized per arm, g = −0.05, 95% CI −0.19 to 0.07, I^2 = 1%.

For depression, thirteen RCTs were aggregated, g = 0.004, 95% CI: −0.20 to 0.21, with low heterogeneity (I^2 = 26%, 95% CI0 to 62). Exclusion of one outlier led to similar estimations, g = 0.07, 95% CI −0.10 to 0.25, I^2 = 0%, as did analyses excluding small N studies, g = −0.03, 95% CI −0.27 to 0.20, I^2 = 0%.

Follow-up anxiety outcomes were reported in 15 RCTs, g = −0.07, 95% CI −0.28 to 0.13, with moderate heterogeneity (I^2 = 40%, 95% CI 0 to 75). Results were similar with the exclusion of one outlier, g = −0.02, 95% CI −0.19 to 0.14, I2 = 8%. Depressive symptoms at follow-up were reported in 5 RCTs, g = −0.19, 95% CI −0.62 to 0.23, with moderate heterogeneity (I^2 = 57%).

Eighteen trials reported non-zero drop-outs in at least one group and ten trials reported zero drop-outs in both groups. Drop-out rates did not significantly differ

between the groups, with similar results for the Mantel-Haenszel (OR = 1.05, 95% CI 0.77 to 1.43, $\chi 2 = 14.06$, $p = 0.66$) and Peto methods (OR = 1.05, 95% CI 0.77 to 1.43, $\chi 2 = 0.12$, $p = 0.72$).

Subgroup and meta-regression analyses

Recruitment setting was a significant moderator for the comparison between VR-enhanced interventions and control ($p = 0.02$) for anxiety, with the smallest ESs for recruitment from army settings and the highest for recruitment from a clinic. The type of anxiety disorder was also a significant moderator ($p < 0.01$), but this result is most likely affected by the high heterogeneity present within some of the small subgroups, as shown by the very large confidence intervals around I^2. Effects were very high for specific phobia (3 trials, $g = 1.79$, 95% CI 0.64 to 2.94) and panic disorder, though the latter was only studied in 2 trials. Effects were also high for flight anxiety (3 trials, $g = 0.82$, 95% CI 0.42 to 1.22). Effects were small for PTSD (4 trials, $g = 0.39$, 95% CI 0.04 to 0.74), and moderate for social anxiety (5 trials, $g = 0.67$, 95% CI 0.25 to 1.09). In the comparison with other active therapies, the type of VR intervention (VRE vs VR CBT) was a significant moderator ($p = 0.02$) for anxiety outcomes. In the subgroup (12 comparisons) where the VR-enhanced therapy was VRE, the non-VR intervention was slightly more effective ($g = -0.18$, 95% CI −0.35 to −0.006). In this subgroup, the non-VR intervention consisted of imaginal exposure (6 comparisons), CBT (2 comparisons) and in vivo exposure (4 comparisons).

Univariate meta-regression indicated significant negative relationships between publication year and both anxiety (slope = −0.06, 95% CI: −0.09 to −0.03) and depression ESs (slope = −0.10, 95% CI: −0.18 to −0.02) in comparison with control conditions, which were maintained in sensitivity analyses excluding outliers. The number of elements of interaction with the virtual environment was positively associated with anxiety outcomes (slope = 0.22, 95% CI: 0.01 to 0.42), but this result did not survive in a sensitivity analysis excluding outliers. For the contrast with other active conditions, publication year, mean age and respectively RoB score were significantly related to anxiety ESs, but only the relationship with age (slope = 0.02, 95% CI: 0.006 to 0.04) survived in analyses excluding outliers.

Small study effects and publication bias

Visual inspection pointed to an asymmetrical funnel for both anxiety and depression. Contour enhanced funnel plots showed that for anxiety, most of the studies with higher standard errors had results overcoming conventional statistical threshold of $p < 0.05$, with a considerable proportion of these even significant at the more conservative threshold of $p < 0.01$. Results were similar for depression though the number of ESs was much smaller. Egger's regression intercept test was statistically significant for both anxiety (intercept = 2.03, 95% CI 0.07 to 3.98, $p = 0.04$) and depression outcomes (intercept = 3.24, 95% CI 0.10 to 6.39, $p = 0.04$). Galbraith plots for anxiety evidenced the same pattern, as studies with low precision (i.e., inverse of the standard error) did not scatter randomly around the regression line, with most of them having effect estimations benefiting the VR intervention. For depression the pattern was inconclusive, probably due to the small number of studies. Finally, Duval and Tweedie's trim and fill procedure also pointed to small study effects for anxiety and depression. For anxiety, adjustment for potentially missing studies ($n = 5$), was

associated with the ES decreasing from 0.79 to 0.62, whereas for depression (n = 3), it rendered the pooled ES non-significant. There was reduced indication of small study effects or publication bias for the comparison with other active treatments, with Egger's test non-significant and no adjustment for missing studies, except for depression.

For drop-out rates, the Harbord test did not indicate small study effects (coeff = 0.16, 95% CI −1.92 to 2.24, p = 0.87). However, it is important to note this analysis may be biased, as it excluded studies with zero drop-out counts in both arms, which were also some of the smaller N studies.

3.1.4. Discussion and conclusions

In the reported meta-analysis, we showed moderate to large effects of VR interventions compared to control conditions (e.g., waitlist, placebo, relaxation, treatment as usual), for anxiety and depression outcomes. The number of studies with follow-up evaluations was too small for a meaningful ES estimation. There was moderate to high heterogeneity and a number of studies with extreme values. Most studies had a small number of participants and there was substantial evidence of small study effects for anxiety outcomes, pointing to potential publication bias. The limited number of studies reporting on depression outcomes precluded us from drawing a meaningful conclusion about small study effects. Adjustment for funnel plot asymmetry, as well as sensitivity analyses excluding outliers or restricted to studies with a moderate number of randomized participants per arm reduced the pooled ES for anxiety, though it still remained moderate to large. Only 7 trials that reported on anxiety outcomes had randomized at least 25 participants in each arm. The persistent evidence of small study effects, as well as the significant heterogeneity, casts doubts over the reliability of the large effects observed for anxiety (Dechartres et al., 2014; J. P. A. Ioannidis et al., 2007; Nüesch et al., 2010). Heterogeneity continued to remain moderate with large confidence intervals even when extreme values were excluded, showing it was not simply the by-product of a few trials. Two thirds of the studies used waitlist controls, and effect sizes were large in waitlist comparisons. Use of waitlist controls might inadvertently and artificially inflate effect sizes for both anxiety and depression outcomes (Cuijpers et al., 2016; Furukawa et al., 2014).

Conversely, compared with established active interventions, effect sizes were non-significant for both anxiety and depression outcomes, at post-test and follow-up. Heterogeneity was small to moderate and there was limited evidence of funnel plot asymmetry or small study effects. Sensitivity analyses excluding outliers or restricted to studies with at least 25 participants randomized in each arm produced similar estimations. There were more trials in the latter category (12) than in the comparison with control conditions (7), but these were still a minority. All but one of the trials were powered to test superiority, not equivalence or non-inferiority (Christensen, 2007), so it would be premature to construe our findings as proof of equivalent effects. Most frequently employed non-VR active interventions were IVE and CBT, both shown to be effective for anxiety and depression, thereby potentially difficult to outperform.

VR-enhanced interventions did not improve attrition, producing similar drop-out rates with control conditions and other active interventions. These findings contradict previous speculation of possible comparative benefit (Botella et al., 2015; Freeman et al., 2017; Meyerbröker & Emmelkamp, 2010).

The vast majority of RCTs of VR interventions had high or uncertain risk of bias across domains. Two previous meta-analyses (McCann et al., 2014; Turner &

Casey, 2014) examined bias using combinations of instruments, which included aspects not linked to any type of trial bias (e.g., training for providers), potentially obfuscating distorting effects. In contrast, we used the Cochrane Risk of Bias tool (J. P. T. Higgins et al., 2011), which evaluates domains likely to distort outcomes. Only four trials could be rated as low RoB on all domains considered, preventing us from reliably assessing the relationship between overall trial risk of bias and outcomes.

Though the presence of the developers of VR interventions among the author pool was not significantly associated with changes in the magnitude of the effects, it is worth underscoring the vast majority of trials did involve such a developer. For instance, for the comparison with control conditions, only five anxiety effect sizes came from independent studies, and 17 from trials involving the developer. As such, it is possible that the insufficient variability in our sample of included trials prevented us from detecting more subtle differences. Moreover, we only examined whether one of the authors had also developed the VR treatment program used, not any potential commercial involvements with VR companies, which could arguably represent a more direct conflict of interest. However, since most articles did not report this information, we could not examine it systematically.

We identified few moderators, owing to the fact most subgroups were small and affected by high heterogeneity within the group. Recruitment setting seemed to have an influence on ESs in comparisons between VR-enhanced and control conditions, with smaller effects for recruitment from army settings, but this may also be a spurious result since some of the subgroups contained a very limited number of studies. Type of anxiety diagnosis also appeared to be a significant moderator, with high effects for specific phobia and flight anxiety, and moderate or small effects for social anxiety and PTSD. The type of active comparison intervention used appeared to matter, with VR-enhanced exposure having slightly smaller effects than non-VR interventions.

Publication year was consistently negatively associated with outcomes, though reasons for this trend remained unclear. A rise in larger or lower risk of bias trials seems unlikely given we observed few such trials. The apparent decrease in effectiveness with the passing of time might also be a by-product of the early use of pilot, low powered studies where only large effects can overcome the significance threshold, a strong initial publication bias for positive findings, as well as time lag bias, whereby studies with positive results are published first and dominate the field, until the negative, but equally important, studies get published (J. P. T. Higgins & Green, 2011; J. P. Ioannidis, 1998).

From the standpoint of dissemination and implementation, our results leave several open questions. Virtual reality enhanced interventions had moderate to large effects compared to control conditions, though these effects were likely inflated by several factors in the design and implementation of the trials. We could find few differences with other active interventions. These might be construed as evidence VR-enhanced interventions could be added to the armamentarium, as another effective choice available to clinicians and patients.

However, other key aspects remain unclear. Though it would be intuitive to consider VR-enhanced interventions as more cost-effective than traditional anxiety treatments, notably in vivo exposure, research substantiating this claim is missing. Moreover, it might hinge on the specific disorder targeted. For instance, for flight anxiety it may seem evident that it would be more cost-effective to conduct VR-enhanced exposure than buy a plane ticket for in vivo exposure. Conversely, for height

anxiety, it could be more cost-effective to scale a flight of stairs with a patient, than to purchase a HMD system and pay for the software development of a fully immersive VR environment. Nonetheless, this kind of tailored, immersive and sophisticated technology does not seem to be used much, even in recent trials, further complicating a realistic calculation of cost-effectiveness. One might also argue VR-enhanced interventions might be particularly suitable for disorders where other active interventions have been less effective.

Most importantly, many existent trials are poorly reported and exposed to bias. The effort to move forward should primarily focus on elevating the quality of VR trials. Larger trials minimizing risk of bias by prospective registration and transparent and complete reporting, as well as using credible control groups, are necessary. A recent ongoing trial described in a published protocol is one such example (Miloff et al., 2016). Trials should also report cost-effectiveness analyses in an attempt to clarify whether and under which conditions are VR-enhanced treatments cost-effective. Moreover, given the predominance of trials conducted by developers of VR treatments, independently conducted trials are also critical. It is essential that negative results are afforded journal space in order to tackle potential publication bias.

3.2. Study 2: The efficacy of cognitive bias modification interventions in anxiety and depressive disorders: a network meta-analysis[2]

3.2.1. Introduction

The current research agenda for psychological treatments recommends moving towards developing interventions mechanistically, by translating experimental findings (Holmes et al., 2018). Cognitive bias modification (CBM) interventions are prototypical examples. These encompass a diversity of approaches with multiple variants in each, such as attention bias modification (ABM), interpretation bias modification (CBMI), or approach and avoidance training (AAT). Across all, a target cognitive bias is manipulated, with participants taught, often without being explicitly made aware, to preferentially attend to, process or otherwise engage with certain types of stimuli (i.e., positive, neutral), while simultaneously avoiding others (i.e., negative, threatening) (MacLeod & Mathews, 2012). CBM interventions are appealing due to accessibility and scalability, as they consist of brief sessions of a computer-based task, possibly administered online.

Nevertheless, the effectiveness of CBM interventions is contentious. Meta-analyses of randomized controlled trials (RCTs) often reached strikingly different conclusions. For the most investigated form (i.e., ABM for anxiety disorders) some meta-analyses reported small, frequently non-significant, symptom reductions compared to control conditions (Cristea et al., 2015; Heeren et al., 2015), while others reported significant effects of larger magnitude (Linetzky et al., 2015; Price et al., 2016). There were fewer trials for depression, with mixed findings (Cristea et al., 2015; Menne-Lothmann et al., 2014).

The diversity of CBM procedures is mirrored by a variety of control groups, rendering the standard for gauging the effectiveness of CBM uncertain. For instance, owing to the computerized tasks, usually not requiring participant awareness, several studies have employed a control condition aimed to function as a "placebo". This "no contingency" or "sham training" control task is identical to the active intervention, without favoring a stimulus type, i.e., positive or neutral stimuli appear as frequently as negative ones. As with placebo, some studies reported benefits for participants randomized to this control arm (Boettcher et al., 2013). Furthermore, it is unclear whether certain versions of CBM are more effective than others for specific symptoms.

Due to the scarcity of studies comparing strains of CBM among each other and with different control groups, these questions cannot be settled in a typical pairwise meta-analysis of direct comparisons. Conversely, network meta-analyses (NMAs) synthesize direct and indirect evidence enabling the estimation of comparative effects even in the absence of trials directly comparing interventions (Leucht et al., 2016).

[2] This study has been published
Fodor, L. A., Georgescu, R., Cuijpers, P., Szamoskozi, Ș., David, D., Furukawa, T. A., & Cristea, I. A. (2020). Efficacy of cognitive bias modification interventions in anxiety and depressive disorders: A systematic review and network meta-analysis. The Lancet Psychiatry, 7(6), 506–514. https://doi.org/10.1016/S2215-0366(20)30130-9

We therefore conducted NMAs to determine the relative effectiveness of CBM procedures (i.e., ABM, CBMI, AAT), compared among each other and with control groups, for anxious and depressive symptomatology.

3.2.2. Methods

Identification and selection of studies

A literature search in PubMed, PsycINFO, EMBASE and Cochrane Central Register of Controlled Trials databases was conducted through February 7th 2020, using the combinations of terms (both as controlled vocabulary thesaurus and free-text) relating to "cognitive bias modification", "attention* bias modification", "attention* bias training", ", "interpret* bias modification", and "anx*", "fear", "depress*", "dysth*", "obsess*", "phob*", "panic", "agoraphob*", "ptsd", "post traumatic", "acute stress", "adjustment disorder". We also inspected references from the most recent systematic reviews and meta-analyses (Cristea et al., 2015; Hallion & Ruscio, 2011; Heeren et al., 2015; Liu et al., 2017). Peer-review publications in English, Romanian, Spanish, Italian, German and Dutch were considered.

Eligible studies were RCTs comparing a CBM intervention to a control condition for anxious or depressive symptom outcomes measured on validated clinical scales, in adults whose primary complaint consisted of symptoms of anxiety or depression, either diagnosed, with a diagnostic interview (e.g., Structured Clinical Interview for DSM-IV) or a validated clinical scale (e.g., Liebowitz Social Anxiety Scale/LSAS), or of subclinical intensity evaluated on a validated clinical scale. Participants with comorbid anxious or depressive symptoms were eligible. Disorders were defined according to the DSM-IV/IV-TR, as recruitment in most trials likely predated the DSM-5. Combination studies of CBM and another intervention were eligible, provided the control group also received the ancillary intervention. Studies contrasting CBM with non-CBM active intervention (e.g., cognitive behavior therapy) were excluded. State measures of anxiety or depressed mood were ineligible because they do not reliably index symptoms of clinical importance.

Data extraction

We extracted information about: (1) Sample: clinical (diagnosed) or subclinical (elevated symptoms); (2) Total number of participants randomized (N); (3) CBM intervention: AAT; ABM; CBM-I; (4) Control condition: Sham training (SHAM), Opposite ABM (OABM); Waitlist (WL); (5) Number of CBM sessions; (6) Delivery: laboratory, home, clinic or combinations; 7) Outcome measures for anxiety and depression; and 8) Publication year.

Primary outcomes

We expected trials to employ multiple outcome measures, hence we pre-specified a hierarchy. For studies reporting both anxiety and depression outcomes, we first considered the investigator-declared primary outcome. If none was identified, we selected it based on the focus of the intervention, e.g., anxiety outcomes for anxiety disorders. Clinician-based instruments were favored over self-report, if available.

Secondary outcomes

As anxiety and depression are highly comorbid (Lamers et al., 2011), we also considered comorbid depression (i.e., in trials of CBM for anxiety disorders) and anxiety (i.e., in trials of CBM interventions for depressive disorders) outcomes.

Risk of bias

We used the Risk of Bias assessment tool, developed by the Cochrane Collaboration (J. P. Higgins et al., 2016), which assesses possible sources of bias in RCTs. The following domains were rated: a) random sequence generation, b) allocation concealment, c) blinding of participants and personnel, d) blinding of outcome assessors, e) incomplete outcome data and f) selective outcome reporting. Domain c) was considered low risk if blinding of participants was attempted, regardless of whether subsequent checks were performed to determine if it was maintained. For domain d), clinician-based measures were prioritized. For self-report, participants were considered their own assessors (J. P. Higgins et al., 2016), with ratings of low risk given if they were blinded to the intervention received. Domain e) was assessed as low risk if all randomized participants were included in the analysis, through the use of an intent-to-treat (ITT) approach or complete data availability. Domain f) was assessed as low risk if primary and secondary outcomes were pre-specified in a prospectively registered protocol or trial registration, with no substantial changes between registration and publication. Retrospectively or non-registered studies were rated as unclear.

Two independent researchers (LAF, RG) extracted outcome data and rated risk of bias, with disagreements resolved by consensus after discussion with another author (IAC).

Meta-analysis

All analyses were conducted in STATA/SE 15 (StataCorp.2017, 2017) (the "network" and "mvmeta" packages (Chaimani et al., 2013; I. White, 2015; I. R. White, 2011)) and R (R Core, 2018) (package "netmeta" (Rucker et al., 2019)).

Means, standard deviations (SD) and sample sizes in each arm were used to calculate between-groups effect sizes (ES) as post-intervention standardized mean differences (SMD) and corresponding 95% confidence interval (CI). The SMD represents the difference in means between the intervention and control arms divided by the pooled standard deviation. ITT data were preferred, when available. If data were insufficient for ES calculation, study authors were contacted. We employed multivariate random effects meta-analysis with restricted maximum likelihood (REML) estimator to conduct four NMAs (one per outcome). We graphically represented results as network plots, whereby the size of the nodes is directly proportional with the number of patients, while the thickness of the lines connecting the nodes is weighted by the number of trials directly assessing the comparison. Additionally, we constructed network plots that incorporated risk of bias for each domain rated, using colored edges to represent low, high and unclear risk of bias. The comparison-specific bias level was set as the rating in the majority of studies in each comparison (i.e., the mode) (Chaimani et al., 2013).

The transitivity assumption was evaluated by visually inspecting relevant study characteristics. Based on previous literature, we considered two potential effect modifiers (number of sessions and delivery setting) and examined their distributions

across comparisons. Network consistency, the extent to which included studies are comparable, both statistically and substantively (J. Higgins et al., 2012), was evaluated with three methods. First, to detect significant overall inconsistency, we used a design-by-treatment interaction model with a global Wald statistic which under consistency follows a $\chi 2$ distribution (Donegan et al., 2013; I. R. White et al., 2012) (non-significant p values indicate no inconsistency). Second, we used a loop-specific approach to estimate the inconsistency factor (IF) in each loop as the absolute difference between direct and indirect estimates, using a Z-test to decide if inconsistency is significant (Veroniki et al., 2013) (i.e., the lower limit of the IF's 95% CI touches zero). Thirdly, we employed a side-splitting method, a frequentist adaptation of the original hierarchical Bayesian method (Dias et al., 2010; Donegan et al., 2013). It reports the estimated direct and indirect treatment effects and their difference, with consistency inferred based on the p-value for the difference.

Contribution plots displayed the differential contributions of direct comparisons to the network summary effect. Interventions were ranked by calculating the surface under the cumulative ranking (SUCRA), which denotes the probability (in percentages) of superior effectiveness for each intervention compared to a theoretical ideal (i.e., always the best without uncertainty) intervention.

Heterogeneity was investigated by displaying forest plots, including summary effects along with their 95% CI and their corresponding 95% prediction intervals (PrI's) for all comparisons. Prediction intervals represent confidence intervals of the approximate predictive distribution of future trials, considering heterogeneity (J. P. T. Higgins et al., 2009). We further conducted three sensitivity analyses excluding studies: (1) employing AAT, initially devised for addiction (Cristea et al., 2016); (2) on PTSD participants, where better outcomes were reported for SHAM than for ABM (Badura-Brack et al., 2015); (3) excluding studies where participants in the SHAM intervention were not exposed to any contingency (e.g., neutral scenarios). We employed network restricted maximum likelihood meta-regression (I. R. White, 2011) using "mvmeta" to examine two possible moderators for the comparison between CBM and SHAM - number of treatment sessions (continuous) and delivery setting (recoded dichotomously as laboratory versus others).

Small study effects were examined through visualization of comparison-adjusted funnel plots and with Egger's linear regression test of funnel plot asymmetry (Egger et al., 1997). Interventions were ordered such that all active interventions were contrasted sequentially to WL, SHAM and OABM control conditions (Chaimani et al., 2013).

3.2.3. Results

The search generated 2125 records (1156 after duplicate removal). We excluded 854 records based on abstract inspection and examined 302 full-texts. The PRISMA flowchart (Moher et al., 2009) (Figure 1) reports the inclusion process. We contacted authors of 8 studies with insufficient ES data and retrieved datasets for 1. Consequently, 82 reports describing 85 separate trials were included in the NMA.

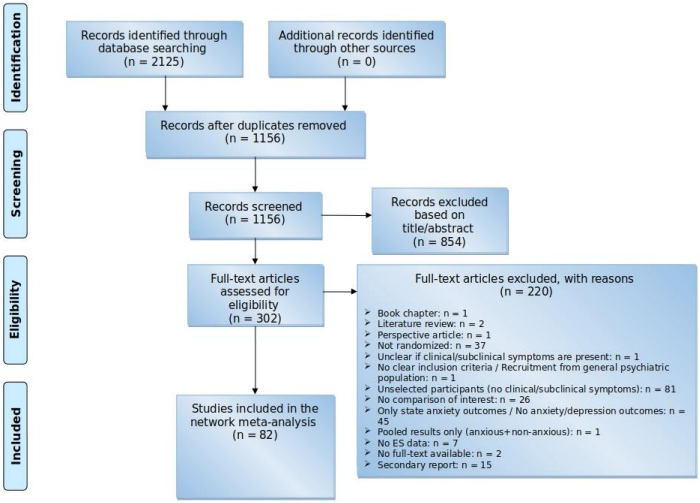

Figure 1. PRISMA flow-diagram of the study selection process

Sixty-five trials (2026 treated and 1871 control participants) focused on anxiety-related disorders, of clinical or subclinical intensity. Twenty trials (544 treated and 572 control participants) focused on depressive disorders or symptoms. Treatment sessions ranged from 1 to 84, with 12 RCTs employing one, and 43 RCTs 8 sessions or more. Most trials employed sham training and directly compared ABM and SHAM. Comorbid depression outcomes were reported in 31 studies (1101 treated, 1070 control participants) on anxiety disorders. Conversely, comorbid anxiety outcomes were present in 11 studies on depressive disorders (250 treated, 251 control).

Most trials had uncertain or high risk of bias for five out of six domains. Four RCTs had low risk of bias for all domains, while six RCTs had low risk for five domains.

For the primary outcome of anxiety, the network plot (Figure 2a) showed a well-connected network, consisting of 8 nodes. The majority of direct comparisons were at unclear risk of bias, except for blinding of outcome assessment (unclear/high) and incomplete outcome data (low). Across methods, there was no evidence for inconsistency. In the NMA, only CBMI significantly reduced the anxiety compared to WL (SMD = -0.55, 95% CI: -0.91 to -0.19) or SHAM (SMD = -0.30, 95% CI: -0.50 to -0.10). However, prediction intervals for these comparisons were large and included 0. SUCRA probabilities indicated that AAT and CBMI presented the greatest likelihood of reducing anxiety outcomes (both ~77%). Egger's test did not detect funnel plot asymmetry, $t(80) = 0.31$, $p = 0.757$.

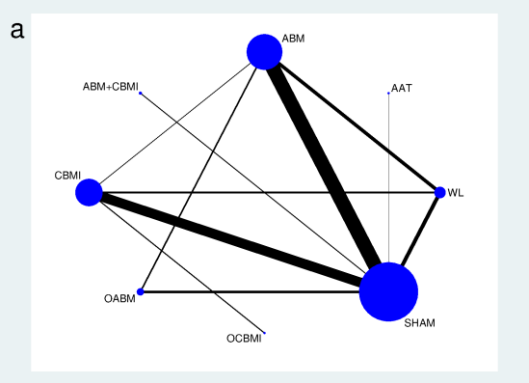

Figure 2a. Network geometry of the CBM interventions for anxiety outcomes

For the primary depression outcome, the network plot (Figure 2b) shows a well-connected network of CBM interventions, except for ABM+CBMI. Across all methods, there was evidence for inconsistency. In the NMA, CBMI significantly reduced depression compared to WL (SMD = -0.63, 95% CI: -1.04 to -0.23). The 95% prediction interval was large and included 0. Other statistically significant differences involved the singly-connected ABM+CBMI node. Egger's test detected funnel plot asymmetry, t(22) = -2.10, p = 0.047.

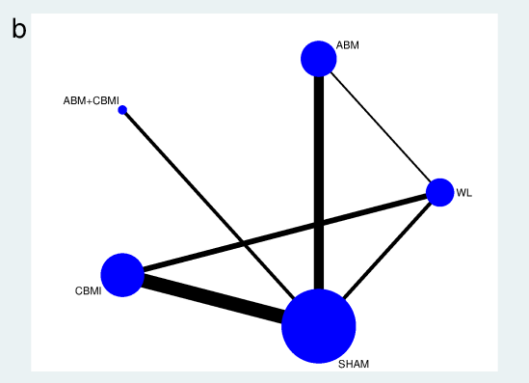

Figure 2b. Network geometry of the CBM interventions for depression outcomes

For the secondary outcome of comorbid depression (in anxiety RCTs), the network plot showed a well-connected network of CBM interventions, consisting of 6 nodes. None of the methods revealed evidence of inconsistency. In the NMA, only CBMI significantly reduced depression compared to WL (SMD = -0.42, 95% CI: -0.68 to -0.15), SHAM (SMD = -0.21, 95% CI: -0.41 to -0.01) and ABM (SMD = -0.24, 95% CI: -0.46 to -0.01). However, all 95% prediction intervals were large and, except for

CBMI versus WL, included 0. Egger's test did not detect funnel plot asymmetry, t(42) = -1.34, p = 0.187.

For the secondary outcome of comorbid anxiety in depression RCTs, the network plot evidenced a well-connected network of CBM interventions, consisting of 4 nodes. The majority of the comparisons were at unclear and high risk of bias. Evidence for inconsistency was mixed, with 2 of the 3 methods indicating inconsistency. The NMA showed no significant differences and Egger's test did not detect funnel plot asymmetry, t(11) = 0.74, p = 0.472.

Post-hoc sensitivity analyses closely replicated the main analyses, with a few differences. With the exclusion of PTSD trials (n=7), ABM significantly reduced anxiety compared to WL (SMD = -0.35, 95% CI: -0.59 to -0.12) and SHAM (SMD = -0.16, 95% CI: -0.28 to -0.04). Excluding trials where SHAM participants were not exposed to any contingency (n= 15), CBMI significantly reduced anxiety compared to WL (SMD = -0.62, 95% CI: -1.07 to -0.18), but not SHAM.

Meta-regression analyses showed that the number of treatment sessions was not significantly related to outcomes. Delivery setting was a significant moderator only for the ABM versus SHAM comparison (beta = 0.44. 95% CI 0.10 to 0.77) for anxiety outcomes.

3.2.4. Discussion and conclusions

In a network meta-analysis of 85 trials, CBM interventions showed limited benefits over control conditions, for both anxious and depressive symptomatology. In 65 trials on anxious participants, CBMI outperformed waitlist or sham training for anxiety outcomes. However, prediction intervals were large and contained the SMD of 0, suggesting that the effects of future similar trials could fluctuate across a wide range of effects. Similar results were reported for comorbid depression outcomes, present in around half of the trials, suggesting that the effects of CBMI might be disorder- rather than symptom-specific. These effects are modest compared to similarly delivered internet-based cognitive behavioral interventions for anxiety disorders (SMDs compared to mostly waitlist control ranging from 0.70 for generalized anxiety disorder to 1.31 for panic disorders) (Andrews et al., 2018). In post-hoc analyses excluding the more inert type of SHAM (neutral scenarios), only differences between CBMI and waitlist remained significant. Few differences emerged among CBM interventions, except for the superiority of CBMI over ABM for comorbid depression.

For ABM, the only significant findings consisted of small effects compared to waitlist and sham on primary anxiety outcomes, in sensitivity analyses excluding PTSD trials. Our definition of anxiety disorders predated the DSM-5, hence including stress-related disorders (all included PTSD trials, relied on the DSM-IV-TR). More generally, findings for ABM corroborate previous meta-analyses reporting very similar estimates (Cristea et al., 2015; Heeren et al., 2015), but contradict others reporting larger effects of ABM for participants with clinical anxiety (Linetzky et al., 2015; Price et al., 2016). A pairwise meta-analysis of 11 studies (Linetzky et al., 2015) showed moderate effects of ABM for clinician-rated, SMD=0.42, 95% CI 0.18 to 0.66, but not self-reported anxiety. In an individual participant data meta-analysis of 13 trials (Price et al., 2016), the authors reported significant effects of ABM on diagnostic remission (OR= 2.57, 95% CI 1.31 to 5.22), but not on the continuous measure, the clinician-administered LSAS. Laboratory delivery was associated with better outcomes for

ABM versus SHAM, corroborating previous reports (Cristea et al., 2015; Heeren et al., 2015).

In the considerably fewer trials on depressed participants (n = 20), only CBMI outperformed waitlist for primary depression outcomes (SMD = -0.57, 95% CI: -0.99 to -0.16). The network geometry revealed one open, singly-connected, node for the ABM+CBMI combination. Aside from a direct comparison with SHAM, the whole evidence for the combined intervention was indirect, rendering the very large effects observed not credible. Hence, the effectiveness of the combined treatment cannot be established. We used a hierarchy of outcomes, favoring the investigator-declared primary outcomes and, barring that, clinician-based over self-report measures. Therefore, it is unlikely that our findings are explained by the choice of measures. Importantly, anxiety trials formed well-connected networks for both anxiety and depression outcomes, with no evidence for inconsistency, making fundamental differences between trials unlikely and further supporting the robustness of the findings.

Few differences emerged among the various control conditions employed. Waitlist was always nominally inferior to sham CBM, supporting the notion that interventions should be compared with more adequate, active control groups (Cristea, 2019). By contrast, a strength of CBM trials is the frequent inclusion of a sham condition, in which participants are not encouraged to preferentially process a certain stimulus type. Analogous to pill placebo, these active control conditions can be targeted (50:50 ratio of targeted versus non-targeted emotional stimuli) or neutral (neutral stimuli) Attempts to blind participants to their group allocations add to the placebo similarity, a rare occurrence in research on psychological interventions. Yet just under half of the trials specifically mentioned participant blinding, with an almost equal number lacking information. Therefore, it is difficult to ascertain whether the sham condition truly remained as such.

The current network meta-analysis aggregates the largest number of CBM trials to date, and has the unique methodological advantage of simultaneously drawing from direct and indirect comparisons. CBMI emerged as promising and could warrant large-scale testing, ensuring blinding of participants and of outcome assessors and avoiding outcome reporting bias. Future trials would also need to clarify whether the intervention should be implemented as stand-alone or added to another, and whether it is cost-effective, given modest benefits observed so far.

3.3. Study 3: The effectiveness of a virtual-reality attentional control assessment task in predicting symptoms of anxiety/depression, as compared with classical computerized neuropsychological and attention bias assessment procedures

3.3.1. Introduction

Anxiety and depression disorders represent the most prevalent categories of mental health problems, with a minimum of 8.2% worldwide prevalence for anxiety disorders and 6.6% for depression, as of 2019 (Twenge & Joiner, 2020). Moreover, when confronted with disruptions to daily life, such as the recent COVID-19 pandemic, it has been shown that these numbers increase more than three-fold, 29.4% for anxiety and 24.9% for depression (Twenge & Joiner, 2020).

One paradigm proposes that deficits in neurocognitive functioning are associated with anxious/depressive symptomatology, with an abundance of evidence highlighting the role of impairments in attentional control (Eysenck et al., 2007; Pacheco-Unguetti et al., 2011; Rock et al., 2014). Effect sizes for comparisons between affected individuals and normal controls were 0.66 for anxiety and between 0.52 and 0.61 for depression (Pacheco-Unguetti et al., 2011; Rock et al., 2014). Traditionally, attentional control has been evaluated by employing pen-and paper (i.e., Trail Making Test) and more recently computerized tasks such as the Continuous Performance (CPT) or Stroop tests. In the case of classical computerised tests, attentional control has been operationalized as 1) response speed to stimuli, 2) sustained attention / vigilance, 3) alertness / arousal and 4) impulsivity / inhibitory control. The response speed to stimuli (i.e., reaction time for correct responses to stimuli) indicates the average time from when the stimulus appears until a reaction occurs (e.g., a button is pressed) for the correct answers. Sustained attention / vigilance (i.e., the standard deviation of reaction time for correct responses to stimuli) indicates the variability of reaction times for the correct answers throughout the test and it is considered a measure of answer consistency. Alertness / arousal indicates if a reaction does not occur when in fact it should have been (i.e., omission errors). Impulsivity / inhibitory control indicates if a reaction occurs when in fact it should not have been (i.e., commission errors).

The classical tests for evaluating attentional control are not without limitations. Firstly, the two aforementioned tests were firstly developed more than 65 (Rosvold et al., 1956) and 86 years ago (Stroop, 1935), respectively, with some authors suggesting that the concepts that formed the basis of these tests are outdated (Eling, P.A.T.M., 2018; Kessels, 2019). Secondly, the computerised tests tend to be lengthy (e.g., a minimum of 25 minutes for CPT) and very specific (e.g., "press the spacebar for every letter that appears on the screen, with the exception of letter X"). Thirdly, and also relating to specificity, these tests have poor predictive and unclear ecological validity (Kessels, 2019).

Especially when it comes to ecological validity, a number of recent technological advances could potentially improve psychological evaluation and treatment. More concisely, evaluation methods in virtual reality (VR) and/or treatments that are augmented by VR have shown great promise (Fodor et al., 2018; Rizzo & Koenig, 2017). The main benefits of VR systems are that 1) they are immersive, without any distractors that could influence the process, 2) they provide a wide range of VR scenarios both for evaluation and intervention, scenarios that especially in case of psychological interventions could not be feasibly replicated in real life, 3) they

provide audio and visual stimuli representing an integrated whole experience (as opposed to separate computer monitors and speakers, for example), 4) the VR scenarios can be modified and applied immediately, based on specific needs (e.g., graduated exposure) and 5) the VR scenarios have the potential to offer a gamified experience, which has been shown to have a significant impact over classical approaches, while reducing treatment attrition (V. W. S. Cheng et al., 2019; Litvin et al., 2020; Pramana et al., 2018).

Another paradigm related to attentional control brings forth evidence for attentional biases (ABM-eval) as having a causal and/or maintaining role in anxiety and depression disorders. Moreover, some aspects of attentional control (i.e., control of attentional inhibition and control of attentional selectivity) have been shown to be strongly related to the magnitude of attentional bias change (Basanovic et al., 2017). While the findings of early studies showed that attentional biases have a causal or maintaining role in anxiety disorders but not in depression (Dritschel, 1992; MacLeod et al., 1986), more recent studies have shown that attentional biases are also present in depression (Mogg et al., 1995; Peckham et al., 2010). More precisely, participants with anxious and/or depressive symptomatology tend to have an attentional bias toward negative stimuli when compared to normal controls (MacLeod et al., 1986; Mogg et al., 1995; Peckham et al., 2010). Two separate meta-analyses have revealed medium effect sizes for the comparison between anxious/depressed individuals and normal controls (Bar-Haim et al., 2007; Peckham et al., 2010). For anxious symptomatology, the effect size was $d = 0.45$, while for depressive symptomatology the effect size was $d = 0.52$.

Taking all of the above into account and knowing that classical tests for evaluating attentional control (continuous performance test - CPT) and attentional bias evaluation procedures discriminate between anxious/depressive individuals and normal controls, our aim in the present study are threefold: 1) to evaluate the separate effectiveness of the new Nesplora Aquarium VR continuous processing task (AQUA-VR), the CPT and the ABM evaluation procedures (ABM-eval) at discriminating between normal controls and individuals with anxious/depressive symptomatology, 2) to investigate if the more ecological, AQUA-VR evaluation method is superior to the classical CPT and to the ABM-eval procedures at discriminating between anxious/depressive individuals and normal controls and 3) to assess the usability, the possible adverse effects, the stress/perceived mental workload and the level of presence of AQUA-VR.

3.3.2. Methods

Participants

Participants were recruited from 1) Babeș-Bolyai University (mainly students that received course credit in exchange for participation in the study) and 2) Psychiatric facilities in Romania (Cluj-Napoca and Timișoara). A total of 87 participants, aged between 19 and 61 ($M = 31.81$, $SD = 9.78$) took part in the study and were included in the analysis. Thirty-nine percent were males ($N = 34$) and had a mean education of 16 years. Forty percent of participants reported previous VR use, exclusively for entertainment purposes. Participants that were younger than 18 or had a history of neurological afflictions/substance dependence or reported previous severe VR-induced motion sickness were excluded.

Based on the severity of anxious/depressive symptomatology, the sample was divided into healthy participants and participants with elevated symptomatology. The criteria that was used for this split was as follows: 1) having a clinical diagnosis of anxiety/depressive disorder (diagnosed by a psychiatrist in the case of psychiatric facility recruitment) and 2) having above-cut-off scores on the Beck Depression Inventory (BDI-II, (Beck et al., 1996) and/or State-Trait Anxiety Inventory (Form Y, STAI-S, (Spielberger et al. 1983). More specifically, to be considered as having elevated symptoms of anxiety/depression, participants had to score equally or above 20 on the BDI-II and/or equally or above 34 on the STAI-S. These scores are considered to represent the threshold between moderate to severe symptoms and low to no symptoms according to the normative studies (Beck et al., 2012; Spielberger et al., 2007). Twenty-two participants were taking medication at the time of the study, however, there were no significant differences between medicated and non-medicated participants on the cognitive outcomes.

Nesplora Aquarium VR test for attentional control assessment (AQUA-VR)

Nesplora Aquarium was developed by Nesplora-Technology and Behavior in order to support clinicians in the assessment of attentional processes and executive functioning in adults over 16 years old (Climent et al., 2019). It consists of several tasks that are administered in a virtual aquarium and has two main interfaces: one VR interface that is intended for the participants and is delivered via a Samsung Galaxy S7 smartphone paired with a Samsung Gear VR headset and a classical on-screen interface that is intended for the experimenter and is delivered on a laptop computer. The laptop computer and the VR headset communicate with each other using a local wireless connection. The participants respond to stimuli via a bluetooth-paired button which is held in the dominant hand. In contrast to the classical CPT tasks in which the stimuli are delivered only visually, AQUA-VR delivers stimuli using both the visual and auditory channels.

There are three types of tasks: a usability task in which the users familiarize themselves with the virtual environment and the controls, a learning task in which the users are trained to learn and respond to the various stimuli (with no data collection) and two dual execution test tasks from which actual data is collected. During the two dual execution tasks, the participants have to press the bluetooth-paired button whenever they see certain types of fish or hear certain fish names. During the procedure, various visual/auditory distractors are introduced for ecological validity (i.e., speaker announcements, baby crying, people walking in front of the aquarium, etc.). In the first dual execution task, the participants must press the button whenever they see or hear a fish name, except when seeing the “clownfish” or hearing the word “sturgeon”, thus offering different targets for the visual and auditory channels. During the second dual execution task, the participants must press the button whenever they see or hear a fish name, except when seeing the “surgeon” or hearing the word “clownfish”. Here the target stimuli are inverted when compared with the first task, thus offering the possibility to evaluate the control of interference. Both tasks comprise 140 visual/auditory items for which the participants have to make an input via the Bluetooth-paired button. In both tasks a series of data is collected, similarly to the classical CPT tasks; namely, the reaction time and the variability of the reaction time are indicative of response speed and sustained attention, while omission and commission errors are indicative of alertness/arousal and impulsivity/inhibitory

control, respectively. All data is provided both as an aggregate and separately for the visual and auditory channels. The whole procedure lasts for around 20 minutes.

Continuous Performance Test (CPT)

The participants were also asked to complete the CPT, a classical method for evaluating attention and inhibitory control, as implemented in the Psychology Experiment Building Language (PEBL (Mueller & Piper, 2014). Participants were instructed to press, as fast as they could, the Space Bar key every time they saw a letter on the laptop screen, with the exception of the letter "X", for which they had to abstain from pressing the key. As opposed to the AQUA-VR evaluation method, the stimuli are delivered only through the visual channel and no distractors are present. The output, in terms of data, are the same as those delivered by AQUA-VR, namely reaction time, reaction time variability, omission and commission errors.

Attentional Bias Evaluation (ABM-eval)

The ABM-eval procedure followed the classical bias evaluation paradigm (MacLeod et al., 1986). The participants were instructed to look at the fixation cross that appears in the centre of the laptop display. After the fixation cross disappears, two paired faces, representing the same individual appear on the left and right of the screen, one face displaying a neutral expression and the other face displaying a disgust expression (i.e., neutral / threatening stimuli). The position of the neutral and threatening stimuli is randomised so that they appear with equal frequency on both sides of the screen. After 500 milliseconds, the faces disappear and a dot-probe appears in the place of one of the faces. The participants are instructed to indicate the location of the dot-probe as fast and as accurately as they can via keyboard input. There were 120 trials in total. As opposed to the classical intervention procedures, where the dot-probe replaces the neutral stimuli 80%-100% of the time, in the evaluation procedure the probe replaces the neutral and threatening stimuli with equal frequency (50%-50%). Attentional bias towards threat is considered to be present when response latencies are shorter for dot-probes that are located behind threatening stimuli as compared to neutral stimuli. The response latencies of the participants are recorded for each instance, that is for each repetition and an attentional bias score is computed by subtracting the average response time for neutral stimuli from the average response time for threatening stimuli.

Questionnaires

In addition to performing the attentional control evaluation procedures, the participants also provided demographic characteristics (age, gender, previous VR use, medical history/medication taken at the time of the study, motion sickness history). The symptoms of depression and anxiety were assessed with the BDI-II (Beck et al., 1996) and STAI-S (Spielberger et al., 1983), respectively. Simulator sickness (i.e., adverse effects) was assessed pre and post exposure to AQUA-VR using the Simulator Sickness Questionnaire - SSQ (Kennedy et al., 1993), while system usability and the level of sense of presence in VR were assessed with the System Usability Scale - SUS (Brooke, 1996) and the Presence Questionnaire – PQ (Witmer & Singer, 1998), respectively. The stress/mental workload was assessed by using the NASA Task Load Index tool - NASA-TLX (Hart & Staveland, 1988).

Procedure

Participants were received either on the SkyRa platform at the the International Institute for the Advanced Studies of Psychotherapy and Applied Mental Health or, in the case of psychiatry inpatients, the experiment was conducted at the psychiatric ward. All participants read and signed the informed consent form, followed by demographic data collection and they completed the pre-SSQ, BDI-II and STAI-S questionnaires. The first step in the experiment was represented by the ABM-eval procedure which was performed by the participants by performing the classic bias evaluation procedure, with all stimuli presented on a laptop screen. The second step consisted in the AQUA-VR test. The participants were asked to sit comfortably in a chair and the VR headset was mounted on their heads. The experimenter performed minor adjustments, so that each participant was comfortable with the VR headset and to ensure that the distance between the focal point of each of the VR lenses was best suited for the participant. The AQUA-VR test had an initial 5 minutes accommodation period in which the participants familiarized themselves with the VR environment and learned how to use the Bluetooth-paired button. Following this, the proper testing began, in which the participants had to listen to the instructions and to respond to the visual / auditory stimuli to the best of their abilities. The entire VR procedure took between 15-20 minutes. After performing the AQUA-VR test, the participants completed the post-SSQ, PQ, SUS and NASA-TLX questionnaires. The last step in the experimental procedure was the CPT test. The participants performed this test by evaluating the stimuli that appeared on the laptop screen and responding via keyboard. This procedure took approximately 15 minutes.

Statistical analysis

In order to evaluate the effectiveness of AQUA-VR in predicting anxious/depressive symptomatology we employed a logistical regression approach, the predictors being reaction time, reaction time variability, omission and commission errors and the target being the status of the participants (anxious/depressive individuals and normal controls).

For evaluating which of the three attention evaluation methods are better at discriminating between anxious/depressive individuals and normal controls with a direct comparison, not just indirect/naïve ones and, since the predictors are not nested, we computed the absolute differences between each models' Bayesian adjusted information criterion (ABIC), a method that is suited both for nested and non-nested models (Long & Long, 1997). The ABIC values were preferred instead of the simple Bayesian information criterion (BIC), since BIC values are more prone to be influenced by sample size and number of predictors. The formula for ABIC calculation is:

$$ABIC = -\chi^2 + no\_param * \ln N$$

where χ^2 represents the chi-square likelihood ratio test for the model, *no_param* represents the number of predictors and *N* represents the number of observations. The absolute differences between models' BAIC coefficients give an indication for which model is better fitted:

if ABIC1 – ABIC 2 > 0 – the second model represents a better fit
if ABIC1 – ABIC 2 < 0 – the first model represents a better fit

Moreover, the absolute value of the difference can be interpreted by following the grid proposed by (Raftery, 1995), the author of the BIC and ABIC concepts, grid detailed in Table 1.

Table 1. Critical values for the absolute differences between regression models

Absolute difference	Absolute difference strength	Probability
0 - 2	Weak	0.50 – 0.75
2 - 6	Medium	0.75 – 0.95
6 – 10	Strong	0.95 – 0.99
> 10	Very strong	> 0.99

3.3.3. Results

The participants had a mean age of 31.81 (SD = 9.78) years old. Sixty-one percent were females and 62% were employed. Only 35% of the participants reported previous VR use and, of these, the vast majority only tried it once, out of curiosity. After participant segregation as a function of their clinical status, we had 41 participants with elevated levels of anxiety and/or depression and 46 healthy participants.

With regard to our first hypothesis, namely to evaluate the effectiveness of the new AQUA-VR at discriminating between normal controls and individuals with anxious/depressive symptomatology, the logistical regression model was significant, $\chi^2(82) = 21.69$, $p < 0.001$. Nagelkerke' R^2 indicated that 29.5% of the probability variance between normal controls and individuals with anxious/depressive symptomatology was explained by the AQUA-VR predictors. The only statistically significant predictors in the model were reaction time and omission errors. The AUC for this model was 75.5%. Secondly, the CPT regression model was statistically significant, $\chi^2(82) = 10$, $p < 0.040$. Nagelkerke' R^2 indicated that 14.5% of the probability variance between normal controls and individuals with anxious/depressive symptomatology was explained by the CPT predictors. However, the individual predictors were statistically non-significant. The AUC for this model was 68.8%. Thirdly, the ABM-eval regression model was statistically significant, $\chi^2(85) = 42.01$, $p < 0.001$. Nagelkerke' R^2 indicated that 51.1% of the probability variance between normal controls and individuals with anxious/depressive symptomatology was explained by the ABM-eval predictor, this predictor being also statistically significant. The AUC for this model was 86.9%.

With regard to the second hypothesis, namely to investigate if the more ecological, AQUA-VR evaluation method is superior to the classical CPT and to the ABM-eval procedures at discriminating between anxious/depressive individuals and normal controls, using direct comparisons via ABICs, the results showed that the ABM-eval is the best model when compared to the AQUA-VR and CPT models. The differences between the ABM-eval model and the AQUA-VR and CPT models respectively were very strong, with a probability of being the best model of over 99%

in both cases. The more ecological AQUA-VR model outperformed its classical counterpart (CPT), with a probability of over 99% of being the best model for the AQUA-VR / CPT contrast.

Table 2. Parameters used for ABIC calculation and ABIC values for the differences between the attentional evaluation procedures

	χ^2	**No. param**	**N**	**ln N**	**ABIC**
AQUA-VR	21.69	4	86	4.45	-3.87
CPT	10	4	86	4.45	7.82
ABM-eval	42.01	1	86	4.45	-37.56
	ABIC difference		**Preferred model**	**Difference strength**	**Probability for preferred model**
AQUA-VR versus CPT	-11.69	< 0	AQUA-VR	Very strong	> 0.99
ABM-eval versus CPT	-45.37	< 0	ABM-eval	Very strong	> 0.99
AQUA-VR versus ABM-eval	33.68	> 0	ABM-eval	Very strong	> 0.99

With regard to usability, the possible adverse effects in VR, the perceived mental workload and the level of presence, the results were more than encouraging.

Firstly, in terms of usability of the AQUA-VR, participants in both groups, as a mean, (i.e., normal controls and individuals with anxious/depressive symptomatology) rated the VR system as having an above average-to-excellent usability (i.e., a score above 68 out of a range from 0 to 100). However, there was a significant statistical difference between the normal controls group and the anxious/depressive group (Welch t (69.01) = 2.49, p = 0.015, Cohen's d = 0.54), with the normal controls group consistently rating the VR system higher than anxious/depressive group, in terms of usability, the effect size being a medium one.

Secondly, in terms of possible adverse effects induced by AQUA VR, the participants in both groups reported little to no symptoms post-VR exposure. The

normal controls group had a M = 4.97, SD = 3.94, while the anxious/depressive group had a M = 6.68, SD = 6.13 (possible score range: 0 – 48, median value: 24). An ANCOVA analysis with the pre-SSQ scores as a covariate, the group as the between factor and the post-SSQ scores as the outcome, revealed no statistically significant difference between groups ($F(1, 84) = 0.30$, $p = 0.584$) in terms of adverse effects (i.e., simulator-induced sickness).

Thirdly, in terms of stress/perceived mental load, both the normal controls and the anxious/depressive groups reported low to medium mental workloads (M = 258.58, SD = 84.08 and M = 244.26, SD = 85.12 respectively; possible score range: 0 – 600, median value: 300). There was no statistically significant difference between groups in terms of mental workload ($t(85) = 0.78$, $p = 0.433$).

Finally, in terms of presence, both the normal controls and the anxious/depressive groups reported medium to high levels of presence (M = 158.56, SD = 24.65 and M = 151.19, SD = 21.89 respectively; possible score range: 32 – 224, median value: 128). There was no statistically significant difference between groups in terms of presence ($t(85) = 1.46$, $p = 0.146$).

3.3.4. Discussion and conclusions

The aims of the present study were to 1) evaluate the separate effectiveness of AQUA-VR, the CPT and the ABM-eval at discriminating between normal controls and individuals with anxious/depressive symptomatology, 2) to investigate if the more ecological, AQUA-VR evaluation method is superior to the classical CPT and to the ABM-eval procedures at discriminating between anxious/depressive individuals and normal controls and 3) to assess the usability, the possible adverse effects, the perceived mental workload and the level of presence of AQUA-VR.

With regard to the first exploratory aim, we found that all three methods of evaluation of selective attention were effective in discriminating between normal controls and individuals with anxious/depressive symptomatology, with ABM-eval having the most explanatory power (51.1%), followed by AQUA-VR (29.5%) and CPT (14.5%). These results differ somewhat from previous research, in which the effect sizes for the comparisons between affected individuals and normal controls on the ABM-eval ($d = 0.45$ for anxiety; $d = 0.52$ for depression) and CPT ($d = 0.66$ for anxiety; $d = 0.52$ to 0.61 for depression) tasks were similar. In the present study, ABM-eval had 3.5 times more explanatory power than CPT. Moreover, AQUA-VR had 2 times more explanatory power than its analogue task, CPT, leading credence to the hypothesis that a VR evaluation medium, in which stimuli are delivered both visually and auditorily, represents a more ecological approach in distinguishing between individuals that present symptoms of anxiety/depression and normal controls than the classical CPT approach. Moreover, in line with previous research (Kessels, 2019), CPT was found to have poor predictive power. An important caveat here is the fact that all the aforementioned comparisons are of an indirect nature and must be regarded with caution.

With regard to the second exploratory aim, in which we directly compared the three evaluation methods via ABIC comparisons, the results enforced the indirect observations mentioned before. The difference coefficient between AQUA-VR and CPT was very strong, with a probability greater than 99% that AQUA-VR is more effective in distinguishing between individuals with anxious/depressive symptomatology and normal controls. ABM-eval was more effective than both

AQUA-VR and CPT respectively, with very strong difference coefficients and a probability of over 99% with regard to effectiveness. This result could be explained by the fact that, while AQUA-VR and CPT use emotionally neutral stimuli (i.e., fish species / fish names and letters, respectively) to evaluate attentional control, ABM-eval uses both emotionally-neutral and threatening stimuli (faces that express neutral or disgust expressions respectively), presented in balanced order. The effects induced by these differences in stimuli could be even more pronounced in individuals with anxious/depressive symptomatology.

With regard to the third exploratory aim, one important find was that all participants rated AQUA-VR as having an above average-to-excellent usability. We identified a statistically significant difference between individuals with anxious/depressive symptomatology and normal controls with regard to usability, the affected individuals rating AQUA-VR lower on average than normal controls. However, mean usability scores in both groups were above 68, leading us to believe that the results we observed are consistent. While there was no significant difference between medicated and non-medicated participants with regard to cognitive outcomes, the statistically significant difference between groups in terms of usability, could be explained by the 22 participants that were medicated, with some of them taking the medication on the same day that the tests were administered. Interestingly, this could also be the case with the level of presence experienced in the VR environment. While the difference between groups was statistically non-significant, and the levels of presence were medium to high in both groups, individuals with anxious/depressive symptomatology reported, on average, lower presence than normal controls. For mental workload, we found low to medium levels with no significant differences between groups and no side effects from VR exposure were identified.

With regard to AQUA-VR, its effectiveness in distinguishing between individuals with anxious/depressive symptomatology and normal controls, its superiority over the analogue classical CPT task with regard to the aforementioned outcome, its above average-to-excellent usability, the medium-to-high levels of induced presence, moderate mental workload and the fact that induced no adverse effects, represent strong advocates in confirming the hypothesis that a VR environment represents a more ecological method of attentional control evaluation than the analogue classical task. Moreover, by delivering stimuli both visually and auditorily, and engaging the user in a VR gamified environment, AQUA-VR has a strong potential in eliminating possible distractors and/or ennui, both of which could be responsible for the poor predictive and unclear ecological validity of the classical CPT task.

With regard to ABM-eval, its effectiveness in distinguishing between individuals with anxious/depressive symptomatology and normal controls, potentially driven by the specific stimuli that are used, opens new avenues of research. An evaluation method of this nature, when implemented in VR and benefitting from potential gamification, could represent an extremely viable, ecological and effective screening / evaluation method.

3.4. Study 4: The efficacy of Virtual Reality-Based Attention Bias Modification Training: A pilot randomized controlled trial

3.4.1. Introduction

Attentional bias evaluation and modification procedures (ABM) have been firstly developed and validated as early as 1986 (MacLeod et al., 1986). Since then, a lot of research has been conducted in order to evaluate the efficacy of ABM procedures in alleviating symptoms of anxiety (in particular with regard to social anxiety disorders), depression and addictions. The allure of these procedures consists in easy implementation and inexpensiveness, owing to the fact that they can be easily designed and have great compatibility with any computer system, while being easily administered, in an almost automatic fashion.

While there is a large body of research that investigates the efficacy of ABM procedures, both in modifying attentional biases and, through this mechanism alleviating anxious and/or depressive symptomatology, the results are often mixed. Meta-analyses conducted on this topic have shown that the effect size for bias modification is a moderate one and tends to get smaller after outlier removal (Cristea et al., 2015). When ABM is administered with the intention to reduce anxious and/or depressive symptomatology, the results are not very encouraging. For example, one meta-analysis revealed no statistically significant differences between ABM and control groups for either anxiety or depression (Cristea et al., 2015), while another more recent network meta-analysis revealed small effect sizes in favour of ABM for anxiety symptoms, but only in sensitivity analyses (Fodor et al., 2020).

With the adoption of virtual reality (VR) technology in augmenting (e.g., in vivo exposure) and in some cases replacing (e.g., attentional control evaluation) classical psychological therapeutic approaches, a new avenue of research is starting to be pursued for ABM interventions. VR implementations have many advantages over classical intervention delivery formats, advantages which were previously described in this thesis and not worth repeating. Presently, there are two studies that investigated the efficacy of VRABM (Ma et al., 2019; Urech et al., 2015). However, one of the studies was conducted as a proof-of-concept study (Urech et al., 2015), adopting a pre-post intervention design, without employing a control group. No statistically significant change was found from pre to post-intervention for attention bias or two out of three social anxiety measures. The other study (Ma et al., 2019) employed a complex randomized controlled trial (RCT) design, with two types of stimuli (2D vs 3D) and four groups (2D sham training, 2D ABM, 3D sham training and 3D ABM). Again, no "classical" intervention control group was employed, all groups experiencing VR immersion, the aim of the study being to discern the efficacy of different stimuli dimensionalities. No differences in attention bias were found either from pre to post-intervention or between experimental groups, while for anxiety measures only a time effect was present, anxiety decreasing over time across for all four groups.

Taking into account the small number of studies employing VRABM, the fact that no study compared a VRABM intervention to a "classical" ABM (PCABM) intervention and the fact that the small-to-moderate effect sizes in favour of ABM can be improved by VR adoption, it is clear that more research needs to be pursued in this direction. With this in mind, we conducted an pilot randomized controlled trial, in which we compared a VRABM active intervention to a PCABM active intervention, aiming at investigating the efficacy of the VR version as compared to the classical PC-

delivered one in reducing attentional bias and improving potential state anxiety symptoms and fear of negative evaluation. We also aimed at evaluating the potential adverse effects induced by VRABM, the sense of presence and the perceived usability of the VRABM intervention and, if the VRABM intervention induces more stress/mental workload as compared to PCABM. Because the superiority of PCABM over placebo and wait-list was previously established, we did not include these types of control groups in our study.

Owing to restrictions and limitations imposed by the COVID-19 pandemic (i.e., mobility restrictions, almost exclusive adoption of online methods of engagement and, as a direct consequence recruitment pool reduction), we were able to recruit only unselected participants through convenience sampling. This can be regarded as a limitation because usually, attentional biases towards threat are related to anxiety and participants with high anxiety levels exhibit the largest attentional bias towards threat. However, previous studies have shown that high threat attentional stimuli are capable of capturing attention in all participants, not only in those with above-threshold levels of anxious symptomatology (Mogg et al., 2000; Wilson & MacLeod, 2003). For the same reasons, the intervention consisted in only one session. However, previous studies have demonstrated that modifications in anxious symptomatology can and do occur in one session, both for ABM interventions (Ma et al., 2019; Sass et al., 2017) and for interpretation bias modifications (CBMI; (Beadel et al., 2016; Capron et al., 2017; Capron & Schmidt, 2016; Grisham et al., 2014; MacDonald et al., 2013; Mobini et al., 2014; Nowakowski et al., 2015; Steinman & Teachman, 2010; Vermeulen et al., 2019), as well as for attention bias (Amir et al., 2008; Buodo et al., 2018).

3.4.2. Method

Participants

Participants were recruited primarily via social media. Taking into consideration the mobility restriction imposed due to the COVID-19 pandemic, especially at the beginning of the study, and in order to maintain a constant flow of participants, recruitment was restricted only to Cluj-Napoca. A total of 42 participants, aged between 15 and 52 (M = 28.16, SD = 6.49) took part in the study and were included in the analysis. Sixty-four percent were females (N = 27). Fifty percent of participants reported previous VR use, while 50% reported that they were using glasses or contact lenses. Participants that were younger than 18 or had a history of neurological afflictions/substance dependence or reported previous severe VR-induced motion sickness were excluded. We also excluded participants that failed to respond in the affirmative on each of the questions from the COVID-19 epidemiological questionnaire and/or had a bodily temperature greater than 37 degrees Celsius at screening.

Apparatus

VRABM was delivered via a HTC Vive head-mounted display (HMD) with a resolution of 2160×1200 (1080×1200 per eye), a field of view of 110 degrees and a refresh rate of 90 Hz. The HMD was paired with an ASUS Republic of Gamers laptop running on a Intel i7-8750H 2.20 Ghz processor, 24 Gb RAM and a GeForce GTX-1080 with 8 Gb VRAM video card. Participants interacted with stimuli by using the

Vive controller that came with the HMD. PCABM was delivered on the aforementioned laptop, on screen, using a resolution of 1920x1080 and participants interacted with the stimuli using a mouse.

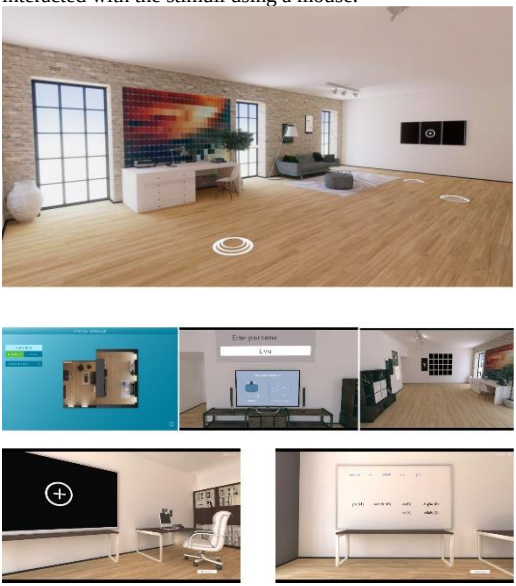

Figure 1. Screenshot of the VRABM environment

Attentional bias assessment and modification

The facial stimuli that we used for both VRABM and PCABM were selected from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998). We selected 70 individuals, each showing a neutral and a negative-valence expression, of which 50% were female, for a total of 140 expressions. We chose disgust for the negative-valenced expressions because it is closely related to social anxiety (Amir et al., 2003; Phillips et al., 1998) and tends to elicit a higher number of complex emotions (i.e., humiliation, rejection and shame) than angry faces for example. The stimuli were identical across VRABM and PCABM and presented in the same environment. While in the PCABM condition the stimuli were presented on the laptop screen, in the VRABM condition the stimuli were presented on screen panels attached to a wall of the virtual room. In both conditions the participant made a dry, trial run, in order to get accommodated with the procedure.

We used the classical dot-probe task for both the pre-post measurement of attentional bias and the modification of attentional bias. There were a specific number of trials for each stage and each trial followed the following steps, also detailed in Figure 2: firstly, a fixation cross appeared in the center of the screen for 500 ms; secondly, after the fixation cross disappeared, two faces of the same individual were presented (one face depicting a neutral expression and the other depicting a disgust

expression), arranged horizontally on the screen, for 500 ms; the position of the faces was counterbalanced, so that the disgust and neutral expressions appeared with equal frequency on the left or right side of the screen; thirdly, after the faces disappeared, a probe appeared in the location previously occupied by one of the faces, the probe position being also counterbalanced; fourthly, as previously instructed, participants reacted as fast as they could in indicating the position of the probe; finally, a 500 ms interval took place before a new trial would begin.

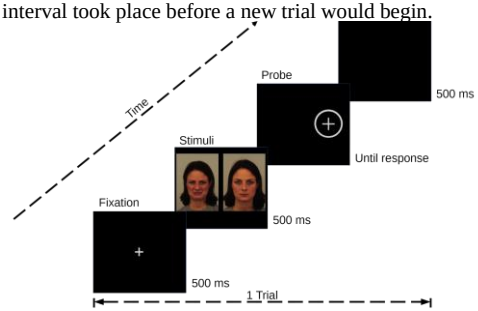

Figure 2. Example trial of a dot-probe task

For bias modification, the probe replaced in 80% of the cases the neutral expression as opposed to the disgust expression, while in 20% of the cases the pairs were neutral-neutral in order to mask the trial contingency. There were a total of 160 trials for both PCABM and VRABM conditions.

For bias measurement, a mock training design was used, in which the probe replaced words that had socially negative connotations / social-threat words (e.g., rejected, worthless, shameful, marginalized, humiliated, criticised, embarrassed) or words that had socially neutral connotations (e.g., amazed, temporary, ongoing, country, original, governmental), with equal frequency (50%-50%). There were 16 social-threat words and 16 neutral words that were matched for length. We chose to use words instead of faces for measuring attention bias in order to firstly avoid task habituation and secondly, to avoid any carryover effects from bias modification to bias measurement, especially at the post-intervention assessment.

In both VRABM and PCABM interventions, the same structure was followed: firstly, the pre-intervention bias score assessment was made, followed by the intervention proper. Lastly, the post-intervention bias score was assessed.

Bias assessments were made by subtracting the mean reaction time of the participants toward disgust faces from the mean reaction time towards neutral faces. Thus, a positive bias index indicated that the participant reacted faster to probes when they appeared behind neutral faces, while a negative bias index indicated a faster reaction to probes behind disgust faces:

$$BiasIndex = Mean\ (RTdisgust) - Mean\ (RTneutral)$$

Questionnaires

The measures that were specific only for VRABM were 1) simulator sickness (i.e., adverse effects) and was assessed pre and post exposure to VRABM using the Simulator Sickness Questionnaire - SSQ (Kennedy et al., 1993), and 2)

system usability and the level of sense of presence in VR that were assessed at post-intervention with the System Usability Scale - SUS (Brooke, 1996) and the Presence Questionnaire – PQ (Witmer & Singer, 1998), respectively.

The measures that were common to both VRABM and PCABM were 1) state anxiety symptoms that were assessed both at pre and post intervention with the State-Trait Anxiety Inventory - STAI-S (Spielberger et al. 1983; cut-off: 40), 2) the fear of negative evaluation that was assessed both at pre and post intervention with the Brief Fear of Negative Evaluation scale (Leary, 1983; range: 12-60), and 3) the stress and mental workload was assessed by using the NASA Task Load Index tool - NASA-TLX (Hart & Staveland, 1988).

Procedure

Participants were received on the SkyRa platform at the International Institute for the Advanced Studies of Psychotherapy and Applied Mental Health. A thorough disinfection procedure was designed and implemented in order to prevent SARS-Cov2 infections and, to this end, before receiving a participant and after the participant had left a thorough disinfection of all surfaces and apparatus was conducted with Hexasept, a coronavirus virucide. Moreover, both the participants and the experimenter wore facial masks. The participants' temperature was taken and they completed the epidemiological triage questionnaire, both of which were used as primary inclusion/exclusion criteria. Participants were then assigned, based on a previously generated random sequence (generated at www.random.org) to either VRABM or PCABM. The VRABM participants completed the informed consent, the demographic data questionnaire, the pre-intervention SSQ, STAI-S and BFNE questionnaires and underwent pre-intervention bias assessment, bias modification and post-intervention bias assessment. Following this, the participants in the VRABM group completed the post-intervention SSQ, STAI-S, BFNE questionnaires and the NASA-TLX, PQ and SUS questionnaires. The participants in the PCABM group followed the same sequence, with the exception that they did not have to complete the pre/post intervention SSQ questionnaire and the PQ and SUS questionnaires.

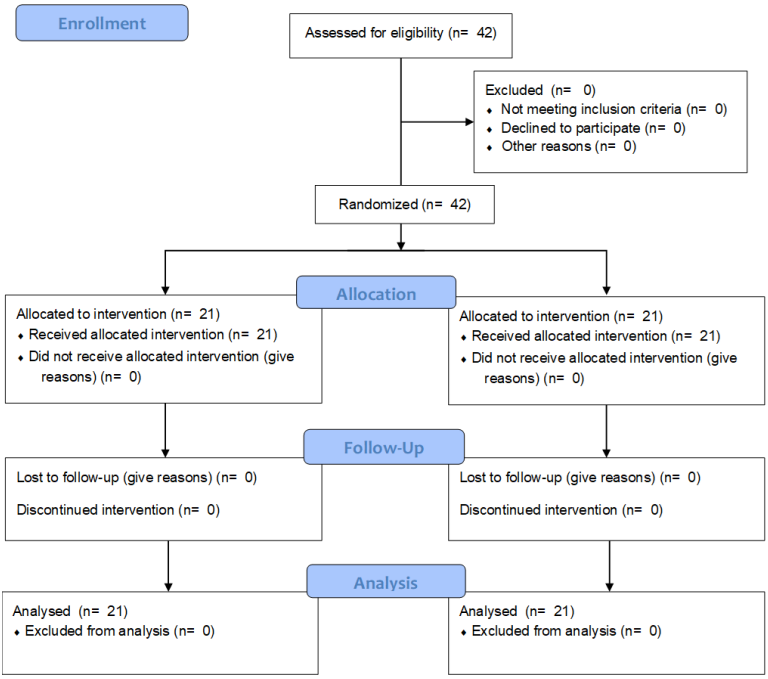

Figure 3. The CONSORT flow chart illustrating the randomisation process

Statistical analysis

Firstly, we ran a descriptive analysis of the data in order to evaluate if there were missing observations or extreme outliers and to check the distribution shapes for all variables. In order to estimate the results, we employed a 3 (intervention group: VRABM, PCABM) x 2 (assessments: pre-intervention, post-intervention) mixed-design ANCOVA, using baseline scores as covariates. This approach has been chosen because using pre-intervention values as a covariate provides more statistical power and more precise confidence intervals with regard to intervention effects than a mixed-design ANOVA (Rausch et al., 2003; "The Oxford Handbook of Research Strategies for Clinical Psychology," 2013). The assumption of homogeneity of variances was tested by employing the Levene test and possibly significant group interactions were followed with Tukey-adjusted pairwise comparisons of estimated marginal means. For the estimation of the effect size in the case of main group effects, η^2p was computed, while for significant pairwise comparisons, Cohen's d was employed. For stress/mental workload, that was measured only at post-intervention in both groups, we performed an independent-samples t-test. For variables that were measured only at post-intervention in the VRABM group (PQ, SUS), we interpreted the results based on range (i.e., median, minimum, maximum), mean and standard deviations. We also computed

the Reliable Change Index (RCI) for each participant in both groups to further explore possible changes in attentional bias and in order to see more clearly how many individual participants deteriorated, improved or did not suffer any changes as a result of the interventions.

3.4.3. Results

The characteristics of the included participants are detailed in Table 1. The mean age was 28.16 years old and 64% of the participants were female. There were no drop-outs from the any of the intervention groups and there were no differences at baseline with regard to any of the investigated variables.

Table 1. Characteristics of the participants at baseline

		VRABM (N = 21)	PCABM (N = 21)	
Female	N (%)	13 (61.90)	14 (66.66)	$\chi^2(1) = 0.104$, p = 0.747
Having vision correction	N (%)	10 (47.61)	11 (52.38)	$\chi^2(1) = 0.09$, p = 0.758
Previous VR exposure	N (%)	12 (57.14)	9 (42.85)	$\chi^2(1) = 0.85$, p = 0.355
Age	M (SD)	27.85 (4.79)	28.47 (7.95)	t(40) = 0.30, p = 0.762
STAI-S pre-intervention	M (SD)	29.04 (6.60)	31.61 (7.66)	t(40) = 1.16, p = 0.251
BFNE pre-intervention	M (SD)	31.57 (8.50)	32.04 (9.56)	t(40) = 0.17, p = 0.866

With regard to the first objective, namely to investigate the efficacy of VRABM as compared to PCABM in reducing attentional bias and improving potential state anxiety symptoms and fear of negative evaluation, the results were mixed. The Levene's test was statistically non-significant for all three outcomes, so the homogeneity of variances assumption was met. For attention bias, the ANCOVA analysis revealed no statistically significant differences between groups: F (1, 39) = 0.43, p = 0.514. However, the RCI analysis revealed that there were more improvements and less deteriorations with regard to attentional bias in the VRABM group than in the PCABM group (VRABM: 12 improved, 5 deteriorated and 4 no change; PCABM: 7 improved, 9 deteriorated and 5 no change).

Also, no statistically significant differences were found with regard to the fear of negative evaluation, F (1, 39) = 0.04, p = 0.839. With regard to state anxiety symptoms, we identified a statistically significant difference between the VRABM and PCABM groups: F (1, 39) = 74.20, p = 0.016, $\eta^2p = 0.07$. Post-hoc analyses revealed that the effect size was medium, Cohen's d = 0.55 and the estimated marginal means were 27.24 (95% CI: 25.72 to 28.76) for VRABM and 29.94 (95% CI: 28.42 to 31.47) for PCABM.

In terms of potential adverse effects induced by the VRABM intervention, the participants in the VRABM group reported little to no symptoms post-VR exposure. The participants in the VRABM condition had a M = 2.33, SD = 1.82 at pre-

intervention, while at post-intervention they had a M = 2.81, SD = 2.80 (possible score range: 0 – 48, median value: 24). A paired sample t-test revealed no statistically significant difference from pre- to post-VR-intervention, t(20) = -0.76, p = 0.454.

With regard to stress/mental workload the assumptions of normality and of equality of variances were met (VRABM: Shapiro-Wilk W = 0.972, p = 0.776; PCABM: Shapiro-Wilk W = 0.973, p = 0.795; Levene's F = 0.35, p = 0.555). The participants in the PCABM group reported statistically significant lower stress/mental workload (M = 159.52, SD = 61.05) than the participants in the VRABM group (M = 205.71, SD = 70.98), t(40) = -2.26, p = 0.029, Cohen's d = -0.69 However, taking into account the possible score range of 0 – 600, with a median value of 300, stress/mental workload was low in both groups.

With regard to presence in VR, the participants in the VRABM group reported medium to high levels of presence (M = 168.76, SD = 16.12; possible score range: 32 – 224, median value: 128). In terms of system usability, the participants in the VRABM group rated the VR system as having an above average-to-excellent usability, the mean score being M = 86.55, SD = 9.94 (i.e., a score above 68 out of a range from 10 to 100).

3.4.4. Discussion and conclusions

The aims of the present study were 1) to evaluate the efficacy of the VRABM intervention as compared to the PCABM intervention in reducing attentional bias and improving potential state anxiety symptoms and fear of negative evaluation, 2) to evaluate if the VRABM intervention induces more stress/mental workload as compared to the PCABM intervention and 3) to evaluate the potential adverse effects induced by the VRABM intervention, the participants' sense of presence in VR and the perceived usability of the VRABM intervention. With regard to the first aim, we found that there was no statistically significant difference between VRABM and PCABM in reducing attentional bias. This result could, in theory, be attributed to two factors: 1) the participants were unselected, both in terms of state anxiety and of fear of negative evaluation, meaning that although the scores, as a mean, extended in the subclinical range for both instruments, they never reached the cut-offs for clinical symptomatology and 2) we compared two active interventions, both of which aimed at reducing the aforementioned symptoms and, although equivalence between interventions cannot be claimed based on a statistically non-significant result, this could still represent a factor. Both arguments are supported, when taking into consideration that, in previous studies, attentional bias did not change even when the ABM VR intervention was compared to an active or placebo classical intervention (Ma et al., 2019), when change in bias was evaluated only from pre- to post-intervention (Urech et al., 2015), when subclinical samples were employed or when single session interventions were employed (Ma et al., 2019; Urech et al., 2015). However, with regard to attentional bias, the RCI analysis revealed that 12 participants improved and 4 did not change in the VRABM condition, while only 7 improved and 5 did not change in the PCABM condition. Moreover, only 5 participants deteriorated with regard to attentional bias in the VRABM condition, while 9 participants deteriorated in the PCABM condition. This represents an encouraging result, albeit anecdotal, with regard to the superiority of the VRABM intervention over the PCABM intervention.

The same argument as in the case of attention bias change can be applied with regard to fear of negative evaluation symptoms, a component of social anxiety,

for which we did not found any statistically significant differences. In the two previous VR studies, changes in social anxious symptomatology were not detected when measured with the Social Phobia Scale or with the Social Interaction Anxiety Scale (Urech et al., 2015) or with the Liebowitz Social Anxiety Scale (Ma et al., 2019). Urech et al., (2015) found a small effect from pre- to post-intervention on the Liebowitz Social Anxiety Scale, but it can be arguably justified as statistical artefact, since on the other two social anxiety scales that were employed, no such effect was identified. Moreover, fear of negative evaluation in special and social anxiety in general represent constructs that may not be so prone to modification in only one-session interventions, even when employing more ecological methodologies, such as VR.

This is theoretically not the case for state anxiety, which is more prone to modifications in single-session interventions, as evidenced by the statistically significant effect that was obtained between VRABM and PCABM ($d = 0.55$). Although it is conceivable that this result can represent a statistical artefact especially when considering a one-session intervention and the small sample size, this result was observed in previous studies ($d = 0.45$ in Amir et al., 2008; $d = 0.48$ in Dennis & O'Toole, 2014), which leads credence to the superiority of VRABM over PCABM in reducing state anxiety symptoms.

With regard to stress/mental workload, the participants in the VRABM group reported having a mode challenging / demanding experience than the participants in the PCABM group, although the scores remained well below the median of the scale. This result was to be expected, when taking into account the fact that the virtual environment, through properties such as enhanced spatiality, sense of presence, near isolation to normal external stimuli and the usage of special joysticks, makes it more challenging for the user to perform the ABM task, especially when said user has not been acquainted with any form of VR technology previously. This is not the case for the participants in the PCABM condition, as they had only to sit in front of a laptop and perform the task by using the mouse, a situation that would be familiar to almost any person.

Finally, with regard to sense of presence in VR and perceived system usability, the participants in the VRABM group reported high levels for both measures. Given the fact that the sense of presence in VR represents a factor that is directly involved in VR treatments' efficacy (Wallach et al., 2012), this result is very encouraging and leads credence to VRABM as an potentially effective intervention in longer time-frames (i.e., multiple VRABM sessions). Similarly, the above average-to-excellent usability, supports the fact that the VRABM system is easy to learn, with minimal instructions and the task performance is not impeded by any properties of the hardware platform or, more importantly by the design of the VRABM intervention.

CHAPTER IV. GENERAL CONCLUSIONS AND IMPLICATIONS

4.1. General Conclusions

We aimed to address a number of methodological objectives related to virtual reality mediated attentional control evaluation and attentional bias modification interventions in this thesis. More specifically, we wanted to elucidate if the introduction of new, virtual reality-based procedures for evaluating attentional control and modifying attentional biases were at least as efficient as the classical pen and paper or computerised techniques. In order to accomplish these objectives, a number of intermediary steps had to be performed, reflected in our original research articles.

First, a systematic review and meta-analysis was conducted, of virtual reality interventions for anxiety and comorbid depression outcomes, as well as treatment attrition. We included randomized controlled trials comparing VR interventions, alone or in combination, to control conditions or other active psychological interventions. The main findings were that VR-based therapies were more effective than passive controls at post-test for anxiety and comorbid depression, but not for treatment attrition. We also revealed that the effect sizes were higher when participants were recruited from a clinical setting, or when the diagnostics were specific phobia, panic disorder, flight anxiety or social phobia. Moreover, in the contrast with other active interventions, the effect size was higher for virtual-reality-based exposure than for virtual reality-based cognitive-behavioural therapy. Also, the number of elements of interaction with the virtual environment was positively associated with anxiety outcomes, a result that lends additional credence to the importance of immersion and presence concepts. There were no significant differences between virtual reality-based interventions and other active interventions.

Second, we conducted a systematic review and network meta-analysis, in which we evaluated the relative effectiveness of CBM procedures (i.e., ABM, CBMI, AAT), as simultaneously compared among each other and with various control groups, for anxious and depressive symptomatology, as well as for comorbid anxious and depressive symptomatology. We included randomized controlled trials comparing a cognitive bias modification intervention to a control condition for anxious or depressive symptomatology, as measured on validated clinical scales, in adults whose primary complaint consisted of symptoms of anxiety or depression. For anxios symptomatology, only the contrast between interpretation bias modification and waitlist or the contrast between interpretation bias modification and placebo were significant. For depression outcomes, again, only the contrast between interpretation bias modification and waitlist was significant, together with the contrast between the combined treatments (attention plus interpretation bias modification) and waitlist. For comorbid depression outcomes in anxiety trials, the contrast between interpretation bias modification and waitlist or the contrast between interpretation bias modification and placebo were significant. For comorbid anxiety symptoms in depression trials, there were no significant results. The attention bias modification interventions were superior to placebo and waitlist only in sensitivity analyses, in which trials concerned with posttraumatic stress disorder symptomatology were excluded. The modest results for attention bias modification interventions, together with the mixed results obtained in previous meta-analyses, lead credence to the theory that newer, more interactive (i.e., virtual reality) implementations might be needed in order to improve on these outcomes.

Third, we conducted a cross sectional experimental study in which we evaluated the effectiveness of a virtual reality attentional control evaluation procedure, as compared to its analogue computerized task or to a computerized attentional bias evaluation task. We also investigated other aspects, relevant for the virtual reality environment, such as usability, adverse effects, stress/perceived mental workload and the level of presence in virtual reality. The virtual reality evaluation procedure was superior to the classical computerized one, but not superior to the attention bias evaluation method, in discriminating between anxious / depressive participants from healthy ones. The virtual reality system had high usability ratings and presence, while the potential adverse effects induced by the virtual reality environment were negligible. The perceived stress/mental workload was low, both in the anxious/depressive group, as well as in the healthy participants group.

Fourth, we conducted a randomized controlled trial in which we evaluated the efficacy of a newly developed, virtual reality-based attention bias modification procedure, as compared to the classical computerized procedure at reducing attentional bias and anxious symptomatology. As in the previous study, we also investigated other aspects, relevant for the virtual reality environment, such as usability, adverse effects, stress/perceived mental workload and the level of presence in virtual reality. While the results for attentional bias score and fear of negative evaluation were not significant, we observed a significant reduction in state anxiety in favour of the virtual reality group. Also, as a tentative result, more participants improved and less deteriorated in the virtual reality group than in the computerized group. The participants in the virtual reality group reported high levels of presence and excellent virtual system usability. Moreover, stress/mental workload was low in both experimental groups, although the participants in the virtual reality group reported significantly more stress/mental workload. There were virtually no adverse effects as a result of the virtual reality intervention.

Summarising, through the present work we found out that 1) virtual reality interventions are superior to controls for both anxious and comorbid depressive symptomatology, 2) attention bias modification procedures are superior to placebo and waitlist for both anxious and depressive symptomatology, in certain conditions, 3) the virtual reality-based attentional control evaluation discriminated better between anxious / depressive participants and healthy ones than the classical computerized attentional control evaluation procedure and 4) that virtual reality-based attention bias modification represents a feasible intervention with tentative results that merit further investigation. These findings compel us to consider a number of methodological and clinical consequences, which are described further below.

4.2. Implications of the present thesis

4.2.1. Methodological implications

From a methodological point of view, the present thesis brings some contributions and fills some gaps in the literature with regard to virtual reality-based evaluation methods and interventions. More specifically, through the first study we updated the methodology regarding virtual reality by taking into account the latest studies in the literature and addressing gaps in previous meta-analytical approaches. More specifically, some of the unique contributions of this study are that we updated the list of included studies to reflect the latest research in the virtual reality, we

investigated the effects of virtual reality-based interventions on comorbid depression, we investigated the effects of virtual reality interventions on treatment attrition and investigated the effects of previously untested potential moderators.

The second study represents in our opinion a significant methodological advance. It is the first network meta-analysis in the field of cognitive bias modification literature. Through this new methodological approach, we were able to investigate the efficacy all types of cognitive bias modification procedures simultaneously and derive indirect contrast between interventions that have never been directly compared before, either in a randomized controlled trial or in a meta-analytical approach. Moreover, we have taken into consideration not only anxious and depressive symptomatology, but also comorbid anxious and depressive symptomatologies.

The third study brings forward some methodological advances, namely the fact that we tested the efficacy of a virtual reality-based attentional control evaluation procedure in discriminating between anxious / depressive symptomatologies and healthy controls, the novelty here being represented by the clinical/subclinical sample and the fact that we demonstrated that the virtual reality procedure can be successfully employed as a better attentional control evaluation method than the classical one.

Finally, the fourth study's main methodological contribution is represented by the fact that the virtual reality-based cognitive bias modification procedures that we used represent a novel and significant addition to the two existing (Ma et al., 2019; Urech et al., 2015) virtual reality attention bias modification interventions. The virtual environment and the evaluation / modification procedures were envisioned and designed by the author of this thesis and Silviu Matu, Ph.D., under the supervision of Professor Daniel David and developed by the E.ON Reality software company, from the ground up. Although not evaluated in the present thesis, the virtual reality-based cognitive bias modification software includes not only the attention bias evaluation and modification procedure, but also a memory bias modification and an interpretation bias modification procedure.

4.2.2. Clinical implications

In addition to the methodological implications, a series of clinical implications can be derived from the present thesis. Mainly, through finding that virtual reality-based interventions are effective in reducing symptoms of anxiety and comorbid depression as compared to control in Study 1, an avenue is opened not only to patients but also to practitioners in using this evidence-based approach in managing anxious / depressive symptomatology, especially when knowing that this type of technology has been proved to be cost effective (Wood et al., 2009; Freeman et al., 2017). Moreover, both patients and therapists can make informed treatment decisions, knowing that the best results are obtained for specific diagnoses (i.e., specific phobia, panic disorder, flight anxiety, social phobia), especially when virtual reality exposure is used. In addition, companies that develop these types of technologies with the specific aim of therapy use can be informed by the fact that number of elements of interaction with the virtual environment was positively associated with better anxiety outcomes. The main clinical implication stemming from Study 2, especially relevant for therapists employing cognitive bias modification procedures either as standalone or as an adjuvant intervention, is that it is recommendable to employ interpretation bias modification procedures at the least, or a combination of attention bias modification and interpretation bias modification procedures at the most, when managing anxious /

depressive symptomatology. Study 3 also has some clinical implications, the main ones being that virtual reality-based attentional control assessment represents a enjoyable and interactive alternative for patients and that this procedure has superior discriminatory power between healthy and clinical populations, thus having the potential to be used as an alternative screening tool. The main clinical contribution of Study 4 is that it shown that a virtual reality-based attention bias modification procedure, at the minimum, has the potential of reducing state anxiety and can be used in this sense as an adjuvant to classical evidence-based therapies.

4.3. Limitations and Further Avenues of Research

As is the case with any research approach, the present thesis has a series of limitations worthy of being mentioned. First, Study 1 revealed high degrees of heterogeneity and large confidence intervals, which add limitations to the solidity of the results. Also, many of the subgroup analyses were underpowered and few moderators were reported in the primary studies. Second, in Study 2 most trials offered no information in relation to study quality, most trials being rated as unclear for most study quality domains. Another limitation of Study 2 is represented by clinical heterogeneity (placebo treatments were considered to be interchangeable across interventions because the principle behind them is the same). Taken together, as in the case of Study 1, these limitations suggest using caution when drawing clinical conclusions. Study 3 also has a series of limitations, the most important one being that we could not separate anxious and depressive symptomatology to run separate comparative analyses with the classical evaluation method, owing to the fact that such a segregation would have lead to underpowered logistical regression models. Moreover, for the same reason, we considered the clinical and subclinical participants as being part of the same group. With regard to Study 4, the main limitation is that we had a small sample size and the comparative analysis between the virtual reality group and the classical intervention group are underpowered. This limitation was mainly imposed by the apparition of the SARS-Cov-2 virus, the study being conducted in the very first year of the epidemic. Another potential limitation of Study 4 is that we did not use clinical samples which could have been more appropriate for the aim of the intervention that were delivered. Taken together, these limitations are indicative of further improvements that can be made in future research, mainly related to recruitment procedures, increased sample sizes and participants clinical status which, if pursued, could make a great difference in the generalizability of the research.

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