A Meta-Analysis of Bias at Baseline in RCTs of Attention Bias Modification: No Evidence for Dot-Probe Bias Towards Threat in Clinical Anxiety and PTSD

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Considerable effort and funding have been spent on developing Attention Bias Modification (ABM) as a treatment for anxiety disorders, theorized to exert therapeutic effects through reduction of a tendency to orient attention toward threat. However, meta-analytical evidence that clinical anxiety is characterized by threat-related attention bias is thin. The largest meta-analysis to date included dot-probe data for $n = 337$ clinically anxious individuals. Baseline measures of biased attention obtained in ABM RCTs form an additional body of data that has not previously been meta-analyzed. This article presents a meta-analysis of threat-related dot-probe bias measured at baseline for 1,005 clinically anxious individuals enrolled in 13 ABM RCTs. Random-effects meta-analysis indicated no evidence that the mean bias index (BI) differed from zero ($k = 13$, $n = 1005$, mean BI = 1.8 ms, $SE = 1.26$ ms, $p = .144$, 95% confidence interval $[-0.6, 4.3]$). Additional Bayes factor analyses also supported the point-zero hypothesis (BF10 = .23), whereas interval-based analysis indicated that mean bias in clinical anxiety is unlikely to extend beyond the 0 to 5 ms interval. Findings are discussed with respect to strengths (relatively large samples, possible bypassing of publication bias), limitations (lack of control comparison, repurposing data, specificity to dot-probe data), and theoretical and practical context. We suggest that it should no longer be assumed that clinically anxious individuals are characterized by selective attention toward threat. Clinically anxious individuals enrolled in RCTs for Attention Bias Modification are not characterized by threat-related attention bias at baseline.

General Scientific Summary
It is widely believed that anxiety is characterized by a tendency to orient attention specifically toward threatening information and that this tendency (called attention bias) can be measured using a computer task called the "dot-probe task." Over the past decade, studies have tested whether a training version of this task can be used to modify bias, which might then be used as a new treatment (Attention Bias Modification). We analyzed levels of attention bias measured before participants started the modification training in 13 studies enrolling 1,005 diagnosed anxious patients. We found no evidence that clinically anxious people are characterized by attention bias toward threat.

Keywords: attention bias, clinical anxiety, meta-analysis, attention bias modification, translational research

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Preferential orienting of attention toward threatening information is theorized to play a role in the etiology and maintenance of (clinical) anxiety.[1] Consequently, it is also considered a putative treatment target in anxiety disorders. Attention Bias Modification (ABM) procedures were initially developed to test whether experimentally inducing or reducing threat-related attention bias results in concomitant changes in anxiety vulnerability. Early findings provided (indirect) experimental evidence for the cognitive theory-derived notion that biased information processing is involved in the etiology and maintenance of anxiety disorders (Harris & Menzies, 1998; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews & MacLeod, 2002). It was not until 2009, however, that further ABM studies were published, several of which were clinical randomized controlled trials (Amir, Beard, Burns, & Bomyea, 2009; Amir, Beard, Taylor, et al., 2009; Hazen, Vasey, & Schmidt, 2009; Schmidt, Richey, Buckner, & Timpano, 2009). These studies were followed within a year by the first meta-analysis evaluating ABM as a treatment (Hakamata et al., 2010). Thus, focus shifted away from studying attention bias's hypothesized role in the etiology and maintenance of anxiety vulnerability, toward establishing the efficacy of ABM as a treatment for clinical anxiety disorders. Since then, it has been assumed that anxiety disorders are indeed characterized by biased attention toward threat. Yet, the meta-analytical evidence of dot-probe bias toward threat in diagnosed anxious samples is not as strong as might be expected.

The first, and largest, meta-analysis on anxiety-related biased attention was published 11 years ago by Bar-Haim and colleagues (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Their meta-analysis includes 172 studies totaling 5,869 individual participants and has been cited over 1,600 times. Meta-analytical estimates were assessed for bias within healthy control, analog high anxious, and clinically anxious samples, as well as for differences in bias between sample types. Studies were included that measured biased processing of negative information with the emotional Stroop ($k = 70/77$ within/between comparisons), dot-probe ($k = 35/44$), or Posner/single cueing task ($k = 7/4$). Relatively consistent evidence of anxiety-related biased processing was found, with medium effect sizes $d \approx .45$. Given our interest in the evidence supporting ABMs proposed treatment target, and because ABM research relies almost exclusively on (variations of) the dot-probe task, we look at the estimates for specifically dot-probe bias in clinically anxious samples (diagnosed with either generalized anxiety disorder [GAD], obsessive compulsive disorder [OCD], post traumatic stress disorder [PTSD], panic disorder, social phobia/social anxiety disorder [SP/SAD], or simple phobia). From Table 2 provided by Bar-Haim and colleagues (2007), it can be seen that dot-probe bias differed significantly from 0 ($d = .34$, 95% confidence interval [CI] [.18, .50]) for 302 clinically anxious participants enrolled in 16 studies. In addition, clinically anxious samples ($n = 337$ in $k = 17$) differed significantly from healthy control groups in magnitude of dot-probe bias (Table 3: $d = .40$, 95% CI [.29, .60][2]). These effects are consistent with those reported for other tasks and anxious analog samples (Bar-Haim et al., 2007). However, a serious limitation on these estimates are the small sample sizes. The clinically anxious groups consisted of ~20 participants on average.

To the best of our knowledge, only two other meta-analyses assessing anxiety-related attention bias have been published

since 2007. In a 2015 meta-analysis (Pergamin-Hight, Naim, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2015), no evidence for disorder-specific threat bias was found in a subset of six dot-probe studies enrolling 115 clinically anxious individuals (PTSD, PD, SAD, or OCD; $d = .12$, $p = .41$). The average sample size of the clinical groups was again ~20, and three of these six studies were also included in the 2007 meta-analysis. A 2016 meta-analysis focused on social anxiety related dot-probe bias for negative facial expressions (Bantin, Stevens, Gerlach, & Hermann, 2016). Three out of 10 studies compared clinically anxious ($n = 89$) to healthy control ($n = 129$) participants on bias for negative faces. Bias was found to differ significantly from 0 across these three clinical samples ($g = .48$, 95% CI [.17, .79]). In addition, magnitude of bias differed between the clinically anxious and healthy control samples ($g = .38$, 95% CI [.10, 0.66]). One of these three studies was also included in the 2007 meta-analysis by Bar-Haim and colleagues (Mogg, Philippot, & Bradley, 2004; also reported in Mogg, Bradley, Miles, & Dixon, 2004). The second was published in 2009 and divided a group of $n = 39$ social phobia patients in two groups who drank either alcohol or orange juice before their dot-probe assessment (Stevens, Rist, & Gerlach, 2009). The third is a study with $n = 35$ generalized social phobia patients (Gotlib et al., 2004), which appears to be the largest clinically anxious sample assessed in the "measuring and comparing dot-probe bias" literature to date. Thus, from three meta-analyses a picture emerges that the, commonly assumed, phenomenon of dot-probe bias toward threatening information has only been documented for 20–25 small clinically anxious samples.

Increased awareness of statistical power, and the necessity of assessing sufficiently large samples, form a major development in psychology research over the past decade. The meta-analysis by Bar-Haim and colleagues (2007) indicated an estimated medium effect size ($d = 0.40$) for the comparison of clinical and control samples on threat-related dot-probe bias. For a single study to detect a between-subjects effect of this size, a total n of 198 (99 per group) would be required to achieve 80% power (and a total n of 328 for 95% power). However, more than a decade after the 2007 meta-analysis, no study has compared biased attention between clinical and control groups even approximately this size. Thus, the assumed association between clinical anxiety and dot-probe bias toward threat has not been verified in a single study with sufficient statistical power.

Yet, there exists an additional source of data on threat-related attention bias in clinical anxiety. In several ABM RCTs, threat-related attention bias was assessed before and after the intervention in relatively large (up to $n = 134$ in Rapee et al., 2013) and relatively well-defined clinical samples. Baseline measures of bias obtained in these RCTs have not previously been meta-analyzed. The previously discussed meta-analyses did not select ABM RCTs

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[1] In DSM–5 (American Psychiatric Association, 2013), PTSD was moved to a newly defined class of "Trauma- and stressor-related disorders." Before that time, it was considered an anxiety disorder. This is reflected in the attention bias and ABM literature, where PTSD is historically understood to be routinely included in the term "anxiety" (Bar-Haim et al., 2007). Throughout this article, we adhere to the DSM–IV definitions and understand the term anxiety disorders to include PTSD.

[2] Throughout this article, the findings of the meta-analysis by Bar-Haim and colleagues are given with 95% confidence intervals calculated from the 85% confidence intervals reported in the original article.

either because the meta-analysis predates publication of ABM RCTs (Bar-Haim et al., 2007); because RCTs tend not to allow comparison of bias for disorder-congruent and disorder-incongruent threat stimuli (Pergamin-Hight et al., 2015), or because RCTs tend not to include healthy control groups in addition to clinical or analog groups (Bantin et al., 2016). Yet, recent literature on biased attention in clinical anxiety consists almost entirely of bias modification studies, that is, studies evaluating ABM interventions (often active vs. placebo training) in groups that are not expected to differ at baseline (e.g., all individuals are clinically anxious or vulnerable at baseline and randomized to treatment conditions). Although the question whether magnitude of bias differs between clinical and control samples is important, the assumption that clinical anxiety is characterized by threat-related bias can be verified using data from ABM RCTs, even if these enrolled only clinically anxious individuals. The dot-probe derived Bias Index (BI) is measured on a bidirectional scale with an inherently meaningful zero value that enables us to test whether the average bias within clinical samples differs from 0 (also see the within-group analyses in Bar-Haim et al., 2007). A one-sample test of mean BI against zero assesses whether individuals in the sample responded, on average, faster (bias toward) or slower (bias away) on trials in which a response cue appeared in the location previously taken by a threat stimulus (congruent trials), compared with trials in which the response cue appeared in the location of a neutral stimulus (incongruent trials; MacLeod, Mathews, & Tata, 1986; MacLeod et al., 2002). If mean BI does not significantly differ from zero, the null hypothesis that no bias is present cannot be rejected.

Apart from adding information based on a body of data that has not yet been meta-analyzed for this question, an additional benefit of meta-analyzing data from ABM RCTs is that it may partly bypass publication bias effects. This is because, in a typical RCT design, the baseline measure is not the outcome of interest. Therefore, bias not being observed at baseline does not necessarily reduce the entire study to a difficult-to-publish null finding. Several published ABM RCTs have been preregistered studies, which strengthens the idea that this subset of the attention bias literature might be less affected by publication bias than the wider literature comparing bias between clinical and control groups.

Thus, we present a meta-analysis of biased attention obtained at baseline in ABM RCTs enrolling clinically anxious samples. The aim of this meta-analysis is to verify the presence of threat-related biased attention, preceding attempted modification thereof. In line with prevailing theory, our formal hypothesis is that biased attention toward threatening information will be observed for the pooled clinically anxious samples.[3] In follow-up analyses, we use Bayesian methods to assess the relative strength of evidence for various BI effect sizes in milliseconds (ms).

Method

The Prisma checklist for this article can be found in Supplemental Material S1 (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). Although no formal review protocol was prepared, a custom-built review app was built using *R* package shiny (Chang, Cheng, Allaire, Xie, & Jonathan, 2017) and detailed below. The code and required data are included as Supplemental Material S2a and S2b.

Record Selection and Data Extraction

The selection of records was done in several stages. First, a search string was developed with the aim of retrieving as many English-written dot-probe ABM studies as possible from the Scopus database (www.scopus.com). The last update to our dataset was done on March 20, 2018 when a search in Scopus using the above string returned 1181 records. The search string used in Scopus was:

(TITLE-ABS-KEY (("dot-probe" OR "probe detection task" OR "visual probe" OR "attentional probe task" OR "probe classification task" OR "atten* bias modification") OR ("atten* retrain*" AND "probe")) AND TITLE-ABS-KEY ("bias*" OR "atten*")) AND LANGUAGE ("English")

Once imported in *R*, records were subjected to a filter selecting those records for which at least one of the terms "RCT," "randomized controlled," "randomized controlled," "intervention," or "program," plus at least one of the terms anx*," "SAD," "GAD," "OCD," phobi*," "PTSD," "panic," and at least one of the terms "patient*," "diagnos*," "clinic*" were found across each record's title, abstract, and (index and author supplied) keywords. Resulting records were subsequently loaded into a purpose-built app to aid the two assessors (SP and AWK) in the process of record selection and data extraction. The app guides the assessor through a two-stage record selection and data extraction procedure. For the first stage, each record's title, abstract, and keywords are shown, and the assessor is asked to fill out their assessment for the following inclusion criteria:

- Study aims to evaluate effects of a bias modification procedure (ABM/CBM/other)?
- Assesses attention allocation bias to threatening information?
- Participants are adults?
- Clinical/diagnosed anxiety?

For each of the above questions, answer options were yes, no, and possibly. If a 'no' answer was entered for any of the above four questions, the answer to the final question ("select for Stage II") was automatically toggled from '?' to 'no' and vice versa if the answer was changed again to yes or possibly. When all four criteria had an answer 'yes' or 'possibly,' "select for Stage II" was toggled to 'yes'. The assessor manually submitted the information for each record before moving on to the next record.

For Stage II, the assessor is again presented with a list of records to assess, now with an additional DOI-based hyperlink to retrieve the article and answer the remaining questions. In Stage II, the four inclusion criteria above had to be reconfirmed. In addition, the assessor was asked to indicate the primary diagnosis (choice of: GAD, OCD, panic disorder, PTSD, SP/SAD, and simple phobia) and the diagnostic instrument used. Assessors also had to indicate whether individuals with comorbid mood disorder were excluded, the number of groups in the

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[3] Yet, from being involved with this field, we also know that a clear bias towards threat is often not observed at baseline in ABM RCTs (also see Mogg, Waters, & Bradley, 2017). We disclose that our personal expectations run counter to the formal theory-derived hypothesis, although we hope that a meta-analysis may uncover what is not clearly visible in separate studies.

study, and various aspects of the bias assessment task used: type (dot-probe or Posner task), stimulus latency (<500, 500–<1,000, ≥1,000, or other/mixed), and stimulus type (words, faces, scenes, or other/mixed). These options were adapted from the procedure described by Bar-Haim and colleagues (2007). If available in the article, the assessors could enter for each group the number of participants as well as the mean and *SD* for the BI obtained at baseline. From these, mean BI and *SD* were calculated, collapsing the two (or more) clinical groups within each study. Mean bias was calculated as the *n*-weighted mean BI ($\sum(n_i \times M_i)/\sum(n_i)$) and pooled *SD* as $sqrt(\sum(n_i\text{-}1 \times SD_i^2)/\sum(n_i\text{-}1))$. The assessor could enter comments, indicate if they felt additional data should be requested, and create additional records if a second study was presented in the same article. Finally: the assessor had to indicate their recommendation for inclusion in the meta-analysis.

A total of 394 records were "Stage I assessed" by each of the two assessors, who selected 36 and 37 records for Stage II assessment, respectively (29 records in common). Following their individual Stage II assessments, all data was gathered and used to reach consensus on the final set of studies to include. For most records, the required data could be extracted from the published articles. It was verified that both assessors extracted identical values for each of these records. This resulted in the discovery of one typing error and one mix-up of values, which were subsequently corrected. As a final check, one of the assessors (AWK) manually compared the resulting selection to three recent meta-analysis assessing effects of ABM (Cristea,

Kok, & Cuijpers, 2015; Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; Price et al., 2016) to verify that all relevant studies included in these meta-analyses were also selected for the current meta-analysis. This resulted in identification of one additional study eligible for inclusion.

For seven records, authors were contacted with a request to provide additional data. Most contacted authors kindly provided us with the requested data, and one group informed us that the bias data for their study was regrettably lost. One corresponding author did not respond to three emails sent over a 9-month period. For one study, mean and *SD* of the baseline bias index was inferred from a plot showing the baseline mean BI plus/min 1 *SD* on the *x*-axis (Kuckertz et al., 2014), while two other studies selected by the assessors could not be included in the final meta-analysis (*n* = 22 and 29; also see Table 1).

Exclusion of Posner Task Assessed Bias

During our initial assessment of records, we also selected ABM RCTs assessing pretraining bias with the Posner/single cueing task with the intention of either reaching agreement with the involved authors on how to calculate an index of its four trial-types that is similar enough to dot-probe's (two trial-types based) index, or performing a separate analysis of these studies. Three RCTs using the Posner task were identified as eligible for inclusion (Amir, Beard, Taylor, et al., 2009; Amir, Weber, Beard, Bomyea, & Taylor, 2008; Boettcher, Berger, & Renneberg, 2012). We became aware, however, that while Posner tasks' four trial-types can be

Table 1
Overview of Studies Selected for Inclusion

No.	Study	Primary diagnosis	Diagnostic instrument	Stimulus type	Additional data?	Included	*n* total
1	Boettcher et al. (2013)	SP/SAD	SCID	Words or words and faces		Yes	129
2	Neubauer et al. (2013)	SP/SAD	SCID	Faces	Authors provided values for baseline BI	Yes	56
3	Rapee et al. (2013)	SP/SAD	ADIS	Words	Authors provided values for BI in the first baseline session	Yes	134
4	Schoorl, Putman, and van der Does (2012)	PTSD	CAPS	Scenes		Yes	102
5	Boettcher et al. (2014)	SP/SAD	SCID	Words and faces		Yes	133
6	Kuckertz et al. (2014)	PTSD	Clinician	Words	No response. Mean and *SD* (BI) inferred from Figure 4	Yes	29
7	Badura-Brack et al. (2015) - S1	PTSD	CAPS	Words		Yes	52
8	Badura-Brack et al. (2015) - S2	PTSD	CAPS	Faces		Yes	46
9	Carleton et al. (2015)	SP/SAD	SCID	Words	Authors provided values for baseline BI	Yes	82
10	Beard et al. (2016)	PD	SCID	Faces		Yes	7
11	Carleton, Teale Sapach, Oriet, and LeBouthillier (2017)	SP/SAD	SCID	Words	Authors provided values for baseline BI	Yes	90
12	Lazarov et al. (2017)	SP/SAD	LSAS	Faces		Yes	50
13	Naim, Kivity, Bar-Haim, and Huppert (2018)	SP/SAD	MINI	Faces		Yes	95
	Amir, Beard, Burns, and Bomyea (2009)	GAD	SCID	Words	No response	No	29
	Fang, Sawyer, Aderka, and Hofmann (2013)	SP/SAD	ADIS	Faces	Authors kindly informed us that BI data is lost	No	22

Note. BI = bias index; SP/SAD = social phobia/social anxiety disorder; PTSD = post traumatic stress disorder; PD = panic disorder; GAD = generalized anxiety disorder; SCID = Structured Clinical Interview for DSM; ADIS = Anxiety Disorders Interview Schedule; CAPS = Clinician-Administered PTSD Scale; LSAS = Liebowitz Social Anxiety Scale; MINI = Mini-International Neuropsychiatric Interview. All included studies assessed bias at 500–1000 stimulus latency and none of the studies excluded participants based on comorbid mood-disorder.

combined into a single index (Mogg, Holmes, Garner, & Bradley, 2008), the interpretation of this index is not straightforward: depending on which of two validity effects occurred (cue facilitation or inhibition of return), opposing scores can be interpreted as indicative of more bias in the sense of more influence of the emotional stimulus on the response time. It is perhaps for this reason that some ABM studies focused on an index based on threat stimulus trials only, yet this contrast does not correct for attention capturing (or inhibition of return) invoked by any stimulus regardless of emotional content. In addition, the corresponding author for two of these three articles did not respond to our requests. For these reasons we dropped the remaining record with the Posner task completely from our analysis (authors of this RCT assessed all four trial-types using analysis of variance (ANOVA) and concluded that "participants in both groups showed a biased attention away from threat at pre- and at post-assessment" (Boettcher et al., 2012, p. 530).

Statistical Analysis

The main meta-analysis was performed in *R*, using the RMA() function in the metafor package to a fit a restricted maximum-likelihood model (REML; Viechtbauer, 2010). Inputs were mean BI values in ms for the effect size, and sampling variance calculated as (SD_i^2/n_i). Metafor functions were also used to assess the model fit, to perform influence tests and the Duval and Tweedie trim and fill procedure, and to create funnel and forest plots.

Bayesian meta-analyses were performed using the meta.ttestBF() function in the BayesFactor package (Morey & Rouder, 2015). The required *t* values to input for each record (*i*) were calculated as $M_i/$ sqrt(SD_i^2/n_i). Our primary Bayes factor analysis tests the relative likelihood of a point zero hypothesis. It differs from the REML analysis in that meta.ttestBF() assesses strength of evidence for a "singular underlying true effect" and is, therefore, essentially a fixed effect analysis. As a secondary Bayesian (and tertiary overall) analysis, we developed effect size interval analyses. To enable these, an overall sigma value was calculated as the "*n*-weighted mean bias index divided by mean delta," in which mean delta is the "*n*-weighted average of effect size *d′*," and *d* is computed as $t_i/$sqrt(n_i). The overall sigma value was used to define null-intervals in milliseconds, to obtain Bayes factors expressing relative support for BI falling within each of a series of millisecond-wide intervals. We will introduce the interval-not_interval Bayes factors further in the results section. The full analysis script and data are available as Supplemental Material S3a and S3b.

Results

The final selection consisted of k = 13 studies, with a total *n* of 1,005 clinically anxious individuals (range: *n* = 7 to *n* = 134; see Table 1 for details).

REML Analysis

The REML model indicated that mean BI does not differ significantly from zero (*k* = 13, *n* = 1,005, mean BI = 1.8, *SE* = 1.26, *p* = .144, 95% CI [−.6, 4.3]). Given *SE* = 1.26 and *n* = 1,005, an average bias of 1.8 ms corresponds to a standardized

effect size *d* = .05. The forest plot for the complete (*k* = 13) dataset is presented in Figure 1.

The *Q*-test for heterogeneity returned significant (*Q*(12) = 46.3, *p* < .001), and influence tests indicated that the first study by Badura-Brack and colleagues forms an outlier in this set of studies (studentized residual = 5.2, Cook's distance = 2.5, *df*β = 4.1). When excluding this record from the analysis, the *Q*-test no longer indicates heterogeneity (*Q*(11) = 16.8, *p* = .115). As would be expected from eyeballing the forest plot (see Figure 1), excluding this record (Badura-Brack et al., 2015 - S1), does not change the result of no support for the hypothesis that the mean BI differs from point zero (*k* = 12, *n* = 953, mean BI = −.16, *SE* = .52, *p* = .767, 95% CI [−1.8, .9]). Yet, given that it is unclear what caused this record to be an outlier in this collection, the record was retained for the remainder of the analyses unless indicated otherwise. The reader may keep in mind that for any analysis, exclusion of this record would lower the estimated mean average bias index.

The Duval and Tweedie trim and fill procedure gave no indication of publication bias based on this outcome (baseline BI), estimating only one possibly missing small-sized study in the lower left quadrant (see Figure 2).

REML Subset Analyses

Repeating the REML analysis for subgroups of studies enrolling SP/SAD or PTSD patients and for subgroups of studies using (only) word or face stimuli did not lead to different or additional insights (see Table 2). It should be noted, however, that the funnel plot for the SP/SAD subset shows substantial asymmetry, which may indicate publication bias. Duval and Tweedie trim and fill procedure suggest that in this set three studies are missing on the left side (see Supplemental Material S4).

Two of the included studies (Boettcher, Hasselrot, Sund, Andersson, & Carlbring, 2014; Boettcher et al., 2013), assessed bias for more negative information with a mixture of negative-neutral, negative-positive, and positive-negative trials. Excluding these two records (totaling 262 participants) does not meaningfully alter
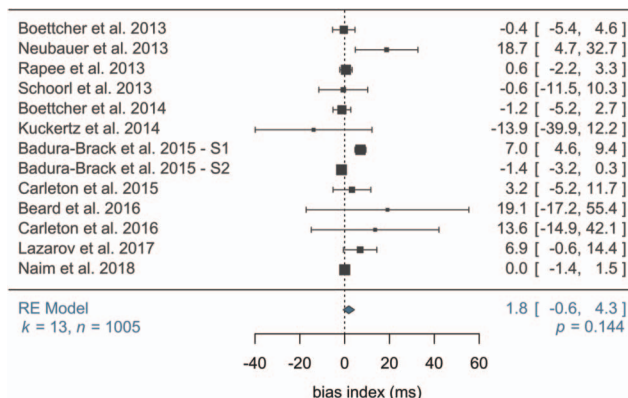

Boettcher et al. 2013		-0.4 [-5.4, 4.6]
Neubauer et al. 2013		18.7 [4.7, 32.7]
Rapee et al. 2013		0.6 [-2.2, 3.3]
Schoorl et al. 2013		-0.6 [-11.5, 10.3]
Boettcher et al. 2014		-1.2 [-5.2, 2.7]
Kuckertz et al. 2014		-13.9 [-39.9, 12.2]
Badura-Brack et al. 2015 - S1		7.0 [4.6, 9.4]
Badura-Brack et al. 2015 - S2		-1.4 [-3.2, 0.3]
Carleton et al. 2015		3.2 [-5.2, 11.7]
Beard et al. 2016		19.1 [-17.2, 55.4]
Carleton et al. 2016		13.6 [-14.9, 42.1]
Lazarov et al. 2017		6.9 [-0.6, 14.4]
Naim et al. 2018		0.0 [-1.4, 1.5]
RE Model k = 13, n = 1005		1.8 [-0.6, 4.3] p = 0.144

bias index (ms)

Figure 1. Restricted maximum-likelihood model (REML) analysis forest plot. Estimates are in milliseconds bias. The individual study estimate squares are sized proportionally to the study weights (i.e. the inverse of each study's effect size variance). The diamond shape indicates the overall effect size estimate and spans its 95% confidence interval. See the online article for the color version of this figure.
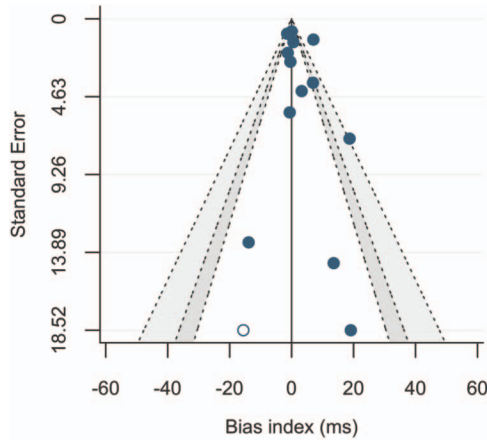
Figure 2. Contour-enhanced funnel plot for the 13 included records (closed dots) and one Duval and Tweedie trim and fill procedure estimated potentially missing record (open dot). The contour lines indicate (from inside to outside) the boundaries for p = .10, .05, and .01. Estimates are in milliseconds (bias). See the online article for the color version of this figure.

the results ($k = 11$, $n = 743$, mean BI = 2.7, $SE = 1.58$, $p = .084$, 95% CI [$-.4$, 5.8]). In this subset, the Q-test for heterogeneity is significant, with the first study by Badura-Brack being marked as an outlier. Removing this study in addition to the two mixed-trials studies yields again a homogenous set for which REML analysis returns: ($k = 10$ $n = 691$, mean BI = .3, $SE = .78$, $p = .34$, 95% CI [-1.3, 1.8]). The funnel plot for this set also shows asymmetry (see Supplemental Material S4).

Bayes Factor Analyses

Bayes factors are indices of relative support for one hypothesis over another. In traditional null hypothesis statistical testing (NHST), the probability of the observed data given a null hypothesis (e.g., "no difference from zero") is calculated. If the probability of the observed data under the null hypothesis falls below a certain threshold (typically $p = .05$), the null hypothesis is rejected and, consequently, the alternative hypothesis is accepted. Notice that there is no actual testing of the alternative hypothesis involved: in NHST it is only possible to reject or to not reject the null hypothesis. Rather than the probability

of the data given the null hypothesis, Bayesian analysis provides the likelihood of competing hypotheses given the observed data. More important, a low likelihood for one hypothesis does not automatically result in acceptance of an alternative. It is possible to conclude that the available data is insufficient to determine which hypothesis is most likely (also see Dienes, 2014). The likelihood of one hypothesis over another can be expressed in a ratio called Bayes factor. A BF10 represents the likelihood of an alternative hypothesis over (divided by) the likelihood of a null hypothesis: a BF10 with value x indicates that the alternative hypothesis (H_1) is x times as likely as the null hypothesis (H_0). Its inverse, the BF01, represents the likelihood of the null hypothesis over the alternative hypothesis: if BF10 = .33, BF01 = 3 (indicating that, based on the available data, the null hypothesis is three times as likely as the alternative hypothesis). Bayes factors take value 1 when both hypotheses are equally likely given the data, leading to the conclusion of insufficient information/data. Finally, when we know Bayes factors for two alternative hypotheses relative to the same null hypothesis, we can divide one by the other to obtain a Bayes factor estimating the evidence in favor of one alternative hypothesis over the other: BFab = BFa0/BFb0. We use this method in our analyses to assess the likelihood that the mean bias index falls within a specified interval rather than outside this same interval. Using the BayesFactor package null interval option, we first obtain two Bayes factors expressing the relative evidence for the hypotheses that the mean falls within a specified interval (iv) and "not in the interval" (niv), both relative to the null hypothesis: BF_iv_0 and BF_niv_0. Next, we divide these two Bayes factors to arrive at the Bayes factor for interval over not-interval (BF_iv_niv = BF_iv_0/BF_niv_0). This Bayes factor expresses the likelihood that the mean BI falls inside the specified interval relative to the likelihood that it falls outside the interval.

Bayesian Point Zero Analysis

The Bayes factor most similar to the NHST assessed one-sample test of null hypothesis "mean BI is zero," is a BF10 comparing the hypotheses "H_0: mean BI is zero" and "H_1: mean BI is not zero." Using a standard Cauchy prior ($r = .707$), BF10 = .23 indicating substantial evidence for the H_0 over the H_1 (Wetzels & Wagenmakers, 2012). In other words: it is about 4.4 times as likely that the mean bias index is point zero than that the mean bias index is not point zero (BF01 = 1/BF10 = 4.4).

Table 2
REML Analysis for Subsets by Diagnosis or Stimulus Type

Subset	k	n	BI	SE	p	95% CI	Duval and Tweedie estimated n missing
SP/SAD	9	769	.4	.59	.531	[$-.8$, 1.5]	3
PTSD	4	229	1.3	3.13	.670	[-4.8, 7.5]	1
Outlier removed	3	177	-1.4	.87	.095	[-3.2, .3]	0
Words only	5	387	3.5	2.28	.128	[-1.0, 8.0]	0
Outlier removed	4	335	.78	1.31	.552	[-1.7, 3.3]	0
Faces only	5	254	4.2	3.47	.221	[-2.6, 11.0]	1
Outlier removed	4	198	$-.23$	.88	.801	[-2.0, 1.5]	1

Note. REML = restricted maximum-likelihood model; BI = bias index; CI = confidence interval; PTSD = posttraumatic stress disorder; SP/SAD = social phobia/social anxiety disorder. When Q-tests indicated heterogeneity, the most influential studies were removed (one at a time) until the resulting Q-test was no longer significant. This approach never resulted in more than 1 record being removed.
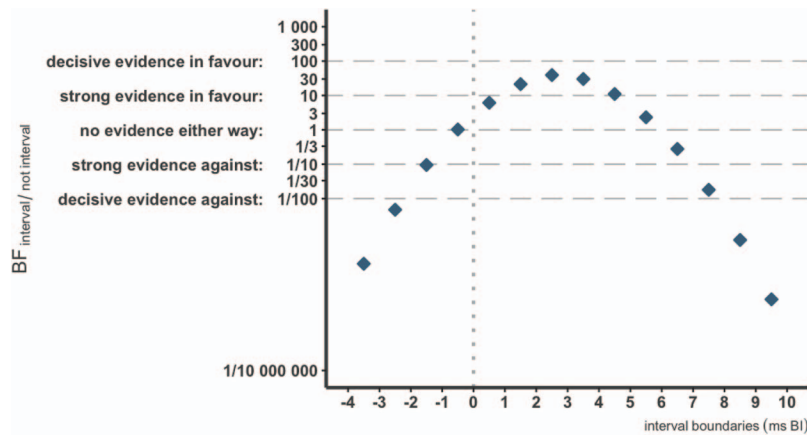
Figure 3. Interval/not interval Bayes factors plot. Intervals are defined in milliseconds bias. Bayes factor evidence labels as defined by Wetzels and Wagenmakers (2012). See the online article for the color version of this figure.

Bayesian Millisecond-Wide Interval Analyses

Yet, the point zero hypothesis is a very unlikely hypothesis: it tests the likelihood that the estimated mean is exactly 0. For this reason, the authors of the BayesFactor package implemented a null interval option, which can be used to define an interval around zero indicating effect sizes that are considered too small to be of interest (Morey & Rouder, 2011). In the context of dot-probe derived bias this could be a minimum mean BI for which consensus exists that such a small difference is likely not meaningful. However, the dot-probe literature does not provide many clues as to what minimum BI size would be broadly accepted as being inconsequentially small. Therefore, we opted for a practical rather than a theoretical threshold and took 1 ms to be the smallest possible meaningful unit: millisecond precision of measurement is the absolute best we can hope to achieve with our current hard- and software, even if in practice this will often not be achieved.

For null interval $[-1:1]$, the BF_iv_0 = .78, indicating "anecdotal" support for the point-zero hypothesis over the hypothesis that the mean falls within an interval of 1 ms around (and including) 0. When we assess the relative support for the hypothesis that mean BI falls outside of the $[-1:1]$ ms interval, the BF_niv_0 is .21, indicating moderate support for the point-zero hypothesis over the hypothesis that BI is larger than 1 ms (in either direction). Next, we "remove" the point-zero hypothesis from the equation (by dividing the BF_iv_0 by the BF_niv_0) and obtain the BF for the competing hypotheses that the mean BI falls outside an interval of 1 ms to either side of 0, versus that the mean BI falls within this interval. The resulting BF_iv_niv = 3.6, indicating that it is 3.6 times as likely that mean BI falls inside the $[-1: 1]$ ms interval as that it falls outside this interval.

Finally, we take this analysis-format several steps further by assessing BF_iv_niv for a series of 14 1-ms-wide intervals that are not centered on zero but "move" along the range from -4 to 10 ms. The results are plotted in Figure 3. This figure allows the reader to assess that strong (yet not decisive) support is obtained for BI to fall in the [2: 3] ms interval (BF_iv_niv = 39.3). It can also be observed that it is highly unlikely for BI to be larger than 2 ms away from threat, or 8 ms toward threat (BFs <1/100). In addition, it can be seen that BI will most likely fall in the 0 to 5 ms range of intervals (BFs >3). Indeed, the BF_iv_niv for the 5-ms-wide interval [0:5] = 369.1, which is a BF value that is typically interpreted as decisive evidence.[4]

Discussion

The current meta-analysis found no evidence for threat-related attention bias in clinically anxious individuals. Data consisted of mean threat-related dot-probe indices obtained from 13 RCTs for ABM, representing a total of 1,005 clinically diagnosed patients. REML estimated mean bias was 1.8 ms, corresponding to a standardized effect size $d = .05$. Secondary analysis using Bayes factors suggested that if attention bias exists in these clinically anxious samples it most likely falls within the 0 to 5 ms range, which we consider to be inconsequentially small.

This meta-analysis adds evidence based on studies not previously included in meta-analyses of biased attention in clinical anxiety. The included clinical samples ranged in size from $n = 7$ to $n = 134$, with the median sample size ($n = 82$) being four times as large as the commonly used sample size of $n \approx 20$ in extant studies measuring and comparing bias between clinical and control groups. The 13 included studies enrolled a total of 1,005 clinically anxious individuals, which is about three times as many as were included in the "dot-probe bias in clinically anxious samples" subanalyses of the largest meta-analysis of attentional bias to date (Bar-Haim et al., 2007).

Data Repurposing

We meta-analyzed baseline measures from ABM RCTs, which were not collected to be analyzed to answer the question we sought to answer. We consider this to be a strength of our design because (a) it is less likely that publication bias has affected this body of

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[4] Note that the denominators (not interval) for the BF_iv_niv are equally sized but not identical (as they "move with" the interval defined) and, therefore, these BFs cannot be used to compute further BFs (for instance summation of the 1 ms intervals to a wider interval).

literature since baseline bias is typically not an outcome of interest for these studies, and (b) this is a larger body of data than is available from studies designed to measure and compare bias, enrolling often relatively well-defined samples of clinically anxious patients.

Specificity of Findings to Dot-Probe Bias

This meta-analysis is specific to threat-related attention bias as measured with the dot-probe. We did not include studies measuring bias by means of other tasks such as the emotional Stroop task, though results obtained with either task have been pooled in the past (Bar-Haim et al., 2007). The main reason is that ABM procedures are predominantly dot-probe based. Further, dot-probe and emotional Stroop tasks likely measure different cognitive processes in the sense that dot-probe bias is assumed to reflect the additional time required to spatially reallocate attention when it has been drawn to a specific position on a display, whereas emotional Stroop bias is thought to reflect the additional time required to resolve a potential conflict in internal response selection. In 2007, considerably more published studies had used the emotional Stroop than the dot-probe task ($k = 77$ vs. $k = 44$ in Bar-Haim et al., 2007) yet, since then, focus has shifted to the dot-probe task. Although the dot-probe task was specifically designed to overcome shortcomings of the emotional Stroop task (MacLeod et al., 1986), we have previously suggested that the near-exclusive focus on dot-probe over the past decade may be at least partly because of the development of dot-probe based ABM procedures (Kruijt, Field, & Fox, 2016). Nonetheless, the current findings do not rule out the possibility that other types of processing bias, measured with other tasks, play a role in clinical anxiety. We are, however, hesitant to imply that the emotional Stroop, or any other currently existing measure of attention bias, might provide a more suitable basis for ABM. We discuss problems to do with task reliability and reliance on analog samples further below and suggest that these may apply also to other, currently existing, bias assessment methods.

Implications Regarding Attention Bias in Healthy Controls

The current meta-analytical results indicate that clinically anxious individuals are not characterized by threat-related attention bias. Yet, our methods did not permit comparison of bias magnitude between clinically anxious and healthy control samples. It is, therefore, possible that healthy control samples display a dot-probe bias that is absent in clinically anxious samples. Nonanxious controls might, for instance, demonstrate a bias *away* from threat, which we found to be absent in clinically anxious samples. This would be a rather different pattern, however, from the pattern implied by the common statement that clinically anxious individuals are characterized by threat-related attention bias. Future research could investigate whether there is evidence for such differential threat-related biased attention by contrasting sufficiently large clinical and control samples on sufficiently reliable measures Yet, given the current results, and in lieu of even a single qualifying study, we propose reconsidering any statements implying that clinical anxiety is shown to be associated with threat-related biased attention.

Lack of Task Reliability and Adequate Samples

While we conclude that clinical anxiety is not characterized by biased attention assessed with the dot-probe task, the simplest explanation for our finding is that the dot-probe task does not reliably assess biased attention. Several recent studies assessed internal reliability of the dot-probe bias index and found it to be unacceptably low (e.g., reliability estimates varying between −.70 and .59 were reported in the following studies: Bar-Haim et al., 2010; Brown et al., 2014; Enock, Hofmann, & McNally, 2014; Kappenman, Farrens, Luck, & Proudfit, 2014; Price et al., 2015; Rodebaugh et al., 2016; Schmukle, 2005; Staugaard, 2009; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014; Waechter & Stolz, 2015; in addition see Jones, Christiansen, & Field, 2018; Kruijt et al., 2016; McNally, 2018; Mogg & Bradley, 2018; Parsons, Kruijt, & Fox, 2018; Roy, Dennis, & Warner, 2015; Sigurjónsdóttir, Sigurðardóttir, Björnsson, & Kristjánsson, 2015). This raises two important questions. First, whether any findings ever reported based on the dot-probe task have been reliable, and second why the notion that clinical anxiety is characterized by dot-probe related threat-bias became so well-established that more than a thousand anxiety patients have been enrolled in RCTs for dot-probe based ABM. Although a reasonably large number of studies assessing dot-probe bias in small clinically anxious samples have been published, a substantial part of the data indicating biased attention in anxiety-related information processing has been obtained from analog samples. Overreliance on, and overgeneralization from, analog samples has been common practice in the biased information-processing field (and indeed throughout experimental psychology) for decades. Similarly, awareness of the problems associated with small sample sizes and the probability of publication bias have long remained low (Tackett, Brandes, King, & Markon, n.d.). These four factors (low task reliability, overreliance on analog samples, low sample sizes, and potential publication bias) may have contributed to the field being firmly under the impression that that anxiety-related biased attention was well established when bias modification methods were first developed, when the evidence base was, in fact, not as strong as was assumed. Two quotes from the seminal article on ABM (MacLeod et al., 2002) may serve to illustrate this. In the beginning of the article, it is stated that "*Although the existence of this association between anxiety vulnerability and negative attentional bias now stands beyond contention, no compelling evidence yet has served to establish the causal nature of the relationship*" (MacLeod et al., 2002, p. 108). The article then details two studies (each enrolling $n = 64$ students) in which it was found that engaging in different versions of a training task, now known as dot-probe ABM, resulted in differential reactivity to a laboratory stressor procedure. Macleod and colleagues end their article expressing that "*we hope that this research may signal the commencement of a new chapter within this literature, characterized by a collective endeavor to exploit the therapeutic potential of novel cognitive–experimental procedures, designed to directly modify the patterns of distorted information processing known to be associated with emotional pathology*" (MacLeod et al., 2002, p. 121). Five years later, the meta-analysis reported by Bar-Haim and colleagues (Bar-Haim et al., 2007) confirmed the assumption that the available literature indicated a consistent threat-related attention bias for clinical as well as analog groups, and ABM RCTs were published from 2009

onward. In hindsight, the field (ourselves included) missed the fact that the very large 2007 meta-analysis included data on dot-probe bias for only a small number of clinically anxious individuals ($n = 302/337$ for the within/between analyses). In retrospect, it might have been better if larger patient samples had first been engaged in, relatively less demanding, studies aimed at establishing whether their information processing tendencies can be reliably observed to differ from healthy controls. By meta-analyzing the RCT baseline bias measures, the current meta-analysis provides part of the information that could have been obtained from such studies.

Implications for Cognitive Models and Development of ABM as a Treatment

The existence of information processing biases is integral to cognitive–behavioral theory, which is an important framework for clinical practice. Information processing-based theories of emotional disorders (e.g., Beck & Clark, 1997; Cisler & Koster, 2010; Eysenck, Derakshan, Santos, & Calvo, 2007; Mathews & Mackintosh, 1998; Mogg & Bradley, 1998; Öhman, 1993; Rapee & Heimberg, 1997; Wells & Matthews, 1996; Williams, Watts, MacLeod, & Mathews, 1988), in particular, rely on the notion that biased information processing is characteristic of emotional disorders. A conclusion that clinical anxiety is not characterized by dot-probe bias toward threat has implications beyond the question of whether dot-probe bias forms a suitable treatment target. Yet, implications of the current meta-analysis will vary for various existing theories. It will be to the wider field to parse our findings with theory and future research. It is, for instance, worth noting that the currently analyzed bias indices all derived from dot-probe tasks using a stimulus duration of 500 ms. While this represents the standard task used in ABM research, several theoretical accounts may be interpreted to predict that bias is optimally measured at earlier timeframes. Moreover, some theories assume involvement of additional factors that are typically not assessed in ABM RCTs and were also not assessed in this meta-analysis. Cognitive-motivational models of anxiety, for instance, propose that multiple motivational and cognitive control processes interact and that this may result in anxiety-related attention being biased *away* from threat as well as *toward* threat (Mogg & Bradley, 2018). Verification of such variable bias will require newly developed tasks to provide a reliable estimation of individual bias. The current result of average dot-probe derived BI not differing from zero, however, could be interpreted to suggest that bias may be balanced, that is, that at any given time-point a roughly equal proportion of clinically anxious individuals tends to orient toward and away from threat. With respect to the ongoing development of ABM, our results challenge the assumption that reducing threat-related biased attention will reduce anxiety vulnerability. All the more so because ABM may be rendered ineffective, on a task-mechanical level, by the absence of baseline bias (Kruijt & Carlbring, 2018). Thus, the current results suggest that fundamental assumptions of ABM need to be reevaluated and provide relevant information for theoretical revisions.

Conclusion

Clinically anxious individuals enrolled in RCTs for ABM are not characterized by threat-related attention bias at the start of their trials. The field should endeavor to set the record straight on this phenomenon that is commonly declared to characterize clinically anxious individuals. We propose that it will be important to (a) develop better and more reliable ways of assessing information processing biases, and (b) explore theoretical approaches that do not specifically predict preferential orienting toward threat to constitute a central feature of clinical anxiety disorders.

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