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Predictive value of attentional bias for the recurrence of depression: A 4-year prospective study in remitted depressed individuals

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ABSTRACT

Previous research showed that individuals who were remitted from a depressive disorder displayed heightened attention towards negative adjectives (e.g., worthless). We tested if this attentional bias (AB) is predictive of future recurrence of depressive episodes and/or having depressive symptoms at 2- and 4-year follow-up. We used a longitudinal approach within the Netherlands Study of Depression and Anxiety (NESDA) and selected participants who were remitted from Major Depressive Disorder (MDD) (n = 918). AB was measured with a verbal Exogenous Cueing Task; using 2 presentation times (500 and 1250 ms) and 3 stimulus types (negative, positive, neutral). Over 4 years, we prospectively assessed recurrence of depressive episodes and depressive symptomatology after participants completed the ECT. Diagnosis of depressive disorder was measured with clinical rating-scales and self-report questionnaires. A heightened probability of recurrence was neither associated with (heightened) AB for negative nor with (lowered) AB for positive adjectives. Thus, the findings do not support the view that an AB toward negative stimuli or away from positive stimuli plays a critical role in the recurrence of depression.

1. Introduction

The recurrent nature of depression strongly contributes to the suffering, disability, and costs of Major Depressive Disorder (MDD) (Ormel et al., 2008; Smit, Ederveen, Cuijpers, Deeg, & Beekman, 2006). A better understanding of the mechanisms involved in the recurrence of depression is important not only from a theoretical perspective, but is also paramount to generating ideas for (more) effective interventions to help prevent recurrence following remission.

Cognitive models of depression emphasize the role of biased processing of emotional information in the development and maintenance of depression (Beck, 1976; Beck & Clark, 1988; De Raedt & Koster, 2010; Ingram, Miranda, & Segal, 1998; Teasdale, 1988). One of the focal points of these cognitive models is the role of attentional bias (AB) (e.g., Gotlib & Joormann, 2010). Findings of a meta-analysis covering 29 empirical studies using emotional Stroop or dot probe tasks in individuals with depressive complaints (clinical depression, nonclinical dysphoria, induced depressive mood) supported the view that depression is associated with biased attention to negative information (Peckham, McHugh, & Otto, 2010). Importantly, longitudinal studies provided further evidence for the proposed role of AB in the vulnerability for development of depressive symptoms. An eye tracking study among 139 participants found that AB for sad faces had predictive value for future increases in depression symptom severity (Beevers, Lee, Wells, Ellis, & Telch, 2011). In a similar vein, a study using an Exogenous Cueing Task (ECT) (1500 ms) with facial expressions as cues in a group of participants with MDD (N = 48), showed that AB for sad faces predicted prolonged persistence of negative mood (Clasen, Wells, & Beevers, 2013). Furthermore, difficulty to disengage attention from negative stimuli, as measured with an eye tracking task, using pictures of emotional and neutral faces, predicted prolonged persistence of negative mood among 16 participants with MDD (Sanchez, Vazquez,

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Marker, LeMoult, & Joormann, 2013). Perhaps, then, AB may also contribute to depression recurrence risk in the group of remitted individuals. The elevated risk for novel depressive episodes in 687 remitted individuals (depression free for at least 6 months) from a general population is estimated 13,2% at 5 years, 23,2% at 10 years and 42,0% at 20 years (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2013). Studying this group is crucial to understand risk mechanisms for depression.

In line with this suggestion, a study using a 1000 ms dot probe paradigm with emotional faces (sad, happy vs. neutral) found that remitted participants (rMDD) (N = 23) showed AB for sad faces compared to a comparison group (N = 19) (Joorman & Gotlib, 2007). Also, a more recent eye tracking study, using emotional faces, found a similar pattern (Soltani et al., 2015). Unfortunately, both studies had a rather small sample size. In apparent conflict with these findings, Vrijsen, Oostrom, Isaac, Becker, and Speckens (2014) failed to find a difference in AB for sad or happy faces between rMDD (N = 337) and a never depressed comparison group (N = 83) as indexed by a dot probe task (1000 ms)[1]. Yet, all participants in this study completed the dot probe task after a negative mood induction; therefore, it cannot be ruled out that this experimental manipulation affected participants' performance and attenuated baseline differences between rMDD and never-depressed participants. Consistent with such an explanation, a more recent study (Elgersma et al., 2018) without such additional manipulation did find a small difference in AB for negative adjectives between rMDD (N = 294) and a never depressed comparison group (N = 474), as indexed by a verbal ECT (1250 and 500 ms).

An important next step to examine the proposed relevance of AB for negative stimuli in the recurrence of MDD, is to investigate if in the group of rMDD, AB is predictive for future depressive episodes and/or depressive symptoms. In the current study, we therefore examined the prognostic value of AB in rMDD participants during the natural course of depression within the context of a large-scale multi-centre cohort study. We examined if the strength of AB for negative adjectives was predictive of depressive symptoms and/or of recurrence of a depressive episode over a 4-year time-period. Although previous research failed to find a systematic difference in the AB for positive stimuli between rMDD and individuals without a history of depression (e.g., Elgersma et al., 2018), it is still well conceivable that remitted individuals with a relatively weak AB for positive stimuli might be at heightened risk for recurrence. As a second aim, we, therefore, also tested the prognostic value of AB for positive stimuli for future depressive episodes and depressive symptoms. Thus, in short, in this study we tested the hypotheses that relatively high AB for negative and relatively low AB for positive stimuli in rMDD individuals would have prognostic value for the recurrence of depressive disorder and/or depressive symptoms during a 2- and 4-year follow-up period.

2. Method

This study was conducted as part of the Netherlands Study of Depression and Anxiety (NESDA; Penninx et al., 2008), an ongoing multi-centre, longitudinal cohort study designed to examine the long-term course and consequences of anxiety and depressive disorders. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Centre (protocol number 2013/183) and subsequently by local review boards of each participating centre (IRBs of the VU University Medical Center, the University Medical Center Groningen and the Leiden University Medical Center). After full verbal and written information about the study, written informed consent was obtained from all participants at the start of baseline assessment. Participants received written study information at home to read before they were invited to the face-to-face interview. Then during the face-to-face contact, the written information was discussed and it was checked whether the information was completely understood. After this process, participants were asked to sign the consent form.

Baseline assessments started in September 2004. This study uses data from the baseline, 2-, 4-year and 6-year follow-up assessments of NESDA (for details see Penninx et al., 2011, and the website www.nesda.nl). Attentional bias was measured during the 2-year follow-up assessment. In this study we refer to this wave as the baseline assessment (in the NESDA study: 2-year follow-up).

2.1. Participants

Participants for NESDA were recruited from the general population, through general practitioners, and in mental health care institutions, and included: healthy comparisons with no history of psychiatric disorders, individuals at risk because of prior episodes (rMDD), subthreshold symptoms or family history, and individuals with a current first or recurrent MDD or anxiety disorders (ADs). ADs were generalized anxiety disorder, panic disorder, social phobia, and agoraphobia.

General exclusion criteria were presence of a psychiatric disorder other than MDD and/or dysthymia or AD (e.g., psychosis, bipolar disorder, severe addictive disorder) or lack of fluency in Dutch. Of the 2981 participants that were included at the NESDA-baseline, 2596 respondents participated in the 2-year follow-up measurements. The Exogenous Cueing Task (ECT) was introduced during the 2-year follow-up measurements and was completed by 2128 out of 2596 (81.97%) participants (61.9% female; mean age 43.63 years, *s.d.* = 14.06); 468 (18.02%) participants had no or too little ECT data (e.g., those interviewed over the phone or at home). Of those 2128 participants, we selected rMDD participants (n = 928; 43.61%); these participants had a past diagnosis of a depressive disorder, but were currently remitted. During the NESDA 2-year follow-up assessment, these participants did not fulfil the criteria for a depressive disorder (Major Depressive Disorder nor Dysthymia) for the last 6 months. These participants could have a current or history of anxiety disorders.

2.2. Measurements

2.2.1. Lifetime Composite International Diagnostic Interview (CIDI)

The lifetime Composite International Diagnostic Interview (CIDI, lifetime version 2.1; Robins et al., 1988) was used to diagnose anxiety (panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without panic disorder, social phobia, generalized anxiety disorder) and depressive disorders (MDD, dysthymia) according to DSM-IV criteria (American Psychiatric Association, 2001). A disorder was considered current if participants fulfilled the criteria during the past month. Assessment was conducted by about 40 specially trained research assistants, who were constantly monitored by checking a random selection of about 10% of all taped interviews. In addition, a continuous monitoring system of interviewer variances and interviewer specific item non-response was maintained.

2.2.2. Inventory of Depressive Symptomatology self-report version (IDS-SR)

Severity of depressive symptoms was measured using the 30-item Inventory of Depressive Symptomatology self-report version (IDS-SR) (IDS; Rush, Gullion, Basco, & Jarret 1996). In this study, total scale scores were used.

2.2.3. Exogenous Cueing Task (ECT)

The ECT is a reaction-time based attention task which was programmed using the E-Prime 1.0.2 software (Psychology Software Tools, Pittsburgh, PA). In the original exogenous cueing paradigm (Posner, 1980), participants are asked to detect a visual target presented at a left or right peripheral location. If a stimulus (a "cue") precedes the target at the same spatial location, it is called a "valid" trial. On the remaining trials, the preceding stimulus is presented at the opposite spatial location of the target and thus invalidly cues the target's location ("invalid" trials). In the emotional modification of this paradigm, the emotional value of the cue varies (i.e., emotional vs. neutral) which allows investigation of AB for an emotional cue. That is, if individuals are slower to disengage their attention from an emotional cue, their response to invalid emotional trials will be delayed, which results in larger cue validity effects for emotional compared to neutral information. In general, at short presentation times, faster responding is found on valid trials compared to invalid trials, a finding that is referred to as the "cue validity" effect. At longer presentation times, the cue validity effect disappears and may even reverse because attention to the location of a previously attended stimulus is inhibited in favor of new locations. This is known as the inhibition of return effect (IOR; Posner & Cohen, 1984).

The task used in this study was modelled after the ECT used in previous research on anxiety and depression (e.g., Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Koster, Leyman, De Raedt, & Crombez, 2006; Leyman, De Raedt, Schacht, & Koster, 2007). Stimuli were presented on a black background. During each trial, a white fixation cross was presented in the center of the screen. A white rectangle placeholder was presented (4 cm high x 10.5 cm long), both on the left and the right side of this fixation cross. The centers of these placeholders were located at 7.9 cm from the fixation cross. Cues (words) and targets (squares) were presented in black in the center of the placeholders. Cues were 16 neutral words, 16 negative adjectives, and 16 positive adjectives (see Appendix A). Because within the NESDA study it was also relevant to examine the AB for threat stimuli related to anxiety disorders (see e.g., Elgersma et al., 2018), the current task also included threat words that were selected from earlier studies on AB (Mathews, May, Mogg, & Eysenck, 1990; Mathews, Mogg, May, & Eysenck, 1989). Yet, trials with threat words were discarded in the current study. The negative and positive adjectives were selected from trait adjectives of depressive and manic persons, which were used in a study on AB in depression (McCabe, Gotlib, & Martin, 2000). These words scored high on subjective familiarity in an earlier study investigating 740 Dutch words on affective and subjective familiarity (Hermans & De Houwer, 1994). See Appendix A for the stimulus words per stimulus type.

Each trial started with the presentation of the fixation cross and the two placeholders for 500 ms. Next, a word cue was presented in the left or right placeholder, for 500 ms (short presentation time) or 1250 ms (long presentation time). The target was presented until a response was made. Directly after responding, the next trial started. If a participant did not respond within 2 s, the next trial started. Participants were asked to focus their attention on the fixation cross and to respond as quickly and correctly as possible by pressing the left key of a response box when the target was presented on the left side or by pressing the right key of the response box when the target was presented on the right side. They were asked to ignore any other information that would be presented. To ensure that attention was indeed directed at the fixation cross, 20 digit trials were added, 10 in the first half of the task and 10 in the second half. In these trials, instead of a word cue, a digit appeared for 100 ms at the location of the fixation cross. Participants were instructed to press both the left and right key of the response box simultaneously upon appearance of a digit during these trials. If a participant gave an incorrect response, the word "ERROR" appeared in the middle of the screen with black letters on a red square for 500 ms. If a participant did not press a key after a digit trail or pressed only one key, the message "Digit missed!" was presented.

The instructions were presented on the computer and the task started with 10 practice trials and one digit trial. Participants were then given the opportunity to ask a research assistant questions before the actual task started. In the first half of the task, word cues were presented for 500 ms, in the second half of the task for 1250 ms. We preferred a fixed order to minimize method variance which we considered important in light of the prospective design of this study (cf. Glashouwer & de Jong, 2010). We started with the short duration trials as we anticipated that prior exposure to long duration word presentations could have a larger impact on performance or mood. Cues were presented at random on the right or left side of the fixation cross and every word cue was presented twice in each half of the task: Once in a valid trial (i.e., word cue is valid predictor for the target location), and once in an invalid trial. In total, the task consisted of 4 stimulus types x 16 exemplars x 2 valid/invalid x 2 presentation times = 256 word trials (including the 64 trials representing threat words that were discarded in this study), 10 practice trials and 21 digit trials. The same fixed random order of trials was used for all participants to make the design more sensitive to individual differences. See Appendix B for an illustration of a valid trial of the ECT.

The internal consistency of the ECT at wave 3 was assessed by calculating split half reliability for the first and the second half of the ECT per presentation time. This was done for the various types of trials within the ECT as well as for the AB indices. For both presentation times, the internal consistency (using Spearman-Brown correlations) was high for the various types of trials ranging from 0.83 (Negative valid 1250) to 0.89 (Neutral invalid 500 ms). The internal consistency for the bias indices (AB Negative 500 ms, AB Positive 500 ms, AB Negative 1250 ms, AB Positive 1250 ms) was very low and ranged between −0.13 and 0.004.

2.3. Procedure

The assessments at baseline and follow-up were largely similar; they lasted between 3 and 5 h and were conducted on one day. The two-year follow-up assessment consisted of a face-to-face visit at the clinic, in which baseline assessments – except those concerning stable concepts – were repeated. A few additional assessments, such as the ECT used in this study, were included. These other measurements are beyond the scope of this study (see Penninx et al., 2008; 2011 for a detailed description). The assessments started with the CIDI-interview. After that, the ECT and questionnaires were completed. After completing the assessment, participants were compensated with a €15 gift certificate and travel expenses.

2.4. Data reduction

In line with previous studies, (e.g. Koster, De Raedt, Goeleven, Franck, & Crombez, 2005) reaction times (RT's) < 200 ms and RT's > 1000 ms were considered respectively anticipatory responding and delayed responding and were discarded. Non-response was considered a missing value. Incorrect responses were also discarded. Variables with RT's that contained > 40% errors were also excluded. Variables that were based on less than 10 valid RTs were discarded. The goal of presenting the digit trials was to ensure that participants would focus their attention on the middle of the screen as instructed. Participants were instructed to press both keys, left and right, when they saw a digit. Statistical analyses were run on 96.24% of the data. For all word types median scores were computed for the different presentation times and type of trials (valid/invalid). Consistent with a series of recent studies using RT-based performance measures (e.g., van Hemel-Ruiter, de Jong, Ostafin, & Oldehinkel, 2013; Jonker et al., 2016; Neimeijer, Roefs, Ostafin, & de Jong, 2017), we decided to use median instead of mean reaction times because this seems the most simple and robust way to deal with outliers without losing too much information. Median scores were computed for the different presentation times and type of trials (valid/invalid), for all stimulus types.

We computed separate indices of AB for each of the presentation times (500 and 1250 ms). AB scores were calculated using the formula suggested by Mogg, Holmes, Garner, and Bradley (2008): Attentional bias score (AB score) = (median RT invalid emotional cue – median RT valid emotional cue) – (median RT invalid neutral cue – median RT valid neutral cue). In the current emotional modification of this paradigm, the emotional value of the cue is varied (i.e., emotional vs. neutral) which allows to investigate AB for emotional information (with the responses to the neutral trials as the reference category). Therefore,

Table 1
Descriptives during baseline and follow-ups (2 and 4 years).

	Baseline (n = 928)	Follow-up 2-year (n = 858)	Follow-up 4-year (n = 801)
Age Mean (s.d.)	43.84 (12.90)	45.69 (12.93)	47.83 (12.89)
Gender % female	68.3	67.2	68.3
Diagnosis of depressive disorder (MDD and/or dysthymia)		21.4%	35.1%
IDS total score Mean (s.d.)	14.55 (9.34) (n = 914)	15.01 (10.06) (n = 834)	14.99 (10.09) (n = 772)

Note:IDS = Inventory of Depressive Symptoms-SR.

higher positive AB scores (i.e., stronger cue validity effects) are indicative of a stronger attentional bias for the emotional information. Lower negative AB scores are indicative of a larger inhibition of return effect.

We computed an AB score for negative and positive words per presentation time. We considered indices deviating more than 3 SDs from the mean of the group as outliers for all the groups. We replaced these outliers with the group mean for that index plus (or minus) 3 SDs.

To index recurrence, we used a new dichotomous variable consisting of a diagnosis of major depressive disorder and/or dysthymia between baseline (AB assessment) and 4-year follow-up (yes/no); where each first diagnosis of a depressive disorder between baseline and 4-year follow-up was counted. We also used a new dichotomous variable consisting of having met the criteria of an anxiety disorder in their history (yes/no).

2.5. Statistical analyses

At baseline and per follow-up measurement moment, i.e. 2 and 4 years after baseline, summary statistics were calculated for the IDS-SR total score. To assess the difference of mean IDS-SR total scores at 2 and 4 years after baseline, a paired *t*-test was performed. Additionally, summary statistics were calculated for four AB variables, resulting from all possible combinations of reaction time (500 and 1250 ms) and stimulus type (negative or positive). The associations between the AB scores, current anxiety and anxiety disorder in history were examined through Pearson's correlations.

To assess whether the presence of a diagnosis of a depressive disorder (yes/no) within 2 and 4 years after baseline could be predicted from baseline AB scores, we carried out two sets of four (logistic) regression analyses (one set of analyses per time period). To test our hypotheses, we first tested the model with only both negative AB scores (500 ms; 1250 ms) as predictors. Next, a model with only both positive AB scores as predictors, followed by a third model with both negative as well as both positive AB scores as predictors. In the final and fourth model, we added the variables current anxiety disorder (yes/no) and anxiety disorder in their history (yes/no) as independent variables into the model, to take into account the current or former presence of anxiety disorders in this group op rMDD participants. A similar procedure was followed with regard to the prediction of the severity of depressive symptoms at 2 and 4 years follow up, resulting in a total of 2 x (2 × 4) is 16 analyses.

For all predictors in each set of four regression analyses, the relationship with the outcome was modelled both as a linear effect and as a nonlinear effect using restricted cubic splines with three knots (Harrell Jr., 2017, p24-26), resulting in one model with linear relationships and one model with non-linear relationships. Akaike's information criterion (AIC) was used to select the best fitting model of these two.

All models were built using step-down variable selection with the AIC as stopping rule. All possible combinations of the predictors per model were assessed examining the best combination of predictors (i.e., the single predictor or combination of predictors producing the lowest AIC-value). The accuracy of the resulting prediction models was assessed with Somers' D for the logistic regression models and Nagelkerke's R^2 for the regression models, both corrected for optimism, thus expressing the so called out sample prediction value. The optimism of Somers' D and Nagelkerke's R^2 were estimated using 500 bootstrap samples. The values of Somers' D could be in between −1 and 1 (Somers, 1962) of Nagelkerke's R^2 between 0 and 1. All analyses were performed in the R version 3.2.3. (R Core Team, 2016); using the rms package (Harrell, 2017). Before we computed the (logistic) regression analyses, we first checked the assumptions (f.e. Cohen, Cohen, West, & Aiken, 2003). Residual plots and qq-plots revealed no major violations of assumptions of linearity, normality, homoscedasticy and independence.

3. Results

3.1. Descriptives

Of the 928 participants at the start of our study, 858 participated in the 2-year follow-up measurements and 801 participants in the 4 years follow-up measurements. Up until the 2-year follow-up, 21.4% (n = 184) of the 858 remaining participants fulfilled the criteria for a diagnosis of depressive disorder: MDD and/or dysthymia. Up until the 4-year follow-up, 35.1% (n = 281) of the remaining 801 participants had received such a diagnosis. The mean IDS-SR score of the 834 participants at the 2-year follow-up and the 772 participants at the 4-year follow-up were 15.01 (*s.d.* = 10.06) and 14.99 (*s.d.* = 10.09), respectively, both indicating that on average participants showed negligible to mild depressive symptom severity. The average severity of depressive symptoms did not substantially change between the 2-year and the 4-year follow-up (t (746) = 0.55, p = .58, CI [-0.73, 0.41]) (see Table 1).

See Table 2 for a detailed description of reaction times (RTs) of participants per AB score per stimulus type and presentation time (mean raw RTs per trial type are presented in a supplementary table).

The independent variables, the AB scores per stimulus type and per presentation time, were only moderately correlated see Table 3. There were significant correlations between AB scores for negative adjectives on presentation time 500 ms and AB scores for positive adjectives on presentation time 500 ms (r = 0.49). There were significant correlations between AB scores for positive adjectives on 1250 ms and AB scores for negative adjectives on presentation time 1250 ms (r = 0.53). There was a very low correlation between AB scores for negative adjectives on 1250 ms and AB scores for negative adjectives on 500 ms (r = 0.07). All other correlations between the independent variables

Table 2
AB scores per stimulus type and presentation time (ms).

AB scores	Negative		Positive	
	500 ms	1250 ms	500 ms	1250 ms
N	905	920	904	920
1st Quartile	−28.50	−35.00	−38.62	−35.63
3rd Quartile	24.50	19.00	19.00	21.50
Median	−1.50	−10.00	12.00	−6.50
Mean	−1.77	−8.94	−13.09	−7.47
Standard Deviation	42.86	45.65	42.65	46.96

Note: AB = attentional bias.

Table 3
Correlations of independent variables of the prediction model (Pearsons'r).

		AB scores Negative		AB scores Positive		IDS baseline	Anxiety disorder current
		500 ms	1250 ms	500 ms	1250 ms		yes/no
AB scores Negative	500 ms					.02	
	1250 ms	.07[a]				.01	
AB scores Positive	500 ms	.49[b]	.06			.007	
	1250 ms	.03	.53[b]	.03		-.007	
	Anxiety disorder current yes/no	.03	-.03	.04	-.03	.35**	
	Anxiety disorder in history yes/no	-.06	-.05	-.02	-.06	.26**	.36[b]

Note: AB = attentional bias.
[a] Correlation is significant at the 0.05 level (2-tailed).
[b] Correlation is significant at the 0.01 level (2-tailed).

Table 4a
Logistic regression estimates from models predicting the presence of a major depressive disorder diagnosis within 2 years and 4 years after baseline from AB predictors and a current or anxiety disorder in history.

	Predictor	Within 2 years after baseline				Within 4 years after baseline			
		B (SE)	*Wald Z*	*p*	Odds ratio (95% CI)	*B (SE)*	*Wald Z*	*p*	Odds ratio (95% CI)
Negative AB model	Intercept	−1.32 (0.09)	−15.14	< .001		−0.63 (0.08)	−8.19	< .001	
	500 ms	−0.002 (0.002)	−0.75	.46	0.92 (0.75–1.14)	0.0008 (0.002)	0.44	.66	1.04 (0.87–1.26)
	1250 ms	−0.002 (0.002)	−0.84	.40	0.92 (0.75–1.12)	−0.001 (0.002)	−0.66	.51	0.94 (0.79–1.13)
	D_{xy}	< .001				< .001			
Positive AB model	Intercept	−1.29 (0.08)	−14.54	< .001		−0.62 (0.08)	−7.82	< .001	
	500 ms	0.0005 (0.002)	0.23	.81	1.03 (0.83–1.27)	−0.0003 (0.002)	0.28	.78	1.03 (0.85–1.24)
	1250 ms	0.0005 (0.002)	0.27	.79	1.03 (0.84–1.26)	0.0005 (0.002)	−0.17	.87	0.98 (0.82–1.18)
	D_{xy}	< .001				< 0.01			
AB model	Intercept	−1.30 (0.09)	−14.33	< .001		−0.63 (0.08)	−7.80	< 0.001	
	AB negative								
	500 ms	−0.002 (0.002)	−1.03	.30	0.88 (0.69–1.12)	0.0006 (0.002)	0.27	.78	1.03 (0.83–1.27)
	1250 ms	−0.003 (0.002)	−1.22	.22	0.86 (0.68–1.10)	−0.002 (0.002)	−0.71	.49	0.92 (0.74–1.15)
	AB positive								
	500 ms	0.001 (0.002)	0.74	.46	1.10 (0.86–1.40)	0.0002 (0.002)	0.11	.91	1.01 (0.82–1.25)
	1250 ms	0.002 (0.002)	0.92	.36	1.12 (0.88–1.43)	0.0005 (0.002)	0.28	.78	1.03 (0.83–1.28)
	D_{xy}	< .001				< 0.01			
AB and anxiety model	Intercept	−2.22 (0.21)	−10.63	< .001		−1.47 (0.16)	−9.03	< 0.001	
	AB negative								
	500 ms	−0.002 (0.002)	−0.72	.47	0.91 (0.71–1.17)	0.001 (0.002)	0.65	.52	1.08 (0.86–1.34)
	1250 ms	−0.003 (0.002)	−1.23	.22	0.86 (0.68–1.10)	−0.001 (0.002)	−0.61	.54	0.93 (0.75–1.17)
	AB positive								
	500 ms	0.001 (0.002)	0.60	.55	1.08 (0.84–1.39)	−0.0003 (0.002)	−0.12	.90	0.99 (0.79–1.23)
	1250 ms	0.003 (0.002)	1.17	.22	1.16 (0.90–1.49)	0.001 (0.002)	0.53	.60	1.06 (0.85–1.33)
	Anxiety disorder								
	Current	0.25 (0.20)	1.24	0.22	1.28 (0.86–1.90)	0.35 (0.19)	1.82	.07	1.41 (0.97–2.05)
	In history	1.15 (0.24)	4.82	< .001	3.15 (1.98–5.02)	1.07 (0.19)	5.52	< 0.001	2.92 (2.00–4.27)
	D_{xy}	.18				0.24			

Note:
Model 1: AB indices as predictors in model.
Model 2: AB indices and current and anxiety disorder in history in the model.

were not significant.

Of all the first prediction models, the values of the D_{xy} and the R^2 indicated that the prognostic value of the predictors were not meaningful (see Tables 4a and 4b). All the first prediction models were built as follows: first with the predictors AB negative, then with the predictors AB positive, then with all AB indices as predictors in the model without the variables current anxiety disorder, history of anxiety disorder. Below we describe all the final models with all AB indices and current anxiety disorder and history of anxiety disorder for all the regression analyses.

3.1.1. Predictive value of AB on diagnosis of a depressive disorder within 2-year time-period[1]

The model resulting from the logistic regression analysis to predict the presence of a diagnosis of a depressive disorder within the 2-year time-period contained one significant but weak main effect (history of anxiety disorder: $B = 1.15$, Wald Z = 4.82, $p < .01$, OR = 3.15, 95% CI [1.98; 5.02]), indicating that within 2 years after baseline the group of participants with a history of anxiety disorder is associated with a marginally increased risk at fulfilling the criteria of a diagnosis of depressive disorder. The prediction accuracy of this model is insufficient (D_{xy} corrected = 0.18).

3.1.2. Predictive value of AB on diagnosis of a depressive disorder within a 4-year time-period

The model resulting from the logistic regression analysis to predict the presence of a diagnosis of a depressive disorder within the 4-year time-period contained one significant main effect (history of anxiety disorder: $B = 1.07$, Wald Z = 5.52, $p < .001$, OR = 2.92, 95% CI [2.00; 4.27]), indicating that within 4-year after baseline the group of participants with a history of anxiety disorder is associated with a marginally increased risk at fulfilling the criteria of a diagnosis of depressive disorder. The prediction accuracy of this model is insufficient (D_{xy} corrected = 0.24).

Table 4b
Regression estimates from models predicting depressive symptoms at 2 year- and 4 year- follow up after baseline from AB predictors and a current or anxiety disorder in history.

	Predictor	2 year follow up				4 year follow up			
		β (SE)	*t*	*p*	Odds ratio (95% CI)	*β (SE)*	*t*	*p*	Odds ratio (95% CI)
Negative AB model	Intercept	14.99 (0.36)	41.58	< .001		14.98 (0.37)	39.96	< .001	
	500 ms	−0.005 (0.008)	0.66	.51	(-0.01–0.02)	0.02 (0.008)	2.21	.03	(0.002–0.04)
	1250 ms	−0.0006 (0.008)	−0.07	.94	(-0.02–0.01)	0.005 (0.002)	0.57	.57	(-0.01–0.02)
	R^2	< .001				< .001			
Positive AB model	Intercept	15.17 (0.37)	40.74	< .001		15.11 (0.39)	39.18	< .001	
	500 ms	0.01 (0.008)	1.50	.13	(-0.004–0.02)	0.02 (0.009)	1.94	.05	(-0.0002–0.03)
	1250 ms	0.0004 (0.008)	0.05	.96	(-0.01–0.03)	−0.004 (0.008)	−0.47	.63	(-0.02–0.01)
	R^2	< .001				< 0.01			
AB model	Intercept	15.17 (0.38)	40.09	< .001		15.10 (0.39)	38.59	< 0.001	
	AB negative								
	500 ms	−0.002 (0.01)	−0.20	.84	(-0.02–0.02)	0.01 (0.01)	1.30	.19	(-0.007–0.03)
	1250 ms	−0.002 (0.009)	−0.17	.86	(-0.02–0.02)	0.01 (0.01)	1.01	.31	(-0.01–0.03)
	AB positive								
	500 ms	0.01 (0.01)	1.41	.16	(-0.005–0.03)	0.01 (0.01)	1.13	.33	(-0.008–0.03)
	1250 ms	0.001 (0.009)	0.14	.89	(-0.02–0.02)	−0.01 (0.01)	−0.97	.26	(-0.03–0.01)
	R^2	< .001				< 0.01			
AB and anxiety model	Intercept	11.57 (0.61)	19.10	< .001		11.99 (0.61)	19.54	< 0.001	
	AB negative								
	500 ms	0.001 (0.009)	0.08	.94	(-0.02–0.02)	0.01 (0.01)	1.49	.14	(-0.004–0.03)
	1250 ms	−0.0005 (0.009)	−0.06	.96	(-0.02–0.03)	0.01 (0.01)	1.23	.22	(-0.007–0.03)
	AB positive								
	500 ms	0.01 (0.009)	1.12	.26	(-0.008–0.02)	0.008 (0.01)	0.83	.41	(-0.01–0.03)
	1250 ms	0.004 (0.009)	0.47	.64	(-0.01–1.49)	−0.007 (0.01)	−0.72	.14	(-0.02– 0.01)
	Anxiety disorder								
	Current	5.09 (0.88)	5.80	< .001	(3.37–6.82)	5.51 (0.94)	5.87	< 0.001	(3.67–7.35)
	In history	3.70 (0.77)	4.78	< .001	(2.17–5.21)	3.03 (0.80)	3.80	< 0.001	(1.46–4.59)
	R^2	0.09				0.09			

Note:
Model 1: AB indices as predictors in model.
Model 2: AB indices and current and anxiety disorder in history in the model.

Most important for the current context, the logistic regression analyses performed to assess the predictive value of the AB scores for the presence of a depressive disorder within a time-period of 2-years and 4-years revealed that none of the four AB indicators, (AB indices for negative adjectives at 500 ms and 1250 ms, AB indices for positive adjectives at 500 ms and 1250 ms) were predictive. These findings suggest that remitted participants' probability of receiving a diagnosis for a depressive disorder within a 2-year and 4-year time-period is not associated with the presence of a relatively strong attentional bias for negative or weak bias for positive stimuli.

3.1.3. Predictive value of AB for the severity of depression symptoms at 2-year follow-up

The regression model estimated to assess how well the severity of depressive symptoms (IDS-SR scores) at 2-year follow-up could be predicted from AB scores and anxiety disorder information showed significant main effects for current anxiety disorder ($\beta = 5.09$, 95% CI [3.37; 6.82], $t = 5.80$, $p < .01$) and for history of anxiety disorder ($\beta = 3.70$, 95% CI [2.17; 5.21], $t = 4.78$, $p < .01$). These main effects indicate that at 2-year follow up the group of participants with a current anxiety disorder or a history of anxiety disorder is associated with a marginally increased risk for heightened level of depressive symptoms. The prediction accuracy of this model is insufficient (R^2 corrected = 0.09).

3.1.4. Predictive value of AB for the severity of depression symptoms at 4-year follow-up

Similar to the results at 2-year follow-up, the regression model estimated to assess how well the severity of depressive symptoms (IDS-SR scores) at 4-year follow-up could be predicted showed significant main effects for current anxiety disorder ($\beta = 5.51$, 95% CI [3.67; 7.35], $t = 5.87$, $p < .01$) and for history of anxiety disorder ($\beta = 3.80$, 95% CI [1.46; 4.59], $t = 3.80$, $p < .01$). These main effects indicate that at 4-year follow up a current anxiety disorder or a history of anxiety disorder is associated with a marginally increased risk for heightened level of depressive symptoms. The prediction accuracy of this model, also similar to what we found for 2 years after baseline, is insufficient (R^2 corrected = 0.09).

From the regression analyses performed to assess the predictive value of the AB scores for the severity of self-reported depressive symptoms at the 2- and 4-year follow-up, it became evident that none of the AB indicators were useful predictors.

4. Discussion

We performed the largest prospective study testing the predictive value of attentional bias for the recurrence of depression in an at-risk sample to date. The main results can be summarized as follows: AB for negative or positive stimuli per se were not associated with prospectively assessed recurrence of a diagnosis of depressive disorder, nor with depressive symptoms, at 2- and 4-year follow-up. We discuss these results in more detail below.

4.1. Predictive value of AB in remitted participants on recurrence

Based on cross-sectional evidence indicating that remitted participants were characterized by AB for negative stimuli (Elgersma et al., 2018), the current study used a longitudinal design to test whether AB in this group of remitted participants might play a role in the recurrent nature of depression. However, the current findings provided no support for the view that AB would play a critical role in the underlying mechanisms, making people vulnerable for a next depressive episode. Neither for relatively short (2-year) nor for relatively long-term follow-up, AB for negative stimuli showed prognostic value for recurrence into a next depressive episode, nor for depressive symptoms. In addition, a relatively low AB for positive stimuli was neither associated with recurrence of depressive episodes nor with depressive symptoms. Previous research showed that in a sample of undergraduate students non-dysphoric participants showed a stronger AB for positive words than did the group of dysphoric participants (Koster et al., 2005). On top of this, a meta-analysis, using 29 studies examining emotional Stroop or dot probe tasks in depressed participants (clinical depression, non-clinical dysphoria, or participants undergoing mood induction), showed that a significant but small effect was found for a bias away from positive stimuli in depressed groups compared to non-depressed groups (Peckham et al., 2010). Although these previous findings pointed to the possibility that similar processes could also be involved in the recurrence of depression, the current findings provided no evidence to corroborate this view. Although our findings provide no further support for cognitive models of depression, the findings neither refute the core assumptions of cognitive theories of depression. Cognitive theories of depression, like the theory of Beck and Clark (1988) imply that latent schemas become manifest in depression. The current study found no support for the hypothesis that heightened AB for negative self-descriptors lowers the threshold for these schemas to become reactivated. Because even in this large sample of remitted patients the overall relationship between the current indices of covert AB and probability of recurrence was practical zero, the findings render it also implausible that AB for negative adjectives might still be relevant in interaction with other variables such as life events or other process such as rumination.

A series of studies using a similar ECT as used in the current study showed that dysphoric participants showed maintained attention for negative words, especially at longer presentation times (e.g., Koster et al., 2005). Sustaining the view that the types of processes that are indexed by the ECT may be different between short and long presentation times, indices for the 500 and 1250 ms presentation times showed only small correlations. However, the current findings did not corroborate the view that specifically stimuli at presentation time 1250 ms would be related to depression as neither of the indices showed prognostic value for recurrence. A recent cross-sectional study in the group of remitted participants found a stronger AB for negative adjectives for remitted participants than for a never depressed comparison group (Elgersma et al., 2018). In a recent analogue study, the first evidence was found that AB for negative stimuli, as measured with a verbal dot probe task (500 ms) had predictive value for the presence and severity of depressive symptoms over a 6 weeks period of naturalistic symptom course (Disner, Shumake, & Beevers, 2017). This suggests that heightened AB for negative stimuli has an influence on short-term development of depressive symptoms. Yet, the current findings do not corroborate such conclusion. Although 294 rMDD participants were characterized by heightened AB for negative words (Elgersma et al., 2018), we found no evidence for the prognostic value of AB for a diagnosis of depression and/or depressive symptoms at 2- and 4-year follow-up. Our results are in line with a recent a meta-analytic commonality analysis considering 463 healthy and sub-clinically depressed participants of four published studies, indicating that across different paradigms and psychological measures attentional bias did not represent a primary mechanism in depression (Marchetti et al., 2018).

In this study, we selected participants who were remitted from MDD. We selected a group of participants who could also have an anxiety disorder in their history and/or have a current anxiety disorder. In this way, we could examine if the predictive value of AB might be due to the presence of (a history of) an anxiety disorder. MDD and AD often co-occur (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). In studies investigating AB in depression, depressed participants also scored high on anxiety questionnaires. Therefore, it cannot be ruled out that any observed AB was mainly driven by heightened anxiety rather than depression levels. Since the current results showed no predictive value of attentional bias, and the prediction models showed insufficient predictive value, the current findings provide no reason to assume that a current or a history of anxiety may have confounded the prospective relationship between AB and recurrence of depression. Yet, the history of anxiety disorder was associated with a marginally increased risk at fulfilling the criteria of a diagnosis of depressive disorder within 2- and 4-years and of an increased risk on higher depressive symptoms at 2- and 4-year follow up. The same pattern was evident for having a current anxiety disorder. One explanation for the heightened probability of recurrence in participants with (a history of) AD could be that a history of AD renders participants more susceptible for threatening interpretations of mood swings and/or negative experiences (e.g., “if I have a bad day, chances are high that it will develop into a next depressive episode”).

4.2. Limitations

A number of limitations of this study need to be discussed. First, although the current measure of AB successfully differentiated between groups of individuals with and without a history of depression (e.g., Elgersma et al., 2018), it can still be that the current indices lacked sufficient sensitivity for being successfully applied as a measure of individual differences. This could be due to insufficient reliability of the index of AB (e.g., in terms of test-retest stability), but could also be due to instability of the targeted underlying process itself. During the design of the) NESDA study, the current ECT was carefully selected on the basis of ample discussions with experts in the field and available empirical findings supporting its sensitivity for differentiating between relevant clinical and sub-clinical groups (e.g. Koster et al., 2005). However, it should be acknowledged that the ECT has not yet been subjected to rigorous psychometric evaluations. The split-half reliability of the bias indices within the current task were close to zero. Clearly, the absence of internal consistency does not support the reliability of the bias index. It is however important to note that within large-scale multidisciplinary studies, such as NESDA, there is generally limited time available for each of the various instruments, requiring a time-efficient approach. The ECT was therefore constructed as short as possible following the rule of thumb that at least 10 observations would be required for each type of trial to retain an acceptable signal to noise ratio. As a compromise between feasibility and optimizing sensitivity we eventually included 16 trials per trial type. Because of this limited number of trials per stimulus category, calculating split half reliability implied that two a priori unreliable indices were to be compared.

In addition, there is a current debate whether internal consistency might be an adequate index of reliability in performance measures like the ECT (see e.g., De Schrijver, Hughes, de Houwer, & Rosseel, 2018). Especially when the target stimuli are task irrelevant and participants' performance profits most from ignoring the target stimuli and to focus on the task, it is doubtful whether internal consistency is to be expected. Furthermore, the stimulus words used in tasks such as the current ECT probably vary both within and across individuals with regard to their relevance and attention attracting properties, which further adds to variability across trials. Moreover, the impact and performance of a particular trial is probably not independent of the previous trial (or trials) and (differential) learning effects may further contribute to variability in responding over trials. Thus the absence of internal consistency cannot be taken to imply that the index is thus unreliable. Unfortunately, there is currently no obvious alternative way that we know of to index reliability, thus one may remain doubtful about whether indeed ECT performance can be considered as a meaningful index of individual differences. However, although internal consistency may not be critical for supporting the usefulness of the AB index as a measure of individual differences, it would still be important to assume that participants’ performance reflects a relatively stable characteristic. It would, therefore, be important for future research to establish stability over time, because if the bias score would not represent a relatively stable characteristic it would be problematic to use such measure as an index of individual differences. More generally, it would be important to replicate the current study using AB measures with verified psychometric properties (see also, Lazarov, Abend, & Bar-Heim, 2016).

As a further limitation, the ECT that we used as an index of AB is not optimally suited to differentiate between enhanced engagement vs. difficulty to disengage attention. Because both processes might play a different role in MDD it would be interesting in future research to use a task that is especially designed for separately assessing attentional engagement and attentional disengagement (e.g., the Attentional Response to Distal vs. Proximal Emotional Information task) (Grafton & MacLeod, 2014).

In this study we investigated the natural course of depression, and we did not use a lab mood induction. It might be that especially AB after mood induction has predictive value. Although Vrijsen et al., 2014 did use a mood induction in the lab prior to the assessment of AB, also that prior study failed to find evidence for the predictive value of AB for the recurrence of MDD in a group of 266 remitted participants. In our study we examined the main effect of AB on the course of depression. It might be important as a next step to study the moderating influence of life events on the relation between AB and recurrence.

Finally, we decided to use 500 ms and 1250 ms presentation times for optimal comparison with earlier studies (Koster et al., 2005). It is possible that other results would have emerged if we would have used shorter or longer presentation times. Furthermore, by using task irrelevant adjectives, this ECT measured the tendency to automatically focus attention (non-intentionally) on stimuli; maybe more controlled spontaneous AB processes that can be indexed in free viewing tasks are more important in MDD. Then, the current study used a relatively large and well-defined sample of participants who were remitted from MDD; on the positive side this resulted in a relatively sensitive design enabling to measure also smaller effects.

5. Conclusion

This large-scale longitudinal study covering a 2- to 4- year follow-up and a large group of remitted participants, provided no evidence to support that AB for negative or positive adjectives is critically involved in the recurrence of depression.

5.1. Footnote 1

Zvielli, Vrijsen, Koster, and Bernstein (2016) recently reanalyzed data of this published dot probe study. They used a new approach of analysing the data of an AB task, taking into account the dynamic nature of AB. Interestingly, the results of this re-analysis showed that rMDD participants were characterized by higher levels of trial level bias scores, specifically increased variability, than non-depressed individuals. This may reflect a greater dysregulation of attentional processing of emotional information in rMDD individuals. However, there is extensive debate about the validity of this novel approach (see e.g., Kruijt, Field, & Fox, 2016).

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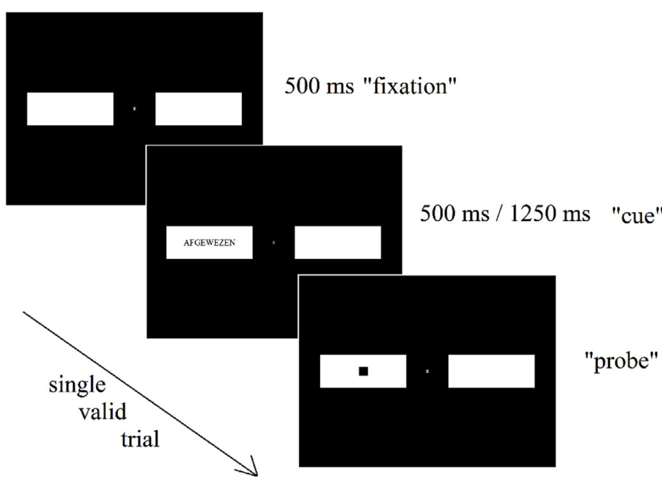
Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2019.01.001.

Appendix A. ECT Stimulus Words: 16 Stimulus Words per Stimulus Type

Stimulus type	Woorden (Dutch)	Words (English)
Positive	Opgewekt	cheerful
	levenslustig	bright
	succesvol	successful
	positief	positive
	populair	popular
	krachtig	powerful
	waardevol	valued
	blij	happy
	winnaar	winner
	vlot	outgoing
	actief	dynamic
	geliefd	beloved
	optimistisch	optimistic
	energiek	industrious
	zelfbewust	assertive
	talentvol	talented

Negative	negatief	negative
	ongewenst	unwanted
	ellendig	vile
	wanhopig	desperate
	leeg	hollow
	saai	dull
	zinloos	aimless
	afgewezen	rejected
	nutteloos	useless
	pessimistisch	pessimistic
	eenzaam	lonely
	verloren	lost
	somber	morbid
	minderwaardig	inferior
	ongeschikt	incompetent
	waardeloos	worthless
Neutral	kapstok	coat rack
	dynamo	dynamo
	paperclip	paperclip
	behang	wallpaper
	kantoorgebouw	office
	potlood	pencil
	plank	shelf
	papieren	papers
	kraan	tap/crane
	woordenboek	dictionary
	spatiebalk	spacebar
	lichtknopje	light switch
	tandenborstel	toothbrush
	braadpan	casserole
	zonnebril	sunglasses
	omgeving	surroundings



Appendix B. Example of a Valid Trial of the ECT.

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