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# A multi-method assessment of attentional processes in chronic, treatment-resistant depression

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ABSTRACT

Attentional deficits as well as attentional biases towards negative material are related to major depression and might maintain chronicity. However, studies investigating attentional deficits and attentional biases in chronic, treatment-resistant depressed are lacking. The aim of the current study was to compare measures of attentional deficits and attentional bias between chronic, treatment-resistant depressed outpatients and never-depressed control participants. Attentional deficits were assessed with the attentional control scale (ACS) and the Stroop Color naming task. Attentional bias was measured with the exogenous cueing task (ECT) and an emotional Stroop task. Chronic, treatment-resistant depressed patients (n = 80) showed significantly more attentional deficits than never-depressed controls (n = 113) on the ACS and Stroop color-naming task. However, in contrast with hypotheses, no differences were found between chronic, treatment-resistant depressed patients and never-depressed individuals on the ECT or emotional Stroop task. The current findings indicate that chronic, treatment-resistant depressed patients present attentional deficits. The results however question whether this patient group shows attentional biases for negative material. Future research should include comparisons of chronic, treatment-resistant and non-chronically depressed patients. If replicated, these current results might indicate that focusing on improving attentional deficits could be a more promising target for treatment than addressing attentional biases.

## 1. Introduction

Chronically depressed patients not responding well to treatment are a major challenge for mental health care (Cuijpers et al., 2017). The prevalence of both chronic and treatment-resistant depression are high. About 20% of all depressed patients develop a chronic course (Spijker et al., 2002) and, depending on the exact definition, about 15%–55% of all patients are treatment-resistant (Thomas et al., 2013; Trevino et al., 2014). The concepts of chronic and treatment-resistant depression are partly overlapping. Patients who do not respond to treatment often develop a chronic course (Berlim and Turecki, 2007) and chronically depressed patients often respond less well to treatment (Cuijpers et al., 2010). Investigating cognitive and psychological factors that characterize patients with chronic, treatment-resistant depression (cTRD) is important to further understand depression and improve treatment.

Research on risk factors and maintaining factors of cTRD are often limited to socio-demographic and clinical characteristics, such as age of onset and suicidality (Köhler et al., 2019; Souery et al., 2007). Importantly, only a minority of studies investigated maladaptive cognitive processes or psychological characteristics that could be implicated in cTRD. It has been found that chronically depressed patients compared to non-chronically depressed patients show higher levels of emotional avoidance (Brockmeyer et al., 2015), more dysfunctional attitudes (Iacoviello et al., 2006; Riso et al., 2003) and higher levels of rumination (Wiersma et al., 2011). Attentional processes have been argued to have a marked impact on such cognitive factors in (recurrent) depression (De Raedt and Koster, 2010; Farb et al., 2015). However, knowledge about attentional characteristics of cTRD is surprisingly limited.

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### 1.1. Attentional processes in depression

Problems in focusing and shifting attention are a well-known symptom of major depression (Snyder, 2013). Deficits in shifting attention seem to be predictive of subsequent depressive symptoms (Letkiewicz et al., 2014). Furthermore, problems in shifting and sustaining attention remain present in remitted depressed patients and have been related to relapse (Demeyer et al., 2012; Paelecke-Habermann et al., 2005). It has therefore been argued that attentional deficits possibly play a role in the onset, maintenance and/or recurrence of depression. However, findings whether longer depressive episodes are characterized by attentional deficits are mixed (Keilp et al., 2008; McClintock et al., 2010).

In addition to general attentional deficits, information processing is also influenced by the valence of information. Cognitive theories of depression (Beck, 2008) propose that depression is characterized by specific attentional biases for negative material. According to these theories, attentional biases are triggered by negative schemata and thereby contribute to depressive symptoms (Disner et al., 2011). A meta-analysis covering 29 studies indeed concluded that biased attention for negative material plays an important role in depression (Peckham et al., 2010). Furthermore, it has been found that depressed individuals also show a lack of attention for positive material (Duque and Vázquez, 2015; Isaac et al., 2014). However, several non-replications exist, finding no attentional bias in depressed individuals (Mogg et al., 2000; Neshat-Doost et al., 2000). Recently, it has been argued that part of these inconsistencies might be explained by focusing on mean levels of attentional biases, where attentional bias is more correctly expressed as a dynamic process, fluctuating over time (Zvielli et al., 2015). It has been found that remitted depressed patients show variability in shifting towards and away from negative information which seems to correlate with the number of depressive episodes (Zvielli et al., 2016). However, in another study using novel dynamic indices no differences were observed between depressed patients and healthy controls (Elgersma et al., 2018). Taken together, these findings suggest that attentional biases are associated with vulnerability of depression. The fact that cognitive theories emphasize the role of attentional biases in maintaining depressive symptoms, would suggest that attentional biases are related to the duration and persistence of depressive episodes. However, it remains unclear whether attentional biases are present in cTRD.

The aim of the current study was to assess whether patients suffering of cTRD show general attentional deficits and/or attentional biases for negatively valenced material. For this purpose, cTRD outpatients were compared to a never-depressed (ND) control sample. We used a multimethod approach including different measures to assess attention deficits as well as attentional biases. Furthermore, we explored whether attentional deficits and/or attentional biases are correlated with chronicity, treatment-resistance or severity of the current depressive episode. We hypothesized that cTRD would show more attentional deficits and more negatively biased attention compared with ND.

## 2. Method

### 2.1. Participants

**Chronic, treatment-resistant depressed patients (cTRD).** Baseline data of an RCT on the effectiveness of mindfulness-based cognitive therapy (MBCT) for cTRD patients (Cladder-Micus et al., 2018) were used. Inclusion criteria were a) age ≥18; b) current depressive episode according to DSM-IV criteria with a duration of ≥12 months; c) moderate to high levels of depressive symptoms [Inventory of Depressive Symptomatology-Self-Report (IDS-SR) ≥21]; d) at least one adequate trial of antidepressant medication during the current episode (defined as: appropriate doses of antidepressant medication for ≥ 4 weeks; or patient's refusal to use medication contrary to the advice of a psychiatrist); e) previous psychological treatment during the current episode (defined as: ≥10 sessions of Cognitive-Behavioral Therapy (CBT) or Interpersonal therapy (IPT); or < 10 sessions if discontinued because of patient's withdrawal). Exclusion criteria were: a) current psychotic symptoms; b) lifetime bipolar disorder; c) current alcohol or drug dependence; d) recent electro convulsive therapy (<3 months ago); e) current somatic disorder partly explaining depressive symptoms; f) physical-, linguistic-, cognitive, or intellectual impairments which might interfere with participation in MBCT or assessments; g) previous MBCT training. For the Stroop tasks, color-blindness was an additional exclusion criterion. Table 1 presents patient characteristics.

**Never-depressed control participants (ND).** ND participants (N = 113) were recruited from the community via flyers, websites and waitlists of mindfulness-based stress reduction (MBSR) courses provided for the general public. Exclusion criteria were: a) current or lifetime depressive episode; b) current anxiety disorder; c) current or lifetime psychotic symptoms; d) current alcohol or drugs dependence; e) physical-, language-, cognitive-, or intellectual impairments which interfere

**Table 1**
Socio-demographic and clinical characteristics of the samples, presented as mean (SD) unless otherwise specified.

| | Never-depressed controls | Chronic, treatment-resistant depressed patients | Test statistics |
|---|---|---|---|
| | n = 113 | n = 80 | |
| Age, years | 45.4 (12.78) | 47.8 (10.37) | $t$ (181) = 1.38, $p$ = .17 |
| Gender, % female | 67% | 60% | $\chi^2$ (1) = 1.07, $p$ = .30 |
| Education level (1–7)[1] | 5.6 (1.5) | 4.1 (1.8) | $t$ (188) = 5.92, $p$ < .001 |
| Depression severity (IDS-SR) | 5.4 (3.7), range: 0–15 | 41.8 (9.7), range: 24–67 | $t$ (191) = 36.42, $p$ < .001 |
| Number of depressive episodes lifetime | – | 2.7 (3.8) | |
| >2 years depressed | – | 80% | |
| Currently using antidepressant medication | – | 81% | |
| Number of antidepressants used during current episode | – | | |
| 1-2 antidepressants | | 55% | |
| 3-4 antidepressants | | 21% | |
| 5-6 antidepressants | | 14% | |
| 7-10 antidepressants | | 2% | |
| >10 antidepressants | | 5% | |
| Refused to use antidepressant[3] | | 4% | |
| Family history of depression | –[2] | 66% | |
| Received CBT during current episode | – | 88% | |
| Received IPT during current episode | – | 22% | |
| Previous day treatment or inpatient treatment during current episode | – | 34% | |

Note. IDS-SR= Inventory of depressive symptomatology-self report; [1] based on Dutch classification system according to Verhage (1964): 1–2 = low educational level (primary school; some secondary education), 3–5 = medium educational level (secondary education, low to medium level), 6–7 = high educational level (secondary education, high level; college degree; university degree); [2] not assessed; CBT = cognitive behavioral therapy; IPT= Interpersonal Therapy for depression; [3] For details see in- and exclusion criteria. Most of the patients refusing to take antidepressant medication (against the advice of their psychiatrist) have had bad experiences with antidepressant use.

with assessments; f) previous mindfulness training or other meditation practice; and g) color-blindness. Individuals were telephonically screened for in- and exclusion criteria using the structured clinical interview for DSM-IV (SCID) axis I disorders (van Groenestijn et al., 1999). Participants recruited via MBSR courses participated before attending MBSR. The group was matched in age and gender to the cTRD sample. Participants received a gift card (€20).

## 3. Procedure

**cTRD sample.** Of the 106 participants included in the RCT (Cladder-Micus et al., 2018) 86 participants (based on study entry[1]) were invited to additionally take part in a task battery including tasks on attention, memory, interpretation, cognitive control and rumination. The study was approved by the Medical Ethical committee Arnhem-Nijmegen (nr. 2012/339). After giving written informed consent participants completed questionnaires and clinical characteristics were assessed including the Dutch Measure of Treatment-Resistance (DM-TRD; Peeters et al., 2016). A second appointment was scheduled for the 90-min (including a break) task battery. Testing was organized within a pragmatic RCT and was embedded in clinical practice. Therefore, individual cognitive capacities, physical limitations and planning restrictions needed to be taken into account, which resulted in different samples sizes per task (ACS n = 80; Stroop tasks n = 70; ECT n = 69).

**ND sample**. Of 116 participants who agreed to participate, three were excluded because of a score ≥21 on the IDS-SR (indicating moderate depression). Two participants did not attend the appointment for the task battery, which leaves 113 participants for the analyses using questionnaires and 111 participants for the tasks. The task battery was identical to the cTRD sample, except for one additional task at the end of the task battery (not reported in the current paper). Participants filled in an online version of the questionnaires at home and completed the task battery in the Radboud University Medical Center in Nijmegen, The Netherlands. Participants gave passive informed consent at the beginning of the online questionnaires and written informed consent before starting the tasks.

## 4. Measurements

### 4.1. Attentional deficits

***Attentional Control Scale (ACS).*** The ACS (Derryberry and Reed, 2002) is an 20-item questionnaire including the subscales 'focus attention' and 'shifting attention'. The internal consistency was good (Cronbach's α ranging from 0.86–.72) except for the subscale 'shifting' in the cTRD sample which showed low internal consistency (Cronbach's α = 0.61). Previous research has concluded that the ACS is a reliable and valid measure of attentional control (Judah et al., 2014). However, the shifting subscale typically shows a lower internal consistency compared with the ACS total score and ACS focusing subscale in healthy samples (Ólafsson et al., 2011), as well as in patients with anxiety disorders (Moradi et al., 2014) or remitted depressed patients (Cerny et al., 2019).

***Stroop task.*** A computerized version of the Stroop color naming task (Stroop, 1935) was used (identical to the task used by Ferrari et al., 2016). Participants were instructed to name the ink color of words as quickly as possible while avoiding mistakes. The computer presented cards with 40 words (5 columns x 8 rows). Words were presented in red, yellow, blue, white, and green on a black background. The task consisted of one congruent card ("green" printed in green), one incongruent card ("green" printed in red) and one card displaying rows of colored crosses ("XXX"). Participants started with a practice card. The cards were a presented in random order, while the incongruent card was always presented last. Participants were allowed to correct mistakes. The research assistant recorded the reaction time (RT) of each card and uncorrected mistakes while being blind for the order of cards (except the incongruent card).

### 4.2. Attentional biases

***Emotional Stroop task***. The emotional Stroop task was embedded within the Stroop task. The emotional Stroop task consisted of three cards presented in random order displaying negative depression-related words, positive words, and neutral words, respectively. Words were selected from a database providing the valence of Dutch words (Moors et al., 2013; see supplementary material for a list of all words used). Instruction for all cards was to name the ink color as quickly as possible.

***Exogenous cueing task (ECT).*** This task is an emotionally modified version of the exogenous cueing task (Posner, 1980). The task is identical to Elgersma et al. (2018) and summarized below. A detailed description of the task can be found in the supplementary material. First, a visual cue was presented on the left or right side of the screen. Next, depression-related self-descriptive words, positive self-descriptors, threat-related words, and neutral words appeared on same (valid trial) or opposite side (invalid trial) as the cue. Participants were instructed to indicate the location of the word as quickly as possible. The task consisted of two parts: 128 trials in which cues were presented for 500 ms and 128 trials in which cues were presented for 1250 ms.

## 5. Data preparation

To compute interference scores of the Stroop task, the latency of the congruent card and the latency on the XXX card were subtracted from the latency of the incongruent card, respectively. We excluded participants who made ≥4 uncorrected mistakes (cTRD n = 9, ND n = 8), therefore allowing on average one uncorrected mistake per card. To compute attentional bias scores of the emotional Stroop task, the latency on the neutral card was subtracted from the latency on the negative card and the positive card, respectively.

Traditional bias indices for the ECT were computed for both presentations times. Based on Koster et al. (2005), Mogg et al. (2008) and Elgersma et al. (2018), for each valence, the following traditional bias indices were computed: engagement scores, disengagement scores, cue validity effect (CV), and attentional bias scores (ABS). In accordance with previous research, we mainly focused on ABS. Trial-level bias scores (TLBS) were computed according to the procedure presented by Zvielli et al. (2014). Each invalid trial was matched with a valid trial, temporally as close as possible and no further than 5 trials away. Per category, a minimum of 20 matches was required. In line with Elgersma et al. (2018), we computed five TLBS indices per presentation time and per valence: mean TLBS Towards, mean TLBS, peak TLBS Towards, peak TLBS away, and variability. In line with previous research (Elgersma et al., 2018; Zvielli et al., 2016) we focused on variability as a key index of the temporal stability of attentional bias. How traditional bias scores and TLBS were computed is presented in Table 1S in the supplementary material.

## 6. Results

### 6.1. Attentional deficits

**ACS**. cTRD patients showed a significant lower score on the ACS compared with ND controls, with a strong effect. There were also significant differences between cTRD and ND on the subscales, $F(2,190) = 131.76$, $p < .001$, $\eta_p^2 = 0.58$. Patients reported to experience less ability

[1] The RCT had already started while the attentional measures presented in the current paper were added to the study protocol. Once additional ethical approval was obtained for adding the task battery all new participants entering the study were asked to participate. Therefore, the first 20 participants were not asked to participate in the task battery.

to focus attention and less ability to shift attention. Table 2 presents the descriptives and test statistics.

**Stroop task.** A mixed ANOVA on RT's with group (cTRD, ND) and card (congruent, incongruent, XXX) as factors revealed a main effect of group, showing that in general cTRD have slower RT than ND, $F$ (1,162) = 34.25, $p < .001$, $\eta_p^2 = 0.18$. There was also a significant effect of card, $F$ (2,324) = 285.19, $p < .001$, $\eta_p^2 = 0.64$. Contrasts reveal that the mean RT's on the congruent card, $F$ (1, 162) = 298.69, $p < .001$,$\eta_p^2 = 0.65$, and on the XXX card, $F$ (1,162) = 305.69, $p < .001$, $\eta_p^2 = 0.65$, were faster than the mean RT on the incongruent card. There was a significant group*card interaction $F$ (2,324) = 10.78 $p < .001$, $\eta_p^2 = 0.06$, meaning that the differences between the cards is not the same for cTRD and ND. Independent samples $t$-tests revealed that cTRD show larger interference effects (incongruent card - congruent card; incongruent-XXX) than ND. Table 3 presents the descriptives and $t$-test statistics.

### 6.2. Attentional biases

**Emotional Stroop task.** A mixed ANOVA on RT's with group (cTRD, ND) and card (negative, positive, neutral) as factors, revealed a significant main effect of group, $F$ (1,178) = 42.5, $p < .001$, indicating that ND showed faster RT's than cTRD. There was also a significant main effect of card, $F$ (2,177) = 7.19, $p$ = .001. Contrasts revealed a significant difference between the positive and negative card, $F$ (1, 178) = 11.25, $p$ = .001, but no significant difference between the neutral and the negative card, $F$ (1, 178) = 0.04, $p$ = .84. There was no significant group*card interaction, $F$ (1.97, 350.33) = 0.92, $p$ = .39. $\eta_p^2 = 0.005$. A mixed ANOVA with bias scores (negative-neutral, positive-neutral) as within-subject factor and group (cTRD, ND) revealed no significant effect of group, $F$ (1,178) = 0.53, $p$ = .47, $\eta_p^2 = 0.003$, a significant effect of bias scores, $F$ (1, 178) = 11.64, $p < .001$,$\eta_p^2 = 0.06$, with slower RT's on the negative-neutral bias score, but no significant interaction between group and bias score, $F$ (1,178) = 1.24, $p$ = .27, $\eta_p^2 = 0.007$. Table 3 presents means and $SD$'s.

### 6.3. Exogenous cueing task

***Traditional Bias Scores.*** Per presentation time (500 ms, 1250 ms) separate mixed ANOVA's were conducted for each traditional bias score (engagement, disengagement, ABS) with valence (negative, positive, threat) as within-subject factor and group (cTRD, ND) as between-subject factor. Cue validity (CV) scores were analyzed in a similar analysis, with four different levels of valence (negative, positive, threat, neutral). Descriptives and test statistics are presented in Table 4. We focused on the group*valence interactions.

Results of both presentations times reveal that for none of the traditional bias scores a significant group*valence interaction was found. There were also no significant main effects of group, except for ABS with an effect size indicating a small effect,$\eta_p^2 = .04$. These results indicate that -in contrast to the hypothesis-cTRD patients did not react differently on negative, threat-related, or positive stimuli compared with the ND sample.

**Table 2**
Mean *(SD)* of scores on the attentional control scale (ACS) for both groups.

| | Never-depressed controls | Chronic, treatment-resistant depressed patients | Test statistics |
|---|---|---|---|
| | n = 113 | n = 80 | |
| ACS total score | 58.65 *(7.52)* | 41.39 *(7.48)* | $t$ (191) = 15.74, $p$ < .001, Cohen's $d$ = 2.30 |
| ACS -focus attention | 22.02 *(3.43)* | 14.60 *(3.60)* | $F$ (1, 191) = 210.25, $p < .001$ |
| ACS -shifting attention | 14.47 *(2.30)* | 10.21 *(2.47)* | $F$ (1,191) = 848.63, $p < .001$ |

**Table 3**
Reaction times in per card of the Stroop color naming task and the emotional Stroop task, presented in mean (*SD*), in seconds.

| | Never-depressed controls | Chronic, treatment-resistant depressed patients | $t$-test statistics |
|---|---|---|---|
| Stroop task | | | |
| | $n$ = 103 | $n$ = 61 | |
| Congruent card | 21.85 (5.15) | 26.17 (6.78) | |
| Incongruent card | 39.08 (10.77) | 51.31 (21.27) | |
| XXX card | 24.55 (4.94) | 29.20 (7.35) | |
| Incongruent - congruent | 17.22 (10.34) | 25.11 (20.95) | $t$ (162) = 3.22, $p$ = .002, Cohens $d$ = 0.48 |
| Incongruent - XXX | 14.53 (8.88) | 22.11 (17.89) | $t$ (162) = 3.09, $p$ < .001, Cohens $d$ = 0.54 |
| Emotional Stroop task | | | |
| | $n$ = 111 | $n$ = 69 | |
| Neutral card | 26.36 (5.15) | 32.70 (8.64) | |
| Negative card | 26.12 (4.63) | 33.27 (9.76) | |
| Positive card | 25.51 (5.18) | 31.88 (8.68) | |
| Negative - neutral | −0.25 (2.51) | 0.57 (4.20) | $t$ (179) = -1.63, $p$ = .10, Cohens $d$ = 0.23 |
| Positive - neutral | −0.85 (2.23) | −0.84 (4.51) | $t$ (178) = -0.2, $p$ = .89, Cohens $d$ < 0.01 |

***Trial Level Bias Scores.*** Table 5 presents the (untransformed) means and *SD* and the test-statistics of the different TLBS indices. TLBS indices (variability, mean Towards, mean Away) were analyzed for both presentation times (500 ms, 1250 ms) with separate ANOVA's with valence (negative, positive, threat) and group (cTRD, ND) as factors. We excluded the peak Towards and peak Away indices, due to the known high correlations (Elgersma et al., 2018). For positive stimuli, <20 possible matches were available in the 1250 ms presentation condition. Therefore, in all analyses based on 1250 ms presentation time the factor valence only consisted of two levels (negative, threat). Scores were log transformed (LG10).

In both conditions, significant main effects of group were found for all TLBS indices, however, for none of the TLBS indices a significant group*valence interaction was found (see Table 5).

To control for general variability in RT's we re-ran the analyses while controlling for mean and SD on neutral trials (Zvielli et al., 2016). When controlling for mean RT's on neutral trials, on all TLBS indices significant effects of group were found (all $p < .001$. $\eta_p^2 = 0.07$–$0.12$), but no significant group*valence interactions. When controlling for SD on neutral trials, no significant effects of group, valence or valence*group interactions were found.

### 6.4. Correlational analyses

Within the cTRD sample, correlation analyses were conducted to explore whether attentional deficits and/or attentional biases were correlated with the duration of the depressive episode, treatment-resistance or severity. No significant correlations were found between the duration of the depressive episode, treatment-resistance and attentional deficits (ACS, Stroop task) or attentional bias (emotional Stroop task, ECT). Depressive symptoms were significantly negatively correlated with scores on the ACS and positively correlated with TLBS variability scores (for all different valences), see Table 6.

## 7. Discussion

The aim of the current study was to investigate whether cTRD

**Table 4**
Means (*SD*) and test statistics of traditional bias scores for each group per presentation time and per stimulus type. Significant effects are presented in bold.

| 500 ms presentation time | | | | | | |
|---|---|---|---|---|---|---|
| | | Negative | Threat | Positive | Neutral | Test-statistics |
| Engagement | ND | −4.32 *(25.26)* | −7.88 *(27.01)* | −7.56 *(26.44)* | – | Group: $F$ (1.178) = .23, $p$ = .63, $\eta_p^2$ = .001 |
| | cTRD | −3.18 *(51.12)* | −15.51 *(56.44)* | −8.13 *(56.52)* | – | Group*Valence: $F$ (2,356) = 1.11, $p$ = .33, $\eta_p^2$ = 0.006 |
| Disengagement | ND | −2.34 *(22.68)* | −3.07 *(23.01)* | −7.75 *(22.89)* | – | Group: $F$ (1,178) = .39, $p$ = .53, $\eta_p^2$ = .002 |
| | cTRD | −0.99 *(30.69)* | −7.24 *(42.33)* | −12.61 *(54.09)* | – | Group*Valence: $F$ (2, 356) = 0.69, $p$ = .50, $\eta_p^2$ = 0.004 |
| CV | ND | −20.65 *(42.49)* | −25.57 *(38.55)* | −29.29 *(39.51)* | −13.98 *(43.40)* | Group: $F$ (1.178) = 3.75, $p$ = .055, $\eta_p^2$ = .02, |
| | cTRD | −3.32 *(49.66)* | −21.91 *(52.50)* | −19.88 *(80.83)* | 0.86 *(57.39)* | Group*Valence: $F$ (3, 534) = 1.15, $p$ = .37, $\eta_p^2$ = 0.006 |
| Attentional bias | ND | −6.67 *(32.51)* | −11.58 *(35.62)* | −15.31 *(35.45)* | – | Group: $F$ (1.178) = .56, $p$ = .45. $\eta_p^2$ = .003 |
| | cTRD | −4.17 *(59.11)* | −22.76 *(58.03)* | −20.73 *(88.56)* | – | Group*Valence: $F$ (2, 356) = 1.40. $p$ = .25, $\eta_p^2$ = 0.008 |
| 1250 ms presentation time | | | | | | |
| | | Negative | Threat | Positive | Neutral | Test-statistics |
| Engagement | ND | −4.71 *(30.59)* | −17.86 *(30.48)* | −0.51 *(26.45)* | – | Group: $F$(1,178) = 1.40, $p$ = .24, $\eta_p^2$ = .008 |
| | cTRD | −9.32 *(51.53)* | −22.28 *(41.27)* | −8.18 *(48.70)* | – | Group*Valence: $F$ (2,356) = 0.21, $p$ = .81 $\eta_p^2$ = .001 |
| Disengagement | ND | −4.48 *(28.68)* | −0.58 *(25.69)* | −7.76 *(26.16)* | – | Group:, $F$ (1,178) = .11, $p$ = .75. $\eta_p^2$ = .001 |
| | cTRD | −9.55 *(49.46)* | −1.55 *(53.08)* | −6.47 *(51.21)* | – | Group*Valence: $F$ (2,356) = .66, $p$ = .51. $\eta_p^2$ = .004 |
| CV | ND | −32.38 *(39.19)* | −41.64 *(34.74)* | −31.46 *(33.45)* | −23.19 *(35.99)* | Group: $F$ (1.178) = .06. $p$ = .80. $\eta_p^2$<.001 |
| | cTRD | −37.85 *(56.14)* | −42.81 *(48.39)* | −33.63 *(49.96)* | −18.97 *(52.49)* | Group*Valence: $F$ (3,534) = 0.55, $p$ = .65. $\eta_p^2$ = .003 |
| Attentional bias | ND | 13.96 *(70.77)* | 4.71 *(63.07)* | 14.88 *(59.09)* | – | Group: **$F$(1,178) = 7.09, $p$ = .008. $\eta_p^2$=.04** |
| | cTRD | −16.21 *(85.05)* | −21.16 *(88.39)* | −11.98 *(86.86)* | – | Group*Valence: $F$ (2,356) = 0.17, $p$ = .85$\eta_p^2$ = .001 |

Note. CV=Cue Validity effect; ND = never-depressed controls; cTRD = chronic treatment resistant depressed patients.

patients show impairments in general attentional processes and biased attention for emotional material compared with ND individuals. As expected, cTRD patients showed more attentional deficits than ND individuals on a self-report scale as well as on a behavioral task. However, in contrast to our hypothesis, cTRD patients did not show more attentional bias towards emotional material compared with ND individuals.

### 7.1. Attentional deficits

With regard to attentional deficits, results show that cTRD patients reported more difficulties to shift and focus attention on a self-report measure. Furthermore, cTRD patients had more difficulties to inhibit habitual responses, reflected in higher Stroop interference scores. The results are in line with previous studies reporting that non-chronically depressed patients show higher Stroop interference scores than healthy controls (Gohier et al., 2009). However, it remains unclear whether these attentional deficits are related to the persistence of depressive episodes. While problems in shifting and focusing attention were correlated with depressive symptoms, we found no correlations with chronicity or treatment-resistance.

### 7.2. Attentional bias

In contrast to our hypotheses, we found no differences in attentional bias between ND individuals and cTRD patients on the emotional Stroop task and the ECT. Furthermore, no differences between the samples were found when examining the temporal dynamics of attention via TLBS. It has been argued that TLBS might be better suited to investigate attentional biases than traditional bias scores (Zvielli et al., 2014). However, in the current study the variability in attentional bias for different valences was not significantly different between patients and controls, even when controlling for general effects of heighted RT and SD (Kruijt et al., 2016). In addition, we found no indications that traditional attentional bias scores on the ECT or emotional Stroop were correlated with chronicity, treatment-resistance or severity of depressive symptoms. Variability in attentional biases (TLBS) was correlated with depressive symptoms, which might indicate that TLBS are somehow related to depressive symptoms. However, as depressive symptoms were positively correlated with variability in negative but also positive trials, the nature of this association is not yet clear.

There are several possible explanations for the result that no attentional bias was found in cTRD patients. As with non-significant findings in general, not finding an effect does not prove its non-existence. Furthermore, one might question the validity of the tasks. We selected two different and commonly used tasks. However, the reliability of RT measures to assess attentional bias has been criticized (Kertzman et al., 2010; Van Bockstaele et al., 2017; Waechter et al., 2014). Moreover, the stimuli selection might have influenced the results. Both of the attentional bias measures used words instead of for example emotional pictures (Becker et al., 2019). It has been argued that biases are larger if stimuli are self-referent (Mathews and MacLeod, 2005), therefore it might be worthwhile to investigate whether using more personalized stimuli would lead to different results.

The current results are in contrast to cognitive theories according to which attentional biases play an important role in the maintenance of depressive symptoms (Beck, 2008). Although a meta-analysis provided evidence for an attentional bias in depressed samples (Peckham et al., 2010), our results may indicate that this bias for emotional information disappears in cTRD. A possible explanation might be the finding that many depressed patients show disturbed emotional reactivity (Bylsma et al., 2008), which may be more pronounced in cTRD patients because they show more emotional avoidance (Brockmeyer et al., 2015). Although cognitive theories (Beck, 2008) would predict a heighted emotional response when facing negative stimuli, studies have shown that depressed patients may present a blunted emotional reactivity to negative as well as positive stimuli, also described as emotion context insensitivity (ECI; Rottenberg and Hindash, 2015). ECI seems to correlate with depressive severity (Peeters et al., 2010), which might explain why no attentional bias has been found in previous reports focusing on currently depressed patients (Baert et al., 2010; Elgersma et al., 2018) and in the current study.

### 7.3. Strengths and limitations

The current study is one of the first attempts to shed further light on the underlying cognitive processes that are associated with cTRD. This severely affected group of patients is not regularly studied, although it is an important group to refine our understanding of the persistence of the

**Table 5**
Mean (and *SD*) of the raw TLBS indices of the ECT per group. Significant effects are presented in bold.

| 500 ms presentation time | | | | | |
|---|---|---|---|---|---|
| | | Negative | Threat | Positive | Test-statistics |
| Variability | ND | 83.93 *(34.98)* | 86.03 *(33.58)* | 80.98 *(32.20)* | Group: **$F$ (1.172) = 39.17, $p < .001$, $\eta_p^2 = .19$** |
| | cTRD | 127.68 *(62.84)* | 124.77 *(60.56)* | 118.12 *(57.16)* | Group*Valence: $F$ (2,344) = 0.86, $p = .42$. $\eta_p^2 = .005$ |
| Mean towards | ND | 62.81 *(27.01)* | 64.65 *(27.60)* | 62.49 *(26.97)* | Group: **$F$ (1,172) = 34.03, $p < .001$ $\eta_p^2 = .17$** |
| | cTRD | 97.71 *(48.45)* | 94.41 *(42.85)* | 87.89 *(45.44)* | Group*Valence: $F$ (2,344) = 1.58, $p = .206$. $\eta_p^2 = .009$ |
| Mean Away | ND | −65.00 *(28.45)* | −67.96 *(28.45)* | −61.52 *(29.73)* | Group: **$F$ (1.172) = 29.16, $p < .001$, $\eta_p^2 = .15$** |
| | cTRD | −91.74 *(47.37)* | −95.64 *(51.01)* | −89.12 *(50.17)* | Group*Valence: $F$ (2,344) = .46, $p = .63$. $\eta_p^2 = .003$ |
| 1250 ms presentation time | | | | | |
| | | Negative | Threat | Positive | Test-statistics |
| Variability | ND | 96.19 *(41.52)* | 96.04 *(36.97)* | – | Group: **$F$ (1,176) = 30.36, $p < .001$, $\eta_p^2 = .15$** |
| | cTRD | 139.01 *(68.57)* | 137.66 *(74.47)* | – | Group*Valence: $F$ (1,176) = .167, $p = .683$, $\eta_p^2 = .001$ |
| Mean towards | ND | 73.20 *(36.66)* | 70.36 *(27.94)* | – | Group: **$F$ (1,176) = 26.718, $p < .001$. $\eta_p^2 = .13$** |
| | cTRD | 99.04 *(50.14)* | 104.32 *(67.46)* | – | Group*Valence: $F$ (1,176) = 0.14, $p = .70$. $\eta_p^2 = .001$, |
| Mean Away | ND | −73.92 *(29.05)* | −76.96 *(33.99)* | – | Group: **$F$ (1,176) = 27.83, $p < .001$, $\eta_p^2 = .14$** |
| | cTRD | −112.80 *(62.11)* | −106.43 *(57.04)* | – | Group*Valence: $F$ (1.176) = 1.498, $p = .223$, $\eta_p^2 = .008$ |

Note. CV=Cue Validity effect; ND = never-depressed controls; cTRD = chronic treatment-resistant depressed patients.

**Table 6**
Correlations between duration of episode, treatment resistance, depressive symptoms, and different measures of attentional processes and attentional bias in chronically, treatment-resistant depressed patients.

| | | Duration of episode | Treatment-resistance (DM-TRD) | Depressive symptoms (IDS-SR) |
|---|---|---|---|---|
| ACS | | -.09 | -.07 | -.45** |
| | ACS focus | -.18 | -.04 | -.40** |
| | ACS shifting | .11 | -.12 | -.31** |
| Stroop task | | | | |
| | Incongruent-congruent | -.04 | .06 | -.17 |
| Emotional Stroop task | | | | |
| | Negative-neutral | .06 | .06 | -.09 |
| | Positive-neutral | .01 | -.17 | .11 |
| TBS | | | | |
| | ABS Negative 500 ms | -.02 | .03 | -.13 |
| | ABS Threat 500 ms | .02 | .17 | -.08 |
| | ABS Positive 500 ms | -.02 | .06 | -.04 |
| | ABS Negative 1250 ms | .15 | -.13 | -.17 |
| | ABS Threat 1250 ms | .13 | .03 | -.18 |
| | ABS Positive 1250 ms | .10 | .05 | -.21 |
| TLBS | | | | |
| | Variability Positive 500 ms | -.18 | .09 | .33** |
| | Variability Threat 500 ms | -.10 | .04 | .36** |
| | Variability Negative 500 ms | -.13 | .08 | .44** |
| | Variability Threat 1250 ms | -.03 | .20 | .41** |
| | Variability Negative 1250 ms | -.15 | .05 | .38** |

Note.
*p < .05.
**p < .01, ACS = Attentional Control Scale, ABS = Attentional Bias Score, IDS-SR= Inventory of depressive symptomatology self-report, DM-TRD = Dutch Method of Treatment Resistance; TBS = Traditional Bias Score, TLBS = Trial Level Bias Score.

disorder. We used a multi-method approach by utilizing common experimental measures and self-reports. However, some limitations should be acknowledged. First, we used a cross-sectional design comparing cTRD patients with ND controls matched on age and gender. It therefore remains unclear whether attentional deficits or attentional biases developed over time. To gauge the relationship of attentional deficits and attentional biases with clinical characteristics, we examined correlations with measures of severity of depression, chronicity and treatment-resistance. However, as the variability of these measures might be suboptimal and due to the explorative nature of these correlational analyses, results should be interpreted as preliminary. Furthermore, the ND sample was somewhat higher educated which might have influenced performance. In addition, while the cards of the Stroop task were presented in a random order, the incongruent card was always presented last to limit difficulty levels for the patients. This however might have influenced the results due to repetition effects. Although in accordance with previous studies (Elgersma et al., 2018) the number of trials in the ECT (128 trials per presentation time) is quite low which may have reduced reliability. To our knowledge, it is the first time the ACS is used in a cTRD sample. Because the internal consistency of one of the subscales (shifting) was not optimal it seems most valuable to focus on the total score and the focusing attention subscale. Finally, it is important to keep the characteristics of the current sample in mind. All patients were resistant to psychotherapy and pharmacotherapy. Theories assume that treatments as CBT would alter automatic information processing (Beck, 2008). It therefore might be possible that previous therapy already altered attentional biases. Additionally, as this study was conducted in clinical practice, most patients used antidepressant medication. Previous research has shown that medications altering serotonin levels influence information processing (Merens et al., 2007). Therefore, results might have been different in a comparable sample

using no antidepressant medication.

## 8. Conclusion and future research

In sum, our results show that, as expected, cTRD patients showed significantly more attentional deficits compared with ND controls. However, we found no evidence of biased attention for emotional material in cTRD patients. Further research is needed to investigate the exact role of attentional processes in chronic and treatment-resistant depression. Preferably, future research should use measures providing more detailed information about attention allocation, such as eye-tracking techniques (Sanchez-Lopez et al., 2019). To further disentangle the effects of attentional processes on chronicity it would be interesting to compare non-chronically and chronically depressed patients and to assess attentional processes in a longitudinal design. Furthermore, it seems valuable to assess whether the absence of an attentional bias might be explained by blunted emotional reactivity in this population, and therefore to include measures of both in the same study. In case the current results are replicated, these findings would have important clinical implications. Recently, attentional bias trainings have been developed (Ferrari et al., 2016). If the conclusion holds that no substantial attentional bias is present in cTRD patients, those patients might benefit more of trainings targeting attentional deficits via strengthening cognitive control (Koster et al., 2017; Siegle et al., 2007) instead of trainings specifically targeting attentional biases. However, more research is needed to elucidate the role of attentional biases and attentional deficits in chronic and treatment-resistant depression.

## Contributors

MCM coordinated data collection, analyzed the data and wrote the first draft of the manuscript. LdP computed trial-level bias scores. EK Formal analysis. JV Formal analysis. All authors contributed to the writing of the manuscript and approved its final version.

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## Declaration of competing interest

The authors declared no potential conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.04.030.

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