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Event-related potentials to task-irrelevant sad faces as a state marker of depression

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Highlights

- Negative bias was present in automatic face processing in depression
- Negative bias was found in P1 amplitude to sad faces
- Negative bias normalized in symptom reduction

Abstract

Negative bias in face processing has been demonstrated in depression, but there are no longitudinal investigations of negative bias in symptom reduction. We recorded event-related potentials (P1 and N170) to task-irrelevant facial expressions in depressed participants who were later provided with a psychological intervention and in never depressed control participants. Follow-up measurements were conducted for the depressed group two and 39 months later. Negative bias was found specifically in the depression group, and was demonstrated as enlarged P1 amplitude to sad faces, which normalized in the follow-up measurements when the participants had fewer symptoms. Because the P1 amplitude recorded at the baseline did not differ between the depression group that recovered and the group that did not recover after the intervention, this brain response did not show potential as a biomarker for treatment response. It could have potential, however, to serve as a state-marker of depression.

Keywords: Depression, ERP, negative bias, N170, P1, preattentive face processing

1. INTRODUCTION

Depression is a common and highly recurrent disorder, which is most typically characterized by lowering of mood and reduction of energy and enjoyment (World health organization, 2010). According to Aaron Beck's cognitive model of depression (Beck, 1967, 1976, 1987), depressed individuals have a cognitive bias in information processing that predisposes them to selectively attend to negative stimuli. It could be a vulnerability factor that can affect the onset and recurrence of depression episodes (Beck, 1967, 1976, 2008). Relevantly for the current study, this bias is suggested to occur also in automatic information processing

facilitating the processing of negative stimuli already at early processing phases (Beck, 2008).

Negative bias in depression postulated in Beck's theory has been demonstrated empirically with different types of stimuli (for reviews, see Mogg & Bradley, 2005; Peckham, McHugh & Otto, 2010), especially with facial expressions (Gollan, Pane, McCloskey, & Coccaro, 2008; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Naranjo et al., 2011, for a review see, Delle-Vigne, Wang, Kornreich, Verbank & Campanella, 2014). Negative bias in these studies was found as bias in attention or in memory to sad faces.

Processing of facial expressions has been studied widely with event-related potentials (ERPs), which give accurate timing for the brain activity related to different processing stages in face perception. The first ERP component that is modulated by facial expressions is P1, and attentive negative bias in emotional face processing in depression has been found in P1. When participants evaluated emotion intensity in faces, sad faces elicited larger P1 responses than happy or neutral faces in the depressed group but not in the control group (Dai & Feng; 2012; for absent negative bias in P1, see Dai, Wei, Shu, & Feng, 2016; Zhao et al., 2015). Negative bias is also demonstrated in subliminally presented, but attended, faces. Sad faces elicited a larger P1 response compared to neutral faces in the depressed group while controls had a smaller P1 for sad faces compared to neutral faces (Zhang, He, Chen, & Wei, 2016).

There is also evidence for depression-related negative bias in the N170 ERP component (Zhang et al., 2016; Zhao et al., 2015), which reflects structural feature processing in faces, including facial expression processing (Batty & Taylor, 2003). In an attentive condition, including a condition where subliminally presented faces are presented, N170 was larger to sad faces than to happy and/or neutral faces in the depressed participants, whereas in the control participants the N170 was the largest to happy faces (Zhang et al., 2016; Zhao et al.,

2015). Furthermore, a direct comparison between the N170 in the depressed and control groups showed that the responses to sad faces were larger in depressed participants compared to control participants (Wu et al., 2016), reflecting mood-congruent bias in facial emotion processing. However, sometimes no differences between depressed and non-depressed have been found in N170 responses to facial expressions (Jaworska, Blier, Fusee, & Knott, 2012).

Beck's cognitive model of depression suggests that negatively biased cognitive schemas function as automatic information processors (Beck, 2008). However, there is very little information on unattended or task-irrelevant processing of facial expressions in depression, especially with brain activity measurements that can reveal the time course for the processing (i.e. electroencephalography or magnetoencephalography studies, MEG; however, for a study applying functional magnetic resonance imaging, fMRI, see Suslow et al., 2010). In one study, ERPs were recorded for changes in emotional faces in depressed and control participants while participants attended faces with different colors (Chang, Xu, Shi, Zhang, & Zhao, 2010). In that study, the oddball condition was applied, in which the visual mismatch negativity (vMMN) component indexing cortical change detection is elicited (for reviews, see Kremláček et al., 2016; Stefanics, Astikainen, & Czigler, 2014). vMMN is calculated as the difference between responses to repeatedly presented standard stimuli and responses to rare deviant stimuli. In study by Chang et al. (2010), vMMN was found in two latencies reflecting mainly modulations in N170 and the following P250 component. Chang et al. observed smaller-amplitude vMMNs to happy and sad faces in the depressed group compared to the controls, thus showing no evidence of preattentive negative bias but instead an overall weakened cortical change detection related to facial expressions. However, in the study schematic faces, which have inevitably low ecological validity, were applied raising the question whether more naturalistic stimuli could reveal depression-related negative bias in task-irrelevant processing of facial expressions. In another study, task-irrelevant MEG

responses were measured in participants with depression symptoms (dysphoric) and non-depressed controls to sad and happy faces presented in an oddball condition (Xu et al., 2018). Dysphoria-related negative bias was only found in later processing phase (M300 response), but no group differences were found in M100 or M170 responses, which correspond to P1 and N170 responses in ERPs, respectively.

Whether negative cognitive bias in depression is a trait-like characteristic or is state-dependent, that is, changes along with the degree of depressive symptoms, is unclear. Behavioral studies that have found similar processing bias in depressed and sub-clinically depressed participants (Dai et al., 2016) or in depressed and remitted participants (Joormann & Gotlib, 2007) or no change in negative bias in follow-up after remission (Bouhuys, Geerts, Mersch, & Jenner, 1996), have interpreted the result as reflecting a trait. However, some fMRI studies have shown normalization of brain activity for sad facial expressions after cognitive behavioral therapy (CBT; Fu et al., 2008) or after antidepressant treatment (Victor, Furey, Fromm, Ohman, & Drevets, 2010) suggesting state-dependency. Further support for state-dependency comes from an ERP study that found a correlation between depression symptom scores and negative bias in the N170 response (Wu et al., 2016) and from another study that found negative bias only in recurrent depressed individuals but not in first-episode depressed individuals suggesting that negative bias is associated with illness progression (Chen et al., 2014).

Brain responses to emotional faces may also have potential as indicators of treatment response. fMRI studies have shown that brain activation to sad expressions is associated with cognitive therapy treatment outcome in depressed participants (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008). Costafreda et al. (2009) found that brain activity patterns related to sad facial expression processing, distinguish clinically remitted patients

from non-remitted patients. Fu et al. (2008) included healthy control participants in comparisons and found better treatment response for patients who initially showed the most similar activity pattern to healthy controls in sad face processing. To best of our knowledge, ERP studies investigating treatment effect correlates of facial expression processing have not been reported, although they could be similarly feasible as the fMRI studies.

We aim to demonstrate automatic negative bias in depression reflected by ERP responses to pictures of real faces. If we find a negative bias related to depression, we will study the stability of the bias over time. In addition, we will investigate whether ERPs recorded in depressed participants for facial expressions can distinguish between those who recover and those who show no recovery after a brief psychological intervention.

We investigated P1 and N170 amplitudes to happy, sad and neutral faces presented in an oddball condition in which emotional faces were presented infrequently. The oddball condition was expected to be beneficial, because the responses to infrequent deviant stimuli could be expected to be enlarged compared to the frequently presented standard stimuli. We applied a stimulus condition where the identity of the faces, and thus, low-level visual features, changed trial-by-trial. Participants were instructed to attend to an audiobook during the face presentation. Since our adaptive behavior relies largely on preattentive cognition (Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010) and cognitive negative bias is expected to exist already in the level of automatic processing (Beck, 2008), it is important to investigate task-irrelevant emotional face processing in depression.

Two groups of participants, depressed and age- and gender-matched non-depressed control participants, were enrolled in the study. We measured brain responses in the depressed group at three timepoints: at the baseline when all the participants were currently depressed and at 2-month (2-m) and at 39-month (39-m) follow-up measurements. At the 2-m measurement,

approximately half of the depressed participants had received a brief psychological intervention for depression, and they were expected to have less depression symptoms (the other half of the group had been the first two months on a wait-list to receive the same intervention and they got the same intervention after the 2-m measurement). At the 39-m measurement, all of the depressed participants had received the intervention. Since it is very probable that some of the participants will have fewer symptoms after the intervention, this design allows us to study changes in brain responses in relationship to changes in depression symptoms. Clinical outcomes were assessed with questionnaires after the intervention for both groups to further divide the depressed participants into groups of recovered and non-recovered.

Based on previous attentive studies, we expect larger P1 and N170 amplitudes to sad faces compared to neutral and happy faces in the depressed group (Dai & Feng, 2012; Zhang et al., 2016; Zhao et al., 2015), reflecting negative bias in information processing in depression (Beck, 1967, 1976, 1987). In addition, larger N170 responses to happy faces than to neutral faces are expected in the control group (Astikainen, Cong, Ristaniemi, & Hietanen, 2013; Astikainen & Hietanen, 2009; Zhao et al., 2015). Based on previous studies, we also hypothesize a positive correlation between depression symptom scores and negative bias (Chen et al., 2014; Wu et al., 2016) and normalization of the responses when depression symptoms are reduced (Fu et al., 2008; Victor et al., 2010). Furthermore, we expect depressed participants who benefit less from the brief psychological intervention to show more pronounced initial negative bias compared to those who respond better to the intervention, while those who recover would show similar processing compared to the controls (Fu et al., 2008).

2. METHODS AND MATERIALS

2.1 Participants

The participants were depressed and non-depressed volunteers recruited with an advertisement in the local newspaper and via email lists at the University of Jyväskylä.

Written informed consent was obtained from each participant before he or she began. The experiment was undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä approved the research protocol.

The depressed participants were recruited as part of a larger-scale study in which the efficacy of a brief psychological therapy intervention was investigated. A total 119 depressed individuals were randomized to treatment and wait-list control group for the intervention study (Kyllönen et al., 2018), and of these individuals 37 volunteered for the ERP experiments reported here. Clinical depression and other inclusion and exclusion criteria were assessed in a psychiatric interview conducted by a physician independent of the study. The physician conducted a structured interview based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; World health organization, 2010). Based on the interview made by the physician, participants were excluded for any of the following reasons: 1) serious suicide risk; 2) depression with psychotic features; 3) current substance abuse or addiction to drugs and intoxicants, including alcohol; and 4) diagnosis of psychotic disorder, bipolar disorder, eating disorder, or history of neurological injury or disease.

Age- and gender-matched non-depressed controls (n = 31) were recruited separately for the ERP study. The inclusion criteria for the ERP study for the depressed and control groups were age of 18-65 years, right-handedness, normal hearing and normal vision or corrected-to-normal vision. Exclusion criteria for the control group were self-reported 1) current substance abuse or addiction to drugs and intoxicants, including alcohol; and 2) current or previous diagnosis of psychiatric disorder, neurological disorder or neurological injury; 3) current symptoms of depression. For the control group, participants' eligibility to the study, in relation to the inclusion and exclusion criteria, was confirmed before the participation. Current depression symptoms were assessed for the depressed and control groups with Beck's Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). Control participants with BDI-II scores of 10 or more were excluded from the study. This cut-off limit was chosen to make clearer difference between the groups and to ensure that the control group did not

include participants with depression. In the depressed group, two participants had BDI-II scores below 14 points, and they were excluded from further analysis because according to the BDI-II instruction manual, 14 points is the cut-off value for mild depression. Anxiety symptoms were assessed in the depressed group with the Depression, Anxiety, Stress Scales (DASS) questionnaire anxiety subscale (Lovibond & Lovibond, 1995).

There remained data of 27 non-depressed control and 27 depressed participants in the final sample after poor-quality data had been excluded (Table 1). There was no difference in age between the control and depressed groups, $t(52) = 0.8, p = .456, 95\% \text{ CI} [-5.01, 11.01]$ (two-tailed independent sample t-test). There were ten depressed participants with current antidepressant medication. Of these participants, one participant had tricyclic antidepressants, four had selective serotonin reuptake inhibitors and five had serotonin-norepinephrine reuptake inhibitors medication. Seven participants were diagnosed with mild depression (*F32.0*), five with moderate depression (*F32.1*), two with mild dysthymic disorder (*F34.1*), nine with recurrent depression with a mild current episode (*F33.0*) and four with recurrent depression with a moderate current episode (*F33.1*).

Two follow-up measurements were conducted for the depressed participants: a short-term (~2-m) follow-up and a long-term (~39-m) follow-up. The control participants attended the baseline measurement only. Out of the 27 depressed participants whose data were available for the baseline comparison, 27 participants attended the 2-m measurement and 17 participants the 39-m measurement. After poor-quality data were excluded, data remained for 25 participants for the 2-timepoint comparison (baseline vs. 2-m measurement). For the 3-timepoint comparison (baseline vs. 2-m vs. 39-m measurement), data of 17 participants was available due to drop-out ($n = 10$). For the demographics of the participants within each comparison, see Table 1. To analyze the effect of drop out for the 3-timepoint sample, the

demographics and clinical factors of participants included (n = 17) and unavailable (n = 10) for the 3-timepoint comparison were compared. Independent sample t-tests showed no significant group differences in the baseline BDI-II-scores, $t(25) = -2.0, p = .062, 95\% \text{ CI} [-10.09, 0.29]$ (included: $M = 21.3, SD = 5.7$; unavailable: $M = 26.6, SD = 8.4$), in age, $t(25) = -0.2, p = .813, 95\% \text{ CI} [-12.66, 10.03]$ (included: $M = 47.9, SD = 13.4$; unavailable: $M = 49.2, SD = 14.5$) or in DASS-A scores, $t(25) = -2.0, p = .058, 95\% \text{ CI} [-10.42, -0.19]$ (included: $M = 3.6, SD = 5.0$; unavailable: $M = 8.7, SD = 2.7$). Analysis of groups differences (two-tailed Fisher's exact test) for other demographics revealed no significant difference between the groups in number of participants according to gender, $p = .535$ (included: 16 females, 1 male, unavailable: 8 females, 2 males), depression severity (diagnosis of mild or moderate depression), $p = 1.000$ (included: 12 mild, 5 moderate; unavailable: 7 mild, 3 moderate) or medication status, $p = 1.000$ (included: 11 non-medicated, 6 medicated; unavailable: 6 non-medicated, 4 medicated).

Table 1. Demographics and clinical measures at the baseline measurement for the participants included in the baseline, 2- and 3-timepoint comparisons.

Comparison	N	Mean age ± SD [range]	Male/ Female	Mild/ Moderate	Mean BDI-II ± SD [range]	DASS-A ± SD [range]	Non-med/ med
Baseline (Ctrl)	27	45.4 ± 15.7 [21-65]	4/23	Na	2.7 ± 3.0 [0-9]*	Na	Na
Baseline (Dep)	27	48.4 ± 13.6 [19-65]	3/24	18/9	23.3 ± 7.2 [15-42]	5.5 ± 6.8 [0-31]	17/10
2-timepoint comparison	25	50.0 ± 12.7 [19-65]	1/24	17/8	23.0 ± 7.2 [15-42]**	5.7 ± 7.1 [0-31]	15/10
3-timepoint comparison	17	47.8 ± 13.4 [19-65]	1/16	12/5	21.3 ± 5.7 [15-39]	3.6 ± 5.0 [0-18]	11/6

Mild/Moderate = diagnosis of mild/moderate depression; BDI-II = Beck's Depression Inventory-II at the baseline; DASS-A = Anxiety score subscale for DASS-questionnaire at the baseline; Non-med/med = no antidepressant medication/antidepressant medication; SD = standard deviation; Ctrl = non-depressed control group; dep = depressed group; Na. = Not applicable. *Missing data for three participants; ** Missing data for one participant.

2.2 Experimental design, psychological intervention and subgroups in the analyses

At the baseline measurement all the depressed participants were currently depressed, and their diagnoses had been recently confirmed. After the baseline measurement, the depressed participants were randomized into two groups because of the intervention study: One group received therapy intervention immediately (the treatment group) and the other group received the same intervention approximately 2 months later (the wait-list control group, W-L) (see Fig. 1). The 2-m ERP measurement was performed for both depressed groups after the treatment group's intervention, and there were on average approximately two months between the baseline measurement and the 2-m measurement (mean = 55 d, SD = 11.3, range 33-91 d). The third measurement was conducted approximately 39 months after the baseline measurement (mean = 38.9 m, SD = 0.3, range 38.5-39.5 m).

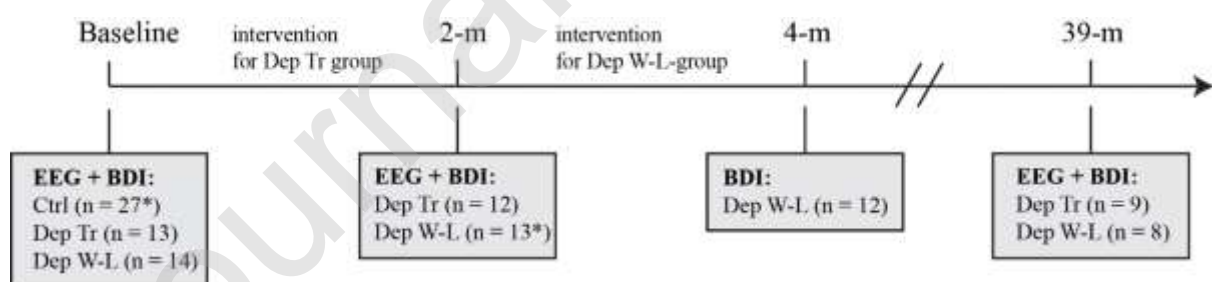


Fig. 1. Outline of the study protocol including EEG measurements, measurement of the BDI-II scores and intervention (brief psychological intervention for depression). The number of participants included in the EEG-analysis and whose BDI-II data was available at each timepoint are indicated in the grey boxes. Ctrl = non-depressed control group; Dep Tr = Depressed group that was a treatment group in the intervention study; Dep W-

L = Depressed group that served as a wait-list group in the intervention study; m = months from the baseline.

*Missing BDI-II score information at the baseline for three participants in the Ctrl group and at 2-m measurement for one participant in Dep W-L. Note that BDI-II at the 4-m (W-L group) is the post-intervention measurement for the Dep W-L group and is used to classify the depressed in W-L to recovery groups.

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Both groups received a six-session psychological intervention based on acceptance and commitment therapy, which is a form of cognitive behavioral therapy (Hayes, Strosahl, & Wilson, 1999). The details of the intervention study are described in Kyllönen et al. (2018). Here we report results related to changes in brain responses in relation to changes in depression symptoms over time. The sample size did not allow us to investigate the effect of the intervention on brain responses separately in the treatment and wait-list control groups.

BDI-II and DASS anxiety questionnaire information was collected for all the depressed participants at the baseline, 2-m and 39-m measurement, and for the wait-list group after they had received the intervention, approximately four months after the baseline measurement (see Fig. 1). Pairwise t-tests (two-tailed) showed a statistically significant reduction in BDI-II-scores from the baseline ($M = 22.8$, $SD = 7.4$) to the 2-m measurement ($M = 14.0$, $SD = 9.1$), $t(23) = 4.5$, $p < .001$, 95 % CI [4.77, 12.81], Cohen's $d = 1.06$ (there was missing BDI-II data for one participant at the 2-m measurement). When the changes in the BDI-II-scores from the baseline measurement to 2-m measurement and to the 39-m measurement were compared, repeated measures of multivariate analysis of variance (MANOVA) showed a significant main effect of time, $F(2,15) = 14.9$, $p < .001$, $\eta^2_p = .665$. Paired samples t-tests (two-tailed) with false discovery rate correction (FDR; Benjamini & Yekutieli, 2001) showed a decrease in the BDI-II-scores from the baseline ($M = 21.3$, $SD = 5.7$) to the 2-m measurement ($M = 12.4$, $SD = 6.2$), $t(16) = 5.0$, $p < .001$, 95% CI [5.14, 12.63], Cohen's $d = 1.49$, but no significant change from the 2-m to the 39-m measurement ($M = 9.6$, $SD = 7.6$), $t(16) = 1.7$, p

= .216, 95% CI [-0.80, 6.44], Cohen's $d = 0.40$. However, the BDI-II-scores were higher at the baseline measurement, $t(16) = 6.4, p < .001, 95\% \text{ CI } [7.83, 15.59]$, Cohen's $d = 1.76$, than at the 39-m measurement. The change in the BDI-II-scores from the baseline to the 2-m measurement and to the 39-m measurement is presented in the Figure 2.

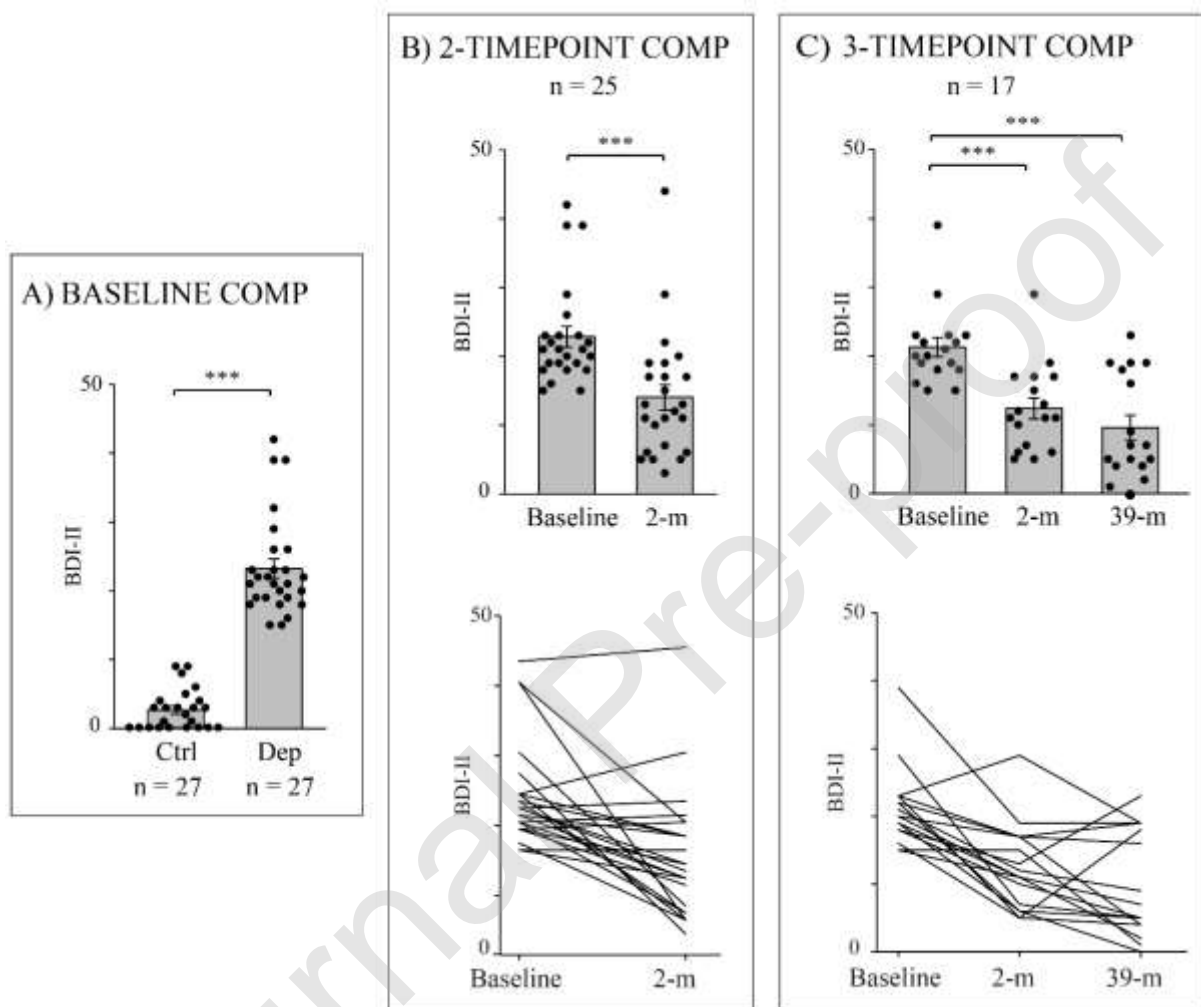


Fig. 2. The BDI-II-scores at different timepoints. A) BDI-II-scores for the control and the depressed group at the baseline measurement. B) The BDI-II-scores at the baseline and at the 2-m measurement for the depressed participants included in the 2-timepoint comparison. Note that data is missing for one participant. C) The BDI-II-scores at the baseline, the 2-m and the 39-m measurement for the participants included in the 3-timepoint comparisons. A, and upper panels of the B and C: The mean values, standard deviations and individual participants' values. Lower panel in B and C: Line graphs showing individual participants' BDI-II-score at different timepoints. Note that approximately half of the individuals in the depressed group (i.e. the wait-list

group) had not yet received the intervention at the 2-m measurement. Baseline = before treatment, 2-m = 2-m after the baseline, when approximately half of the participants had received treatment, 39-m = 39 m after the baseline measurement. Comp = comparison, Ctrl = the control group, Dep = the depressed group; * $p < .05$, ** $p < .01$, *** $p < .001$

(Suggested width for the Figure is 2-columns)

To evaluate the response to treatment, the depressed group was divided into recovered and non-recovered groups based on the change in the BDI-II-scores from the baseline to the measurement after the intervention. The clinical significance of the change in the BDI-II-score was evaluated by using the method suggested by Jacobson and Truax (1991). First, a reliable change index (RCI) was calculated, which assesses whether the change is large enough not to be regarded as a measurement error. Next, a cutoff was calculated that estimates the weighted midpoint between the means of the depressed and non-clinical populations. For the calculations, the normative values of the non-clinical population (i.e. a BDI-II mean score of 5.7 and a standard deviation of 6.8) and Cronbach's alpha for the BDI-II (0.86), were derived from the Kjaergaard, Arfwedson Wang, Waterloo, and Jorde (2014) article. Values for the clinical population were derived from the present study from all the depressed participants whose data were available for the baseline ERP analysis ($n = 27$, BDI-II mean 23.3, $SD = 7.2$). The RCI value and the cutoff values were used to classify participants into two groups: recovered and non-recovered. A participant was regarded as recovered if the RCI value was lower or equal to -1.96 (which indicates a significant clinical change) and the post-intervention BDI-II value was lower than the calculated cutoff value (which was 14.2). Participant was regarded as non-recovered if both criteria were not met. Because the method considers the RCI value and the cutoff value, the non-recovered group includes participants with post-intervention BDI-II values similar to those of the recovered group (i.e., below the cutoff point). However, in these cases, the RCI value indicated that the

change from the baseline to post-intervention measurement was not large enough to be clinically significant.

Twenty-four participants out of 27 were classified as recovered or non-recovered (three were excluded, because of missing data). Sixteen participants were classified as recovered and eight as non-recovered. In the recovered group, there were five participants diagnosed with mild depression (*F32.0*), four with a moderate depression (*F32.1*), five with recurrent depression with a mild current episode (*F33.0*) and two with recurrent depression with a moderate current episode (*F33.1*). In the non-recovered group, there were two participants with a mild depression (*F32.0*), two with mild dysthymic disorder (*F34.1*), three with recurrent depression with mild current episode and one with recurrent depression with moderate current episode.

One-way univariate analysis of variance (ANOVA) revealed no significant difference between the recovered, non-recovered and control groups in age, $F(2,48) = 1.0$, $p = .404$, $\eta^2_p = 0.04$. There was no significant difference in the baseline BDI-II scores, $t(22) = 0.8$, $p = .537$, 95% CI [-11.92, 6.67], Cohen's $d = 0.36$, or in the DASS anxiety scores, $t(22) = 0.6$, $p = .570$, 95% CI [-4.71, 8.33], Cohen's $d = 0.26$, between the recovered and non-recovered groups. In addition, no difference was found between the groups in number of participants with mild or moderate depression, $p = .352$ (two-tailed Fisher's exact test) or in the number of medicated or non-medicated participants, $p = .325$ (two-tailed Fisher's exact test).

Table 2. The demographics and clinical measures at the baseline measurement for the control, recovered and non-recovered groups.

Group	N	Mean Age \pm SD [range]	Male/ Female	Mild/ Moderate	Mean BDI-II \pm SD [range]	Mean DASS-A \pm SD [range]	Non-med/med	TR group/ W-L group
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Ctrl	27	45.4 ± 15.7 [21-65]	4/23	Na.	2.7 ± 3.0 [0-9]	Na.	Na.	Na.
Recovered	16	44.5 ± 13.4 [19-64]	2/14	10/6	22.5 ± 5.4 [16-39]	6.4 ± 8.4 [0-31]	11/5	8/8
Non-recovered	8	52.6 ± 13.0 [33-65]	1/7	7/1	25.1 ± 10.9 [15-42]	4.6 ± 3.7 [0-11]	4/4	5/3

Mild/Moderate = diagnosis of mild/moderate depression; BDI-II = Beck's Depression Inventory-II scores at the baseline; DASS-A = Anxiety score subscale for DASS-questionnaire scores at the baseline; Non-med/med = no antidepressant medication/antidepressant medication; SD = standard deviation; Na. = Not applicable. TR = treatment group in the intervention study; W-L = wait-list group in the intervention study; Ctrl = the non-depressed control group; for the definition of Recovered and Non-recovered see 2.2 Experimental design, psychological intervention and subgroup analyses.

2.3 Stimuli

Neutral, sad and happy faces derived from the Ekman's and Friesen's pictures of Facial Affect (1976) were used as the stimuli in the ERP measurement. Four identities were used (male actors EM and JJ, female actors PF and NR). The expressions in this series of pictures present the basic expressions that have been found to be universally recognized regardless of the person's cultural background (Ekman & Friesen, 1971). E-Prime software version 2.0.8.90 (Psychology Software Tools, Inc, Sharsburg, MD, USA), a Dell 5500 computer and a 23" monitor (Asus VG236 series H; refresh rate = 120 Hz; display resolution = 1920 × 1080) were used to present the stimuli. The pictures were presented at a visual angle of 11° × 16°.

Two separate oddball stimulus conditions were applied in a counterbalanced order where the frequently presented 'standard' stimulus was always a neutral face. The neutral standard stimulus ($p = 0.86$) was rarely replaced by a 'deviant' stimulus ($p = 0.14$) which was either a sad (Sad condition) or a happy face (Happy condition). The standard and deviant stimuli were presented pseudo-randomly with a restriction that at least two standards were presented between two deviant stimuli and the identity of the face was always different between

consecutive stimuli. In both Happy and Sad conditions 480 standard stimuli and 80 deviant stimuli were presented. The stimulus duration was 200 ms, and the randomly assigned stimulus onset asynchrony was 400, 450 or 500 ms.

2.4 Procedure

During the experiment, the participants sat on a chair in a dimly lit, soundproof and electrically shielded room and were monitored via a video camera. Participants were presented with the facial stimuli on a screen 1 m in front of them. Simultaneously, the participants were listening to an audiobook from a loudspeaker above them. The participants were instructed to keep their gaze in the middle of the screen, focus on the story and ignore the visual stimuli. To ensure that participants focused on the story, they were asked questions about it between the stimulus conditions.

2.5 EEG recording and preprocessing

The EEG and electro-oculogram (EOG) was recorded with a high input impedance amplifier, i.e. Net Amps 200 amplifier, with 128-channel HydroCel Geodesic Sensor Net (Electric Geodesic Inc; Eugene; USA) and Net Station software (version 4.2.1). The impedances were kept below 50 k Ω during the recording, as recommended by EGI Inc. The data was recorded at a 1000 Hz sampling rate, filtered online from 0.1 to 400 Hz and referenced to vertex electrode (Cz).

The analysis of the EEG data was conducted with Brain Vision Analyzer 2.1 (Brain Products GmbH, Munich, Germany). First, all bad channels with notable noise were interpolated.

Next, the Gratton-Coles algorithm (Gratton, Coles, & Donchin, 1983) as implemented in Brain Vision Analyzer was used to reject artifacts originating from eye movements. The electrode signals were filtered with the low cutoff at 0.1 Hz and the high cutoff at 30 Hz, both with 24 dB/octave roll-off. In addition, a 50 Hz notch filter was applied. Offline, the data were re-referenced to average over all channels.

In the oddball condition, only the responses to standard stimuli immediately preceding the deviant stimuli were averaged. Eight hundred millisecond segments were extracted relative to the onset of the stimulus: from 200 ms before the onset of the stimulus to 600 ms after onset of the stimulus. The mean of a 200-ms pre-stimulus period served as a baseline for each segment. Segments with a voltage difference of more than 200 μ V within a 200-ms time period were removed. The segments were averaged separately for the standard and deviant stimuli.

Data were excluded from further analysis if fewer than half of the trials were available for averaging. The mean number of accepted trials over all groups and conditions varied from 75.9 (SD = 8.3) to 77.8 (SD = 2.4) per condition. There were no significant differences in the number of accepted trials between the groups or between the measurement timepoints, $p > .148$.

Based on visual inspection of the data and previous findings for the P1 and N170 (e.g. Astikainen et al., 2013; Batty & Taylor, 2003), electrodes at the left and right occipital sites for P1 and at left and right parieto-occipital sites for N170 were selected (see Supplementary Figure S1). Two electrode clusters (left and right) were created for the analyses of P1 and N170 in order to examine the responses separately for both hemispheres. The most positive peak within 80-150 ms after the onset of the stimulus for P1 and the most negative peak within 130-210 ms after the onset of the stimulus for N170 were detected separately for each

channel. The peak values were averaged over an electrode cluster separately for the left and right site.

2.6 Statistical analysis

The statistical analysis was conducted with the IBM SPSS Statistics 24.0 program (Armonk, Ny: IBM corporated). Repeated measures of MANOVA were applied at the baseline measurement to assess differences within the stimulus type (happy vs. sad vs. neutral), hemisphere (left vs. right) and component (P1 vs. N170) between the control and depressed groups. As described above (see Stimuli), there were two experimental conditions, which included different deviant stimuli (sad or happy) among standard neutral stimuli, and the neutral stimuli was always the same for both conditions. For the baseline comparison, an average of the responses to neutral faces derived from the two conditions (sad and happy collapsed) were calculated, to reduce the levels in the repeated measures of MANOVA analysis. At the baseline the amplitude values for each stimulus types (sad vs. happy vs. neutral) were applied to inspect in which stimulus type the depression-related alterations would arise. Whenever significant interaction effects of group x stimulus type or group x stimulus type x component were found they were followed with a further repeated measures of MANOVA analysis separately for the components and/or the groups. Two-tailed independent-samples t-tests were applied whenever a stimulus type difference was found between the groups and paired-samples t-tests whenever a stimulus type difference was found within the groups.

The sad negative bias found in the depressed group at the baseline measurement was analyzed in the follow-up timepoint comparisons with separate repeated measures of MANOVAs for the 2- and 3-timepoint comparisons. The 2-timepoint comparison included the available data from participants who participated to both baseline and 2-m measurements

($n = 25$) and the 3-timepoint comparison included the data from those who participated to baseline, 2-m and 39-m measurements ($n = 17$). Because some of the participants dropped out before the 39-m measurement, the samples are only partly overlapping. The negative bias was operationalized as a difference between the peak amplitude to the sad faces and that to the neutral faces preceding the sad faces (sad – neutral differential response). In the 2-timepoint repeated measures of MANOVA for the differential response the within-subject variable was timepoint (baseline vs. 2-m). The timepoint variable in repeated measures of MANOVA for the 3-timepoint comparison had three levels (baseline vs. 2-m vs. 39-m). To further investigate the timepoint effects, two-tailed paired sample t-tests were conducted comparing differential responses between the timepoints, whenever repeated measures of MANOVA indicated a main effect of time.

To further investigate group differences in negative bias, a one-way ANOVA comparing the differential responses (sad minus neutral) between the groups (recovered vs. non-recovered vs. control group) was conducted.

The p-values for multiple t-tests were corrected with an FDR-correction (for independent sample t-tests; Benjamini and Hochberg, 1995); for paired samples t-tests: Benjamini and Yekutieli, 2001). For the baseline group comparison, only the significant main effects of group or stimulus type or their interaction effects are reported. For repeated measures of MANOVA, partial eta squared (η^2_p) and for t-tests Cohen's d with pooled standard deviation are reported as effect size estimates.

Two-tailed Pearson's correlation coefficient were used to examine the correlations between the P1 differential responses (indicating negative bias) and BDI-II-scores. In addition, baseline BDI-II-scores were correlated with post-intervention BDI-II-scores and with BDI-II-score change from baseline to post-intervention (baseline BDI-II-scores minus post-

intervention BDI-II-scores), to investigate the effect of number of the initial depression symptoms on treatment response. For the correlation tests, a bootstrap based on 1000 iterations and CI of 95% were applied.

P-values of less than .05 were considered significant.

2.7 Analysis of reliability of the ERPs

The split-half reliability of the ERPs were investigated for the baseline measurement by comparing the P1 amplitudes between the even and odd trials of the neutral faces derived from the Sad condition. There was a large correlation between the even and odd incidences of the P1 responses in the left hemisphere, $r = .923$, $n = 54$, $p < .001$, 95% CI [0.87, 0.96] and in the right hemisphere, $r = .892$, $n = 54$, $p < .001$, 95% [0.79, 0.94]. Paired samples t-tests (FDR corrected) showed no significant differences between the even trials ($M = 4.3$, $SD = 3.0$) and the odd trials ($M = 3.9$, $SD = 2.9$) in the left hemisphere, $t(53) = -2.0$, $p = .144$, or between the even ($M = 4.0$, $SD = 2.7$) and the odd trials ($M = 3.9$, $SD = 2.8$) in the right hemisphere $t(53) = -0.5$, $p = .963$.

3. RESULTS

3.1 Baseline comparison between depressed and control participants

Results for the P1 and N170 amplitudes are reported at the baseline measurement, when all the participants in the depressed group had a recently confirmed depression diagnosis and self-reported symptoms of depression (BDI-II-scores ≥ 14). The peak amplitude values for P1 and N170 are presented in the Figure 3 and the waveforms for P1 and N170 in the Figures 4 and 5, respectively.

Repeated measures of MANOVA investigating peak amplitude values (sad vs. happy vs. neutral) showed a main effect of stimulus type, $F(2,51) = 8.8, p = .001, \eta^2_p = .257$, and stimulus type x component interaction effect, $F(2,51) = 27.8, p < .001, \eta^2_p = 0.522$, and stimulus type x component x group interaction effect, $F(2,51) = 4.2, p = .022, \eta^2_p = 0.139$.

The stimulus type x component x group interaction was followed with separate repeated measures of MANOVAs for each component. The stimulus x group interaction was non-significant for P1, $F(2,51) = 2.2, p = .122, \eta^2_p = .08$, and for N170, $F(2,51) = 0.52, p = .597, \eta^2_p = 0.02$. Follow-up repeated measures of MANOVAs with within-subjects factors stimulus type (sad vs. neutral vs. happy) and component (P1 vs. N170) were conducted separately for the groups. Repeated measures of MANOVA showed a significant stimulus x component interaction within the control group $F(2,25) = 5.7, p = .009, \eta^2_p = .313$, and within the depressed group $F(2,25) = 28.7, p < .001, \eta^2_p = .697$. Therefore, repeated measures of MANOVAs with within-subjects factor of stimulus type (sad vs. neutral vs. happy) were conducted separately for the groups and components.

For the P1, the repeated measures of MANOVA showed a significant stimulus type effect in the depressed group, $F(2,25) = 4.2, p = .026, \eta^2_p = 0.253$, but not in the control group, $F(2,25)$

= 0.01, $p = .987$, $\eta^2_p < 0.01$. The following paired-samples t-tests in the depressed group showed that the sad faces elicited larger P1-responses than the neutral faces (see Table 3). The effects of medication and baseline BDI-II-scores on the responses was investigated within the depressed group, by adding medication status (medicated vs. non-medicated) and the baseline BDI-II-scores to the repeated measures of MANOVA model for the depressed group. The medication x BDI x stimulus type interaction was non-significant, $F(2,22) = 0.02$, $p = .977$, $\eta^2_p = 0.120$. Next, the medication and BDI-II-scores were inspected independently by adding them as covariates to separate repeated measures of MANOVAs. Both the stimulus type x medication interaction, $F(2,24) = 2.6$, $p = .775$, $\eta^2_p = .021$, and the BDI x stimulus type interaction, $F(2,24) = 0.4$, $p = .658$, $\eta^2_p = 0.03$, were non-significant.

The repeated measures of MANOVA for the N170 showed a main effect of stimulus type for the control, $F(2,25) = 6.5$, $p = .005$, $\eta^2_p = 0.342$, and the depressed group, $F(2,25) = 13.5$, $p < .001$, $\eta^2_p = 0.520$. The paired-samples t-tests within both groups showed larger N170 responses for the happy faces compared to the neutral faces. In the depressed group, responses for the happy faces were also larger than those to the sad faces (see Table 3). The covariate analysis with medication and BDI-II-scores showed no significant medication x BDI x stimulus type interaction in the depressed group, $F(2,22) = 0.6$, $p = .569$, $\eta^2_p = 0.05$. There was no significant stimulus type x medication interaction, $F(2,24) = 0.7$, $p = .520$, $\eta^2_p = 0.05$ or BDI x stimulus type interaction, $F(2,24) = .04$, $p = .717$, $\eta^2_p = 0.03$, when covariates were added separately to the model.

Table 3. The mean amplitude values (μV) and standard deviations (SD) of the P1 and N170 responses and the results of the follow-up paired-samples t-tests investigating the significant effects in repeated measures of MANOVA at the baseline.

P1								
Group	Condition	Mean neutral \pm SD	Mean emotional \pm SD	df	t	P	d	95% CI
Dep	Sad	3.9 \pm 2.5	4.4 \pm 2.4	26	2.9	.039*	0.20	0.14, 0.84
	Happy	3.9 \pm 2.5	3.9 \pm 2.4	26	0.4	1.000	0.02	-0.22, 0.34
P1 sad vs. happy deviant								
Group	df	t	P	d	95% CI			
Dep	26	2.5	.052	0.21	0.08, 0.78			
N170								
Group	Condition	Mean neutral \pm SD	Mean emotional \pm SD	df	t	P	d	95% CI
Ctrl	Sad	-1.6 \pm 3.5	-1.7 \pm 3.7	26	0.6	1.000	0.03	-0.39, 0.21
	Happy	-1.6 \pm 3.5	-2.2 \pm 3.4	26	3.6	.006*	0.17	-0.93, -0.26
Dep	Sad	-1.8 \pm 2.1	-2.0 \pm 2.2	26	1.3	.400	0.09	-0.48, 0.11
	Happy	-1.8 \pm 2.1	-2.5 \pm 2.3	26	5.3	.008*	0.32	-1.00, -0.44
N170 sad vs. happy deviant								
Group	df	t	P	d	95% CI			
Ctrl	26	2.3	.091	0.14	-0.94, -0.05			
Dep	26	3.3	.008*	0.22	-0.87, -0.21			

Ctrl = control group; Dep = depressed group; Sad = Sad condition; Happy = Happy condition; SD = standard deviation; df = degrees of freedom; d = Cohen's d; CI = confidence intervals; P = p-value, * significant ($p < .05$).

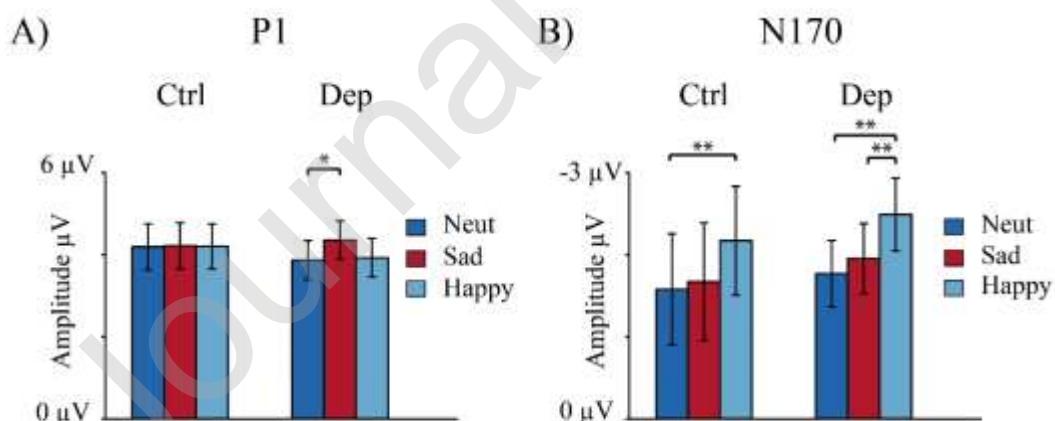


Fig. 3. The peak amplitude values and standard deviations for the neutral standard, sad deviant and happy deviant faces for the control and depressed groups for P1 (A) and N170 (B). Error bars represent standard error.

Ctrl = the control group, Dep = the depressed group; * $p < .05$, ** $p < .01$.

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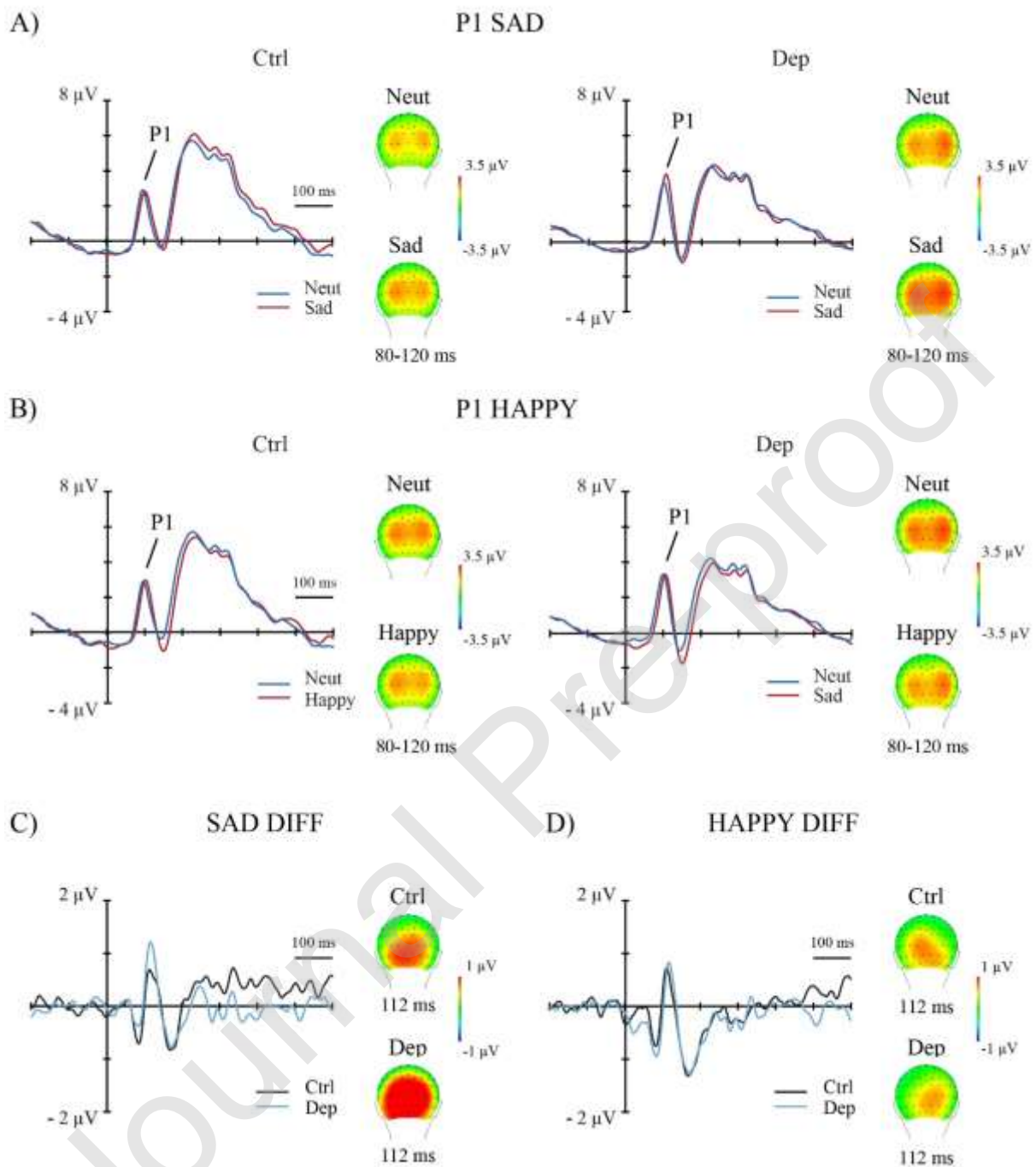


Fig 4. The grand-averaged P1 waveforms averaged for the left and right occipital electrode cluster for the control ($n = 27$) and the depressed ($n = 27$) groups at the baseline measurement. Responses to sad (A) and happy (B) deviant faces and neutral faces and differential responses (emotional minus neutral) (C-D). The topographical maps for A and B show mean amplitude value from 80-120 ms after stimulus onset to the emotional faces and neutral faces preceding the emotional face (neut). The topographical maps for C and D

show the differential response between emotional faces and neutral faces preceding the emotional face (peak value at 112 ms after stimulus onset). Ctrl = control group; Dep = depressed group.

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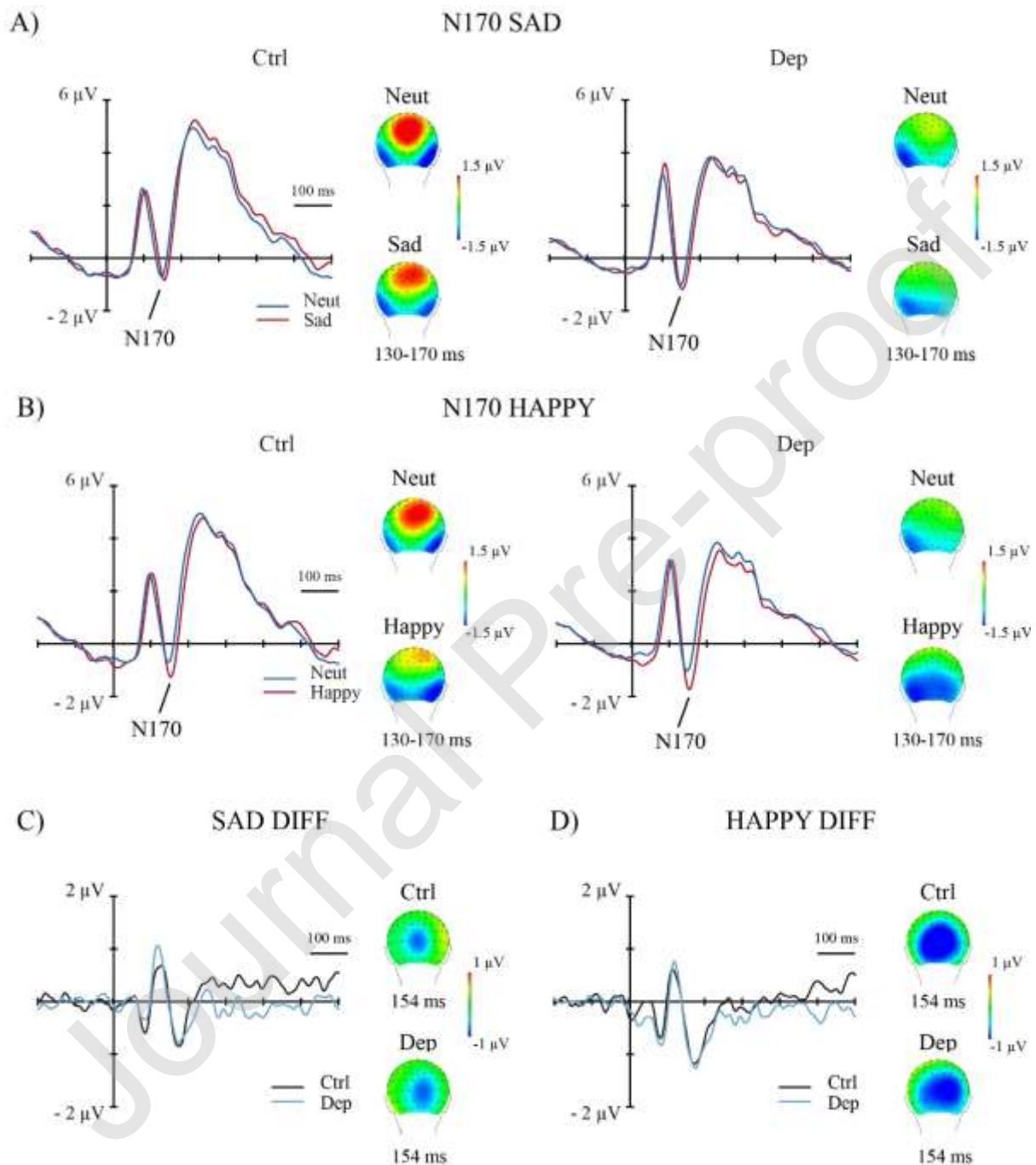


Fig 5. The grand-averaged N170 waveforms averaged for the left and right parieto-occipital electrode cluster for the control ($n = 27$) and the depressed ($n = 27$) groups at the baseline measurement. Responses to sad (A) and happy (B) deviant faces and neutral faces and differential responses (emotional minus neutral) (C-D). The

topographical maps for A and B show mean amplitude value from 130-200 ms after stimulus onset to the emotional faces and neutral faces preceding the emotional face (neut). The topographical maps for C and D show the differential response between emotional faces and neutral faces preceding the emotional face (peak value at 154 ms after stimulus onset). Ctrl = control group; Dep = depressed group.

(Suggested width for the Figure is 2 columns)

There was no significant correlation between the amplitude of the P1 differential responses (sad minus neutral) and the BDI-II-scores within the whole sample, $r = .207$, $n = 51$, $p = .146$, 95% CI [-0.05, 0.45] or within the depressed group, $r = -0.170$, $n = 27$, $p = .396$, 95% CI [-0.56, 0.39].

3.2 The 2-timepoint comparison within the depressed group

In this section, the changes in the P1 differential responses (sad minus neutral) from the baseline measurement to the 2-m measurement in the Sad condition are reported. At the 2-m measurement, 48 % of the participants had completed the intervention. The P1 responses for the Sad condition at the baseline measurement and at the 2-m measurement are presented in the Figure 6.

Repeated measures of MANOVA for the P1 differential response, showed a main effect of time, $F(1,24) = 4.4$, $p = .046$, $\eta^2 = 0.155$. The differential response decreased from the baseline measurement ($M = 0.6 \mu\text{V}$, $SD = 0.9$) to the 2-m measurement ($M = -0.03 \mu\text{V}$, $SD = 1.1$).¹

¹ Repeated measures of MANOVA for the P1 differential response was also computed without the data of the participant with missing BDI-II scores at 2-m. There was a main effect of time, $F(1, 23) = 4.4$, $p = .048$, $\eta^2 = 0.160$. The differential response decreased from the baseline measurement ($M = 0.6 \mu\text{V}$, $SD = 0.9$) to the 2-m measurement ($M = 0.0 \mu\text{V}$, $SD = 1.1$).

To control for the possible effect of between-subjects variability in the time-interval between the baseline and the 2-m measurements (mean = 55 d, SD = 11.3, range 33-91 d), a repeated measures of MANOVA was conducted for the differential responses with time-interval as a covariate. The time x time-interval interaction was non-significant, $F(1,23) = 0.5$, $p = .469$, $\eta^2 = 0.02$. To control for the effect of anxiety, a repeated measures of MANOVA was conducted with DASS-A scores (at the baseline) as a covariate. The time x DASS-A interaction was non-significant, $F(1,23) = 0.3$, $p = .584$, $\eta^2 = 0.01$.

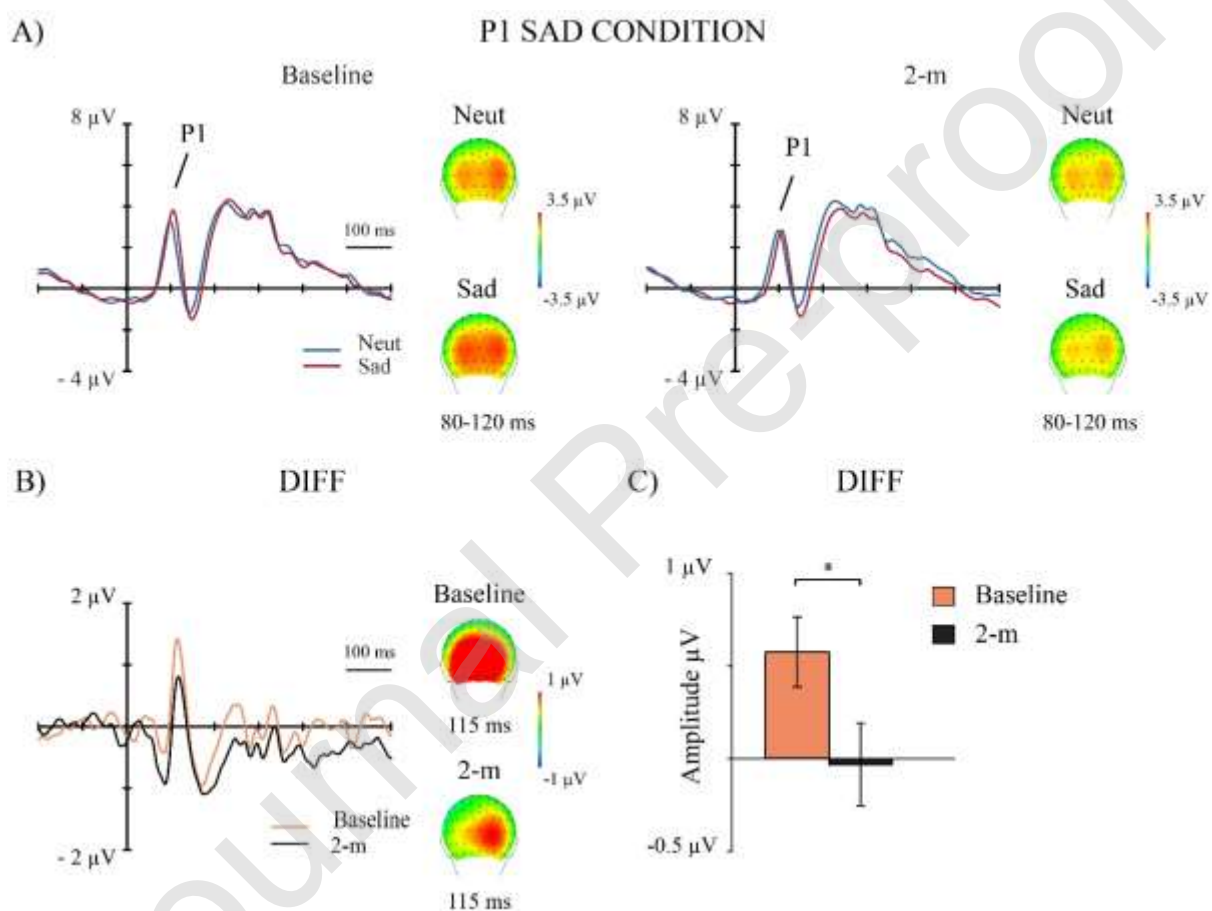


Fig. 6. The grand-averaged P1 responses in the Sad condition for the depressed group (n = 25) at the baseline measurement and at the 2-m measurement. A) The waveforms averaged for the left and right occipital electrode cluster and the topographical maps of the P1 responses (mean amplitude value at 80-120 ms after stimulus onset) to the sad faces and the neutral faces preceding the sad face (neut). B) Differential waveforms (Diff; sad minus neutral) and the topography of the differential responses (peak value at 115 ms after stimulus onset) at the

baseline measurement and at the 2-m measurement. C) The amplitude values for the differential responses for the baseline and the 2-m measurements. Error bars represent standard error. * $p < .05$.

(Suggested width for the Figure is 2 columns)

3.3 The 3-timepoint comparison within the depressed group

In this section, the significant changes in P1 differential responses (sad minus neutral) from the baseline measurement to the 2-m measurement and the 39-m measurement in the Sad condition are reported (Fig. 7).

In repeated measures of MANOVA a significant effect of timepoint was found for the differential response, $F(2,15) = 5.2, p = .019, \eta^2_p = 0.411$. The paired-samples t-test showed a significant decrease in the P1 differential response from the baseline measurement ($M = 0.6 \mu\text{V}, SD = 1.0$) to the 39-m measurement ($M = -0.2 \mu\text{V}, SD = 0.8$), $t(16) = 3.4, p = .022, 95\% \text{ CI } [0.27, 1.21]$, Cohen's $d = 0.82$. No change in the P1 differential response was found between the baseline and 2-m measurement ($M = 0.02 \mu\text{V}, SD = 0.9$), $t(16) = 1.5, p = .457, 95\% \text{ CI } [-0.25, 1.35]$, Cohen's $d = 0.61$ or between the 2-m and 39-m measurement, $t(16) = 0.5, p = 1.000, 95\% \text{ CI } [-0.57, 0.95]$, Cohen's $d = 0.26$. To control for the effect of anxiety, a repeated measures of MANOVA for the differential responses was conducted with DASS-A scores (at the baseline) as a covariate. The time x DASS-A interaction was non-significant, $F(2,14) = 0.03, p = .968, \eta^2 < 0.001$.

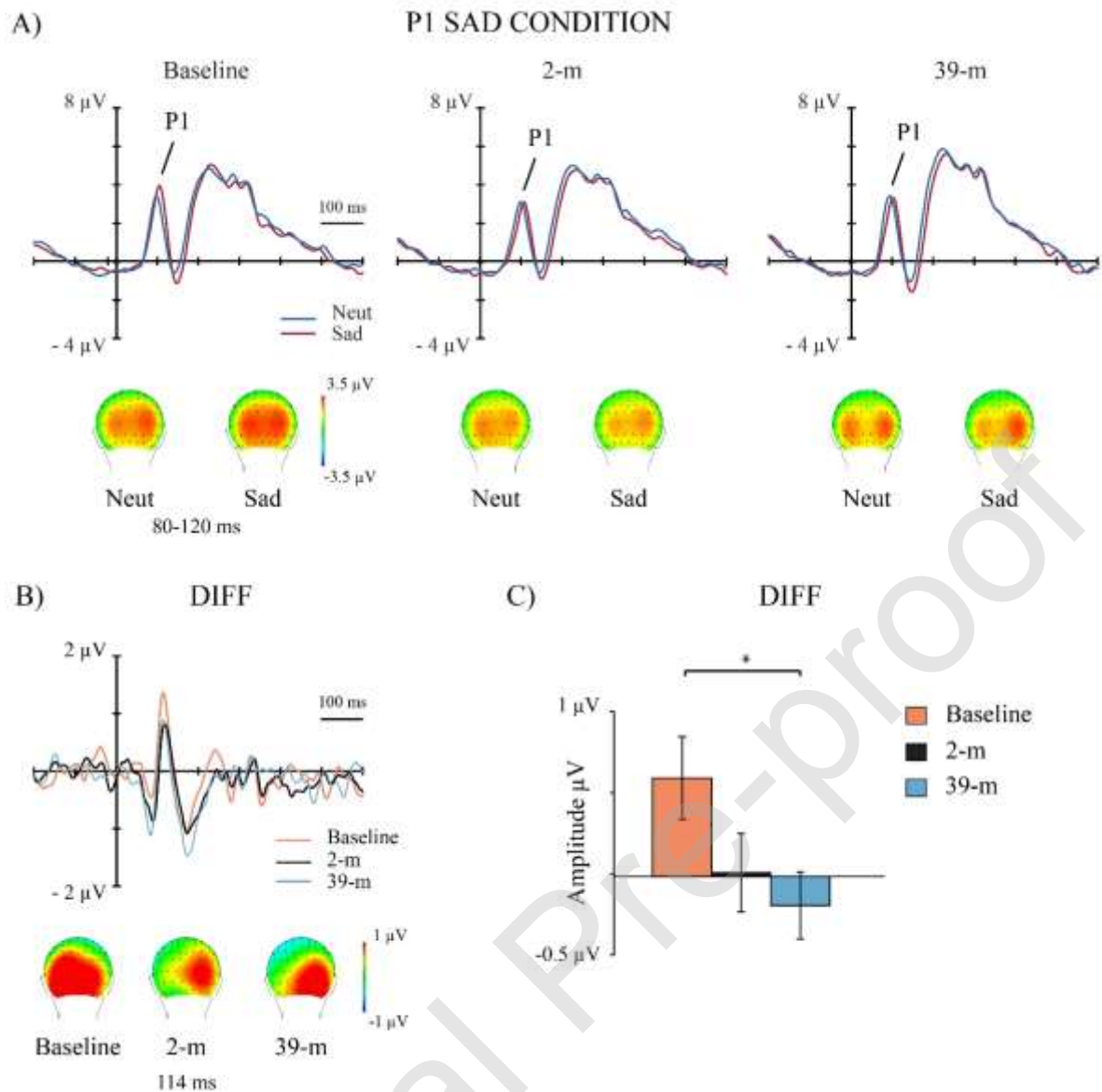


Fig. 7. The grand-averaged P1 responses in the Sad condition for the depressed group ($n = 17$) at the baseline, 2-m and 39-m measurements. A) The waveforms averaged over the left and right occipital electrode cluster and the topographical maps of the P1 responses (mean amplitude value at 80-120 ms after stimulus onset) to neutral (neut) and sad faces at the baseline, 2-m and 39-m. B) The P1 differential waveforms (Diff; sad minus neutral) and the topographies of the differential responses (peak value at 114 ms after stimulus onset) in the depressed group at the baseline, 2-m and 39-m measurements. C) The amplitude values for the differential responses for the baseline, 2-m and 39-m measurements. Error bars represent standard error. * $p < .05$.

(Suggested width for the Figure is 2 columns)

3.4 Treatment response

In this section, the significant group differences in P1 differential responses (sad minus neutral) at the baseline measurement between the recovered, non-recovered and control groups are reported. A one-way ANOVA was performed to compare the groups in P1 differential responses.

The ANOVA showed significant group differences, $F(2,48) = 4.0$, $p = .024$, $\eta^2_p = .144$. The post hoc independent sample t-tests between the groups showed a larger differential response in the non-recovered group ($M = 1.1 \mu\text{V}$, $SD = 1.0$) compared to the control group ($M = 0.2 \mu\text{V}$, $SD = 0.8$), $t(33) = 2.9$, $p = .021$, 95% CI [0.28, 1.61], Cohen's $d = 1.10$, but no significant difference in responses was found between the recovered ($M = 0.5 \mu\text{V}$, $SD = 0.9$) and non-recovered group, $t(22) = -1.5$, $p = .203$, 95% CI [-1.44, 0.21], Cohen's $d = 0.67$, or between the recovered and control group, $t(41) = 1.3$, $p = .203$, 95% CI [-0.19, 0.85], Cohen's $d = 0.37$. The averaged P1 differential responses for the three groups are presented in the Figure 9.

To control for potential effects of medication and baseline BDI-II-scores on the differential responses, medication status and BDI-II-scores were added as covariates to the ANOVA model. There was no significant medication x BDI x group interaction, $F(2,41) = 1.0$, $p = .790$, $\eta^2_p = 0.01$. When the effect of medication and BDI-II-scores were studied in separate ANOVA models, there was no significant BDI x group interaction, $F(2,42) = 3.0$, $p = .062$, $\eta^2_p = 0.12$, or medication x group interaction, $F(1,46) = 0.2$, $p = .648$, $\eta^2_p < 0.01$.

The effect of the baseline BDI-II-scores on treatment response was further investigated with Pearson correlation. There was no significant correlation between the baseline BDI-II-scores and the post-intervention BDI-II-scores (2-m measurement for the treatment group and 4-m measurement for the wait-list control group), $r = .245$, $n = 24$, $p = .249$, 95% CI [-0.35, 0.62].

There was a positive correlation between the baseline BDI-II-scores and the baseline minus post-intervention BDI-II difference, $r = .769$, $n = 24$, $p = .001$, 95% CI [0.57, 0.89], indicating that those with larger baseline BDI-II-scores had larger change in the BDI-II-scores from baseline to post-intervention.

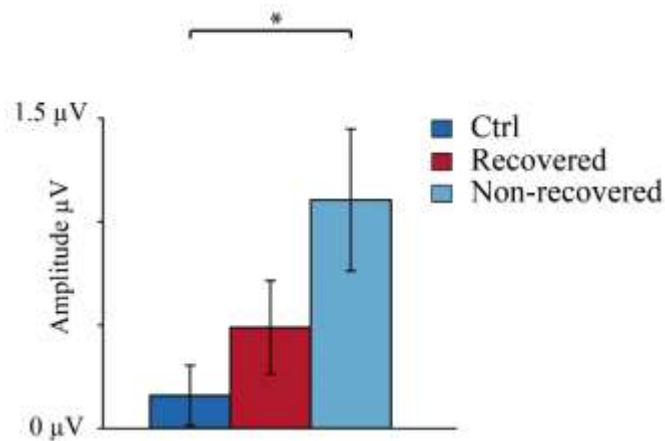


Fig. 8. The amplitude values of the differential responses (sad minus neutral) for each group at the baseline measurement. Error bars represent standard error. * $p < .05$, Ctrl = control group, Recovered = recovered group, Non-recovered = non-recovered group.

(Suggested width for the Figure is 1 column)

There were no significant correlations between the P1 differential response (at the baseline) and the BDI-II-scores at the post-intervention, $r = .327$, $n = 24$, $p = .119$, 95% CI [-0.03, 0.64] or between P1 differential response and the change in the BDI-II-score from the baseline measurement to the post-intervention measurement, $r = -0.124$, $n = 24$, $p = .563$, 95% CI [-0.56, 0.29].

4. DISCUSSION

The purpose of the present study was to investigate whether there is negative bias in task-irrelevant processing of facial expressions in depression and whether the bias remains if depression symptoms subside. In addition, it was investigated whether the brain responses recorded at the baseline when all the participants were currently depressed are associated with recovery after a brief psychological intervention. Consistent with our hypothesis, we found a negative bias in depressed participants in the P1 responses to sad faces. The bias normalized when the depression symptoms alleviated, suggesting that the bias is state-related rather than a permanent trait. The brain responses recorded at the baseline did not differ between those depressed participants who recovered and those who did not recover after the brief psychological intervention.

Negative bias was demonstrated as increased P1 amplitudes to rare sad faces compared to frequent neutral faces in the depressed group, whereas in the control group no differences between the responses to the different facial emotions were found. P1 has been suggested to reflect early global processing of faces (Itier & Taylor, 2002, 2004; Taylor, 2002). In accordance with absent modulation of the P1 to emotional faces in the control group, previous studies conducted in healthy participants have not found differences between P1 amplitude for neutral and emotional faces when an ignore oddball condition was applied (fearful and happy deviant faces and neutral standard faces: Astikainen & Hietanen, 2009) or have reported it to fearful deviant face, but not for happy faces (fearful and happy faces as standard and deviant stimuli: Stefanics, Csukly, Komlósi, Czobor, & Czigler, 2012). Also in line with our finding, in an attended task, where the participant was asked to evaluate the expressions, depression-related negative bias was found in the P1 response to sad faces, while no such difference was found in the control group (Dai & Feng, 2012). However, in one

study, subliminally presented attended sad faces elicited a larger P1 response compared to neutral faces in the depressed group, while controls had a smaller P1 for sad faces compared to neutral faces (Zhang et al., 2016).

We did not find depression-related negative bias in N170, similarly to Jaworska et al. (2012) who applied sad, neutral, joyful and surprised faces with varying emotional intensities and with a task to detect the surprised faces. However, in a few previous studies negative bias has been found in N170 amplitudes to sad faces in depressed participants (Wu et al., 2016) or in early vMMN which occurred in the latency of the N170 (Chang et al., 2010). Chang et al. (2010) found decreased vMMN amplitudes to happy and sad faces in the depressed compared to the control group in the N170 latency range. However, the stimuli in Chang et al.'s (2010) study were schematic faces, and it is possible that more naturalistic faces, as applied in the present study, enables elicitation of a normal N170 in depressed participants. In addition, by using the oddball condition, Wu et al. (2016) found a larger N170 in response to sad faces in the depressed group compared to the control group. In contrast to our study, their results reflected attentive processing. The N170 response has also been studied in stimulus conditions other than the oddball paradigm with a task to discriminate emotional faces from non-emotional faces (Zhang et al., 2016) or to attend to the emotion of the face cue and then respond to a number target presented after the face cue (Zhao et al., 2015). These studies showed negative bias as reflected by increased N170 amplitude to sad faces compared to neutral faces in the depressed group (Zhang et al., 2016; Zhao et al., 2015) or decreased amplitude for happy faces in the depressed group relative to the control group (Zhao et al., 2015). The discrepancy between the previous results and the results of the present study can thus be possibly explained by differences in the experimental tasks (attend vs. ignore condition). Although in Zhang et al.'s (2016) study the faces were presented subliminally, the task was to identify the emotion. Thus, it is possible that the depression-related negative bias

in N170 is more evident with task-relevant stimuli but may not arise when the stimuli are task-irrelevant.

Although we did not find depression-related negative bias in the N170 response, we found in both groups an emotional modulation of it, which was demonstrated as larger amplitudes to rare happy faces compared to frequent neutral faces. In the depression group the responses were also larger for happy compared to the sad faces. The finding of no negative bias in the depression group is similar to a previous study that also found no depression-related negative bias in N170, but a larger response to joyful compared to sad and neutral faces (Jaworska et al., 2012). Also in a MEG study in which task-irrelevant changes in emotional faces were presented in the oddball condition no negative bias in M170 was found for the dysphoric group (Xu et al., 2018). However, in that study a larger M170 response was found at the whole sample level for rare sad than to rare happy faces. The stimulus condition in Xu et al. (2018) was different to that of the present study, since it applied only emotional faces (both sad and happy faces as deviant and standard). Our finding of a larger N170 amplitude to happy than neutral faces is also in line with the previous oddball studies conducted in healthy participants (Astikainen et al., 2013; Astikainen & Hietanen, 2009; Stefanics et al., 2012; Stefanics, Heinzle, Horváth, & Stephan, 2018; Zhao & Li, 2006) and also with the studies using stimulus conditions other than the oddball condition (Batty & Taylor, 2003; Japee, Crocker, Carver, Pessoa, & Ungerleider, 2009; Miyoshi, Katayama, & Morotomi, 2004; Wronka & Walentowska, 2011).

The second aim of the present study was to investigate the dependence of negative bias on the state of the depression. To study this, we investigated the changes in negative bias (reflected by P1 differential response, i.e. sad-neutral) from the baseline measurement to the 2-m measurement and the 39-m measurement in the depressed group. At the 2-m measurement,

approximately half of the depressed participants had received a brief psychological intervention, and the depression symptoms had been significantly reduced at the whole group level (BDI-II mean at the baseline measurement 22.8 ± 7.4 , mean at the 2-m measurement 14.0 ± 9.1). A decrease in the P1 differential responses to sad faces was found at the 2-m measurement. In addition, the differential responses decreased from the baseline measurement to the 39-m measurement, when all the depressed participants had received the intervention and the BDI-II scores were low (mean at the 39-m measurement 9.6 ± 7.6). The results resemble previous fMRI findings that showed normalized facial expression processing after cognitive behavioral therapy (Fu et al., 2008) or after antidepressant treatment (Victor et al., 2010). The present results indicate that as depression symptoms decrease, negative bias normalizes.

The third aim was to examine whether the negative bias in face processing in depression can distinguish between the depressed group who recovers and the group who shows no recovery after a brief psychological intervention. Finding predictors of treatment response is important, because the remission rate after antidepressant treatment or psychotherapy treatment is usually less than 50 % (Thase et al., 2001, for reviews, see Cuijpers et al., 2014; De Maat, Dekker, Schoevers, & De Jonghe, 2006). If reliable predictors for treatment responses could be found, better treatment options could be selected individually in the future. Several fMRI studies (Fu et al., 2008; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Siegle, Carter, & Thase, 2006) have found potential brain correlates for treatment response to psychotherapy, but ERP studies are rare (see, however, Stange et al., 2017, who reported that the late positive potential to aversive pictures predicts the response to cognitive behavioral therapy). Studies on ERPs are warranted, because compared to fMRI measures, EEG is cost-efficient and widely available in public health care and therefore has more potential for clinical use.

The brain responses recorded at the baseline did not differ between the depression group who recovered and the group that did not recover after the intervention. It is possible that this null finding may be related to small sample size. Group difference was only found when comparing the non-recovered group to non-depressed controls. We found larger negative bias at the baseline, as reflected by the P1 differential response (sad minus neutral), in the group who did not recover after intervention compared to the control group, while the recovered group did not show larger negative bias than the control group. To best of our knowledge, this is the first ERP study to investigate facial expression processing in association with treatment response for psychological intervention.

Our finding that only the non-recovered group differed from controls in negative bias may not be explained by the initial number of depression symptoms, although some previous studies have found that greater number of depression symptoms can predict poorer treatment response for CBT (Elkin et al., 1989; Thase, Simons, Cahalane, McGeary & Harden, 1991, however, more recent meta-analyses found no effect of baseline depression symptoms on treatment outcomes to CBT: Furukawa et al., 2017; Weitz et al., 2015). Namely, the recovered and non-recovered groups did not differ in number of symptoms at the baseline and there was no significant interaction effects between the number of the baseline depression symptoms and the P1 responses. Correlation analysis revealed that participants with greater baseline depression symptoms showed actually better treatment response (change in BDI-II scores) as indicated by change in depression symptoms. This direction of the correlation is in discrepancy with the previous findings of poorer CBT treatment response in those with greater baseline symptoms (Elkin et al., 1989; Thase et al., 1991).

It is unlikely that the larger negative bias in the non-recovered group relative to controls is explained by this group having lower number of participant with antidepressants, because

there was no significant difference between the recovered and non-recovered groups in the number of medicated and non-medicated participants. Furthermore, no interaction effects of medication were found in the group comparison analyses. It can be speculated that negative bias can undermine the therapist–patient interaction, which is one factor that can affect the outcome of therapy (for reviews see, Horvath & Symonds, 1991; Martin, Garske, & Davis, 2000). Problems in social interaction are common in depression and can increase risk for depression (Chou, Liang, & Sareen, 2011; Teo, Choi, & Valenstein, 2013, for a review see Kupferberg, Bicks, & Hasler, 2016).

It remains an open question whether negative bias can cause depression or whether negative bias is a symptom of depression. If negative bias can maintain depression as Beck's (1967, 1976) model suggests, then modification of the bias may affect depression symptoms. It can be speculated that those patients with greater negative bias could benefit from treatments that specifically target perceptual and attentive negative bias. Several studies showed a reduction in depression symptoms after attentional training where participants are taught to direct attention toward positive emotional stimuli and away from negative stimuli (see e.g. Wells & Beevers, 2010; Yang et al., 2015, for reviews, see Gold et al., 2016; Hallion & Ruscio, 2011).

The small sample size, especially in the comparison including all the three timepoints and in the comparison of the recovered and non-recovered groups, as well as the uneven gender distribution with the significant majority of the participants being female, must be taken into account when generalizing the results of the study. In contrast, a definite strength of this study was the longitudinal study design that was utilized to investigate the changes in facial expression processing over time in the depressed group. However, the limitation is that the control group was assessed only once.

Another limitation of the study is that we cannot disentangle the effects of rareness and emotional modulation in the face processing. This is because we applied the oddball paradigm where emotional faces were always presented as infrequent deviant stimuli. Therefore, it is possible that the enhanced responses to the stimuli can also reflect deviance detection as indexed by the vMMN (Astikainen et al., 2013; Astikainen & Hietanen, 2009; Stefanics et al., 2012; Stefanics et al., 2018; Zhao & Li, 2006) instead of (or in addition to) emotional modulation of the canonical ERP components (Batty & Taylor, 2003; Japee et al., 2009; Miyoshi et al., 2004; Wronka & Walentowska, 2011). However, the main focus in this study was finding ERP markers related to the illness course and treatment outcome.

In sum, the present results indicate negative bias in early automatic processing of sad faces in depression. This finding adds to the literature that has shown attentional bias towards sad emotions in depression. The results also indicate that early negative bias is state-dependent; in other words, the bias is reduced when the depression symptoms decrease. The results show that alleviation of negative bias in face processing can be detected very rapidly after depression symptoms subside. However, since the brain responses recorded at the baseline did not differ between the recovered and non-recovered depression groups, there is no indication that negative bias in P1 could serve as a biomarker for treatment response.

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All the authors had full independence from the funders. The authors report no conflicts of interest

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