Manipulating serotonin function in depression

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Residual cognitive impairments in remitted depressed patients

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Abstract

Depressive disorders are associated with various cognitive impairments. Studies on whether or not these impairments persist into the euthymic phase have shown conflicting results, due to differences in test versions and in study samples. In the current paper we aimed to compare the cognitive performance of remitted depressed patients with that of age- and gender matched healthy volunteers across a wide range of cognitive domains. In two studies we found few differences on neutral as well as emotional information processing tests. The findings indicate that remitted depressed patients who use antidepressant medication still show an increased recognition of facial expression of fear compared to healthy controls. Patients also performed worse on a test of recognition of abstract visual information from long-term memory. No other residual cognitive impairments were found. These results indicate that most of the cognitive impairments associated with depression resolve with recovery through medication, even when recovery is incomplete. Considering the finding that remitted depressed patients have higher levels of cognitive reactivity future studies may investigate the possibility that these cognitive impairments have not resolved but have become latent, and may therefore easily be triggered by small changes in mood state.

Introduction

Problems concentrating and making decisions are part of the diagnostic criteria of major depressive disorder (American Psychiatric Association, 1994). Experimental research has shown that memory, learning, attention, motor function and problem solving may also be affected in depressed patients (Austin et al., 2001; Elliott, 1998; Weiland-Fiedler et al., 2004). The cognitive functions that are most impaired in depression are those which require effortful executive functioning, which is highly dependent on the prefrontal cortex (Elliott, 1998). Some studies have focused on impairments in emotional (as opposed to neutral) information processing in depressed patients. For example, the recognition of facial expressions of emotions has been found to be affected in depressed patients (Bouhuys et al., 1999; Gur et al., 1992). Also an increased attentional bias for negative information (Williams et al., 1996) and an increased level of dysfunctional attitudes (Ingram et al., 1998) are found compared to healthy controls.

Given the high risk of relapse in depression, it is important to investigate whether cognitive impairments persist into the euthymic phase and if so, whether these impairments may be predictive of depressive relapse. Research on cognitive impairments in recovered depressed patients has shown conflicting results. These conflicting results may be a function of differences in study sample, such as gender distribution, age, education level, residual depressive symptoms, medication status, and diagnosis. Marcos et al. found differences on tests measuring paired learning, immediate and delayed visual memory, delayed logical memory and block design between euthymic patients and healthy controls (Marcos et al., 1994). Part of the patient sample was medicated with imipramine, part of the sample was unmedicated at the time of study. The two groups consisted of both men and women and were equal in

age (mean ages 54 and 52 years) and education level. In another study, differences between depressed and non-depressed subjects on different memory tests (verbal memory, immediate and delayed recall, learning, retrieval) disappeared following imipramine treatment, but only in treatment responders. Improvement in depressive symptoms led to significant improvement in memory performance (Peselow et al., 1991). Again both groups were equal in age (mean 48-50 years), gender distribution (both men and women were tested) and level of intelligence. Paradiso et al. (1997) compared cognitive performance of patients with a –relatively chronic- history of unipolar and bipolar depressive disorder to that of age- (mean age 50-57 years) and education matched controls. Only male subjects were included and almost all patients were taking some form of psychotropic medication (benzodiazepines, tricyclics, trazodone). They found that euthymic unipolar patients performed worse on tasks measuring executive function (Trail Making B, Stroop CWT), visual-motor sequencing (Trail Making A), immediate memory (word-list memory test) and attention (digit symbols) compared to healthy controls. In another study, unmedicated male and female remitted depressed patients were impaired on tasks of rapid visual information processing (sustained attention), psychomotor speed and spatial working memory compared to healthy controls (Weiland-Fiedler et al., 2004). However, after correcting for residual depressive symptoms, only the difference in sustained attention remained significant. In this study mean ages were 36 and 38 years and all patients had been taking antidepressant medication in the past. These results were supported by another study that found medicated and unmedicated euthymic patients to be impaired in attentional and executive function (Paelecke-Habermann et al., 2005).

Regarding emotional information processing, persisting impairments have been found in the specificity of autobiographical memory (Spinhoven et

al., 2006), the recognition of facial emotions (Bouhuys et al., 1999) and attentional bias (Williams et al., 1996). Some of these impairments are also related to risk of relapse (Bouhuys et al., 1999; Williams et al., 1996).

Overall, depressed patients show cognitive impairments across a wide range of domains. Some of these impairments improve with clinical recovery, while others may persist into the euthymic phase. Some cognitive impairments may even be related to depressive relapse. However, following the results of Weiland-Fiedler et al. (2004), it remains questionable whether remitted depressed patients show any cognitive impairments in comparison to an adequately matched control group and, most importantly, when residual depressive symptoms are taken into account. The current study investigated cognitive performance in medicated, remitted depressed patients, who are expected to show relatively high levels of residual depressive symptoms, and two matched control groups. To cover a wide range of tests, two separate studies were undertaken. The two studies differed in the type of information processing that was assessed. Study 1 included mainly tests of emotional information processing; study 2 included tests that assessed neutral information processing. To check for possible differences between the study samples, both studies included a fluency test and a measure of attentional bias. No precise hypotheses were formed since the literature does not provide unequivocal results.

Materials and Methods

Study 1:

Participants:

Patients: As part of a larger study, two samples of remitted depressed patients were recruited from a Mood Disorders Program. Participants were male and female outpatients (of the Mood Disorders Program of Parnassia Psycho-medical Center, The Hague). Patients were at different stages in treatment, but were referred to the study only when their therapist thought they would meet criteria for remitted or recovered depression. Age limits were 18 to 65 years. Participants had to fulfill the following inclusion criteria: primary intake diagnosis of DSM-IV major depressive disorder; no longer fulfilling DSM-IV criteria for depression and Hamilton-17 scores lower than or equal to 15 (Frank et al., 1991); ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or selective serotonin and noradrenalin reuptake inhibitor (SSNRI) for at least four weeks; no history or current psychotic disorder; no substance abuse in the past 3 months, based on DSM-IV criteria; BMI equal or higher than 18; free of neuro-endocrine or neurological disease; no pregnancy or lactation (females). [1]

Controls: Healthy control participants were recruited through advertisements in local newspapers. Participants were matched to the patient group on age and gender. Inclusion criteria were: no mood disorders (lifetime); no first degree relatives with a mood disorder (lifetime); no history or current psychotic disorder; no substance abuse in the past 3 months, based on DSM-IV criteria; no use of psychotropic medication, free of neuro-endocrine or neurological disease.

[1] The patients in Study 1 are the same sample as in Merens et al. (Journal of Psychopharmacoly, in press); those in Study 2 are the same as in Booij et al. (2005), Journal of Psychopharmacoly 19, 267-275. The present data are slightly different, because in these two reports, baseline data were calculated on the basis of the screening session and a post-intervention session.

Materials

Self-report: The Beck Depression Inventory (Beck et al., 1996) is a self-rating scale that assesses the presence and severity of depressive symptoms. The Dutch version was used (BDI-II-NL, Van der Does, 2002b). The Dysfunctional Attitudes Scale (DAS, Weissman, 1979) assesses the level of dysfunctional attitudes. A 22 item version was used, based on the original form A. The Leiden Index of Depression Sensitivity (LEIDS) (Van der Does, 2002a) consists of 34 items and assesses the effects of dysphoric mood on cognitions ('cognitive reactivity').

Depression severity: The Hamilton Depression Rating Scale (HAM-D-17) was administered to patients to assess the severity of depressive symptoms (Hamilton, 1967).

Cognition: The cognitive test-battery took about 50 minutes to complete.

Word Learning Test (Saan & Deelman, 1986): A list of 15 unrelated, neutral words was presented on a tape. Immediate recall was tested after each of five consecutive presentations. After the fifth trial, subjects continued with a non-verbal task. Fifteen minutes later delayed recall was tested. Immediate recall performance was defined as the total of correct words remembered over the five trials. Delayed recall performance was defined as the number of correct words produced at delayed recall.

Verbal fluency: This task is a measure of strategy-driven retrieval from semantic memory within a fixed time span (Schmitt et al., 2000). Participants were instructed to produce as many correct four letter words as possible with the same initial letter within one minute. The starting letters were H, M, R or L; these were randomized over the participants. The total number of correct reported words was registered.

Implicit Association Test: The IAT is a sorting task that assesses implicit associations on the basis of reaction times (Egloff & Schmukle, 2002; Greenwald et al., 1998). This test is extensively used in social psychological research to assess stereotypes (Greenwald & Banaji, 1995). Participants are asked to sort stimuli representing four categories by pressing the appropriate key (each response key was assigned to two categories). If two categories are strongly related, the sorting task will be easier (i.e. faster RTs) when the categories share the same response key than when they share different response keys. We used an emotional and a neutral version of this task. Only median latencies for correct responses were included in the analyses. Reaction times to congruent (e.g. self and positive stimuli, insect and negative stimuli) and incongruent stimuli (e.g. self and negative stimuli, flowers and negative stimuli) were calculated.

Dot-probe test: This task measures attentional bias to emotional stimuli (MacLeod et al., 1986). Word pairs (threat words with neutral words and depression related words with positive words) were presented on a computer screen for 500 ms, one in the upper part of the screen and one below. Following the termination of that display, a dot appeared on the location of either word. Participants had to indicate the location of the dot by pressing a key. All word pairs were preceded by a white fixation cross for 500 ms. To control for possible outliers, only median latencies for correct responses were included in the analyses. Attentional bias was calculated by subtracting the RT for positive (neutral) words from the RT for depressive (threatening) words.

Facial Expression Recognition test: The facial expression recognition task, adapted from Harmer et al. (2003c), features examples of five basic emotions—happiness, sadness, fear, anger, and disgust (Ekman & Friesen, 1976). Emotional expression intensity was averaged between neutral (0%) and

emotional standard (100%) in 10% steps, providing a range of emotional intensities. Each emotion-intensity was presented by two examples (one male and one female face) in random order. Each face was presented on a computer screen for 500 ms. and immediately replaced by a blank screen. Participants made their response by pressing a labeled key, after which the next face appeared on the screen. They were instructed to respond as quickly and accurately as possible. Accuracy of recognition was calculated over the different intensity levels in five (20%) blocks. Reaction times for correct responses were calculated.

Procedure

Patients: After showing interest in taking part, all volunteers were given oral and written information about the study. Informed consent was obtained and participants who seemed to meet criteria were invited for the first session. During this session, the SCID-IV interview was administered to ensure patients no longer fulfilled criteria for MDD (First et al., 1995). Participants filled out all questionnaires and afterwards the cognitive tests were done. The session lasted two to three hours. Clinical background information was checked in medical records. The study was approved by an independent medical ethics committee (METIGG, Utrecht).

Controls: The healthy control subjects came in for one session in which the SCID-IV interview was administered to check the absence of mood disorders and other exclusion criteria. All questionnaires were filled out and the cognitive tests were performed during the same session, which lasted two to three hours.

Study 2:

In- and exclusion criteria, methods and procedures were identical to study 1. However, the DAS was not filled out and the LEIDS was only completed by patients and therefore not reported here.

Cognition: The cognitive tests took approximately 60 min.

Verbal Fluency: This test was identical to the fluency test in study 1.

Stroop Colour Word test: This test measures focused attention and response inhibition. Names of colours (red, yellow, blue and green) printed in black were presented one by one for a maximum of 1500 ms on a computer screen. Participants were instructed to read these words as fast as possible (Condition I). Next, coloured patches were presented (Condition II). Finally, the names of colours printed in an incongruent colour were presented and participants were instructed to name the colour of the ink (Condition III). Median reaction times (RTs) were recorded. Interference was defined as the extra time needed for condition III relative to the average of conditions I and II.

Emotional Stroop test: This test was used to assess attentional bias for emotional material. The stimuli were positive, neutral or depression-related words. Words printed in colour were presented consecutively on a computer screen. Participants were asked to name the colours as quickly as possible. The order of the word categories was randomized over the patients. The order of the words within each category was randomized.

Left/Right Choice RT: This test assesses motor speed and response inhibition as a function of task difficulty. The word 'left' or 'right' was presented in randomized order (1000 ms) either at the left or the right side of the screen. Participants were instructed to respond to the meaning of the word

but to ignore its location, as fast as possible. Correct responses and RTs were registered.

Tower of London (TOL): The TOL (Owen et al., 1995a) is a planning task consisting of three coloured balls (red, yellow and blue) placed on three sticks in various arrangements. Two arrangements were presented on the upper and lower half of the screen. The patient was instructed to indicate the minimal number of moves necessary to change the first arrangement into the second (two to five moves). Correct responses and RTs were registered.

Abstract Patterns Recognition task (APRT): The APRT (Rubinsztein et al., 2001) measures (speed of) recognition of non-verbal abstract information from short- and long-term memory. Sixteen abstract patterns were presented consecutively for 3000 ms, with 500 ms intervals. Participants were instructed to memorize the patterns. After three presentations of the complete series, two patterns were presented simultaneously; one that had been learned and a new pattern. Participants had to indicate as fast as possible which one had been previously presented. The recognition procedure was repeated after 35 min, during which verbal tasks were administered. Sensitivity measures (A') were calculated for the proportion of correctly recognized patterns, corrected for response tendency by the formula: A' = 1 – ¼ [fr/ cr + (1-cr) / (1– fr)], in which fr = the proportion of falsely recognized patterns and cr = proportion of correctly recognized patterns, following signal detection theory (Pollack & Norman, 1964).

Statistical analysis

Data were first screened for missing values, outliers, normal distributions and homogeneity of variance. Differences between patients and controls were analyzed with GLM ANOVA with Group as a fixed factor and BDI-II total

score as a covariate. Since matching for Level of education was unsuccessful in study 1, this variable was also entered as a covariate in the analyses of the cognitive measures from study 1. Data from the Facial Emotion Recognition task were analyzed with GLM repeated measures analysis with Emotion (happiness, sadness, fear, anger, and disgust) as a within-subjects factor and Group (controls vs. remitted depressed patients) as a between-subjects factor and BDI-II and Level of education as covariates. The TOL was also analyzed using GLM repeated measures with Steps (2, 3, 4, 5) as a within-subjects factor and Group as a between-subjects factor and BDI-II as a covariate. Data are reported as means ± standard deviations. All tests were corrected for multiple testing using Bonferroni corrections.

Results

Study 1:

Data screening

On the Facial Expression Recognition task, reaction time data were missing for one emotion in two control participants, one of whom did not recognize any sad faces correctly, the other did not recognize any angry faces correctly. On the Word Learning Test, data were missing for one control subject for the immediate recall, due to technical problems. One control subject was an outlier on the Word Learning Test as well as the IAT Neutral. Another control was an outlier on the Dot-probe test. Analyses were conducted with and without statistical outliers, however results were similar.

Participants:

Twenty healthy controls and nineteen remitted depressed subjects were included in the study. Participants were well matched on age and gender, however the control group had a higher level of education compared to the patient group ($\chi^2 = 10.6$, $p = .005$). Current comorbid diagnoses in the remitted depressed group were Social phobia (n = 1), Specific phobia (n = 2), chronic PTSD (n = 1) and Dysthymia (n = 4). Table 1 and 2 show clinical and demographical characteristics of both patients and controls of Study 1 and Study 2.

Self report measures

Recovered depressed patients scored higher on the BDI-II ($t(19.6) = -5.5$, $p < .001$) compared to controls. Patients also scored higher on the DAS ($t(37) = -3.7$, $p = .001$) and on some subscales of the LEIDS compared to the control group: Harm Avoidance ($t(37) = -6.6$, $p < .001$), Rumination ($t(37) = -9.6$, $p < .001$), Hopelessness ($t(37) = -2.2$, $p = .037$) and on the Total score ($t(37) = -4.2$, $p < .001$). Controls scored higher on Acceptance/Coping ($t(37) = 2.3$, $p = .026$) and Aggression ($t(37) = 2.2$, $p = .031$). When controlled for residual depressive symptoms, only the differences on the LEIDS Total score ($F(1,36) = 7.3$, $p = .010$), Rumination ($F(1,36) = 39.9$, $p < .001$) and Harm Avoidance ($F(1,36) = 16.5$, $p < .001$) remained significant.

Table 1. Characteristics of Study 1 and Study 2 (mean (SD))

	Study 1				
	Controls (n = 20)	Patients (n = 19)			
			t	**df**	***p***
Age (SD)	47.7 (14.1)	44.2 (13.0)	0.8	37	.426
BDI-II	1.4 (1.7)	11.7 (8.0)	-5.5	19.6	.000**
LEIDS totalscore	24.7 (12.6)	40.0 (9.7)	-4.2	37	.000**
DAS	58.8 (15.9)	80.2 (19.8)	-3.7	37	.001**
			χ^2	**df**	***p***
M/F	1/19	2/17	0.4	1	.517
Education level			10.6	2	.005**
- low	n = 2	n = 7			
- medium	n = 8	n = 11			
- high	n = 10	n = 1			
	Study 2				
	Controls (n = 21)	Patients (n = 20)			
			t	**df**	***p***
Age	44.1 (10.2)	48.7 (7.9)	-1.6	39	.114
BDI-II	5.2 (5.3)	12.9 (10.1)	-3.0	28.4	.006**
			χ^2	**df**	***p***
M/F	9/12	11/9	0.6	1	.437
Education level			0.8	2	.665
- low	n = 5	n = 3			
- medium	n = 6	n = 8			
- high	n = 10	n = 9			

BDI-II = Beck Depression Inventory, 2nd edition; LEIDS = Leiden Index for Depression Sensitivity; DAS = Dysfunctional Attitudes Scale
** $p < .010$

Table 2. Clinical characteristics of both patient groups (mean ± SD)

	Study 1 (*n* = 19)	**Study 2** (*n* = 20)
$HAM\text{-}D_{17}$	7.7 ± 3.6 [range 1-13]	5.6 ± 3.8 [range 0-13]
Type of medication		
- SSRI	*n* = 13	*n* = 13 †
- SSNRI	*n* = 6 (150-375 mg)	*n* = 7 (75–225 mg)
Type of remission[1]:		
- partial remission	n = 8	n = 13
- full remission	n = 11	n = 7
Duration of remission (months) ± SD	13.1 ± 22.3 [range 1-102]††	5.9 ± 5.6 [range 1-24]
Number of episodes ± SD	4.9 ± 4.1 [range 1-15]	4.8 ± 4.4 [range 1-16]
Single / recurrent episode(s)	2 / 17	4 / 16
Diagnosis, subtype[2]:		
- MDD, melancholic	*n* = 16	*n* = 11
- MDD, atypical	*n* = 1	*n* = 6
- MDD, seasonal pattern	-	*n* = 2
- Not melancholic, atypical or catatonic	*n* = 2	*n* = 1

HAM-D = Hamilton Rating Scale for Depression; SSRI = Selective Serotonin Reuptake Inhibitor; SSNRI = Selective Serotonin and Noradrenalin Reuptake Inhibitor; † two SSRI treatment free for 1 month; [1:] according to the criteria of Frank et al. 1991; †† this wide range is caused by one patient who had been recovered for over 8 years; without that patient the range is [1, 21]; [2:] subtype of most recent depressive episode

Cognition

See Table 3a for the cognitive tests of study 1.

Facial Expression Recognition test: Only a significant effect of Emotion ($F(3.9,137.6) = 10.3$, $p < .001$) was found on the overall accuracy data, indicating that participants were better at recognizing certain emotions compared to others (see Figure 1). The main effect of Group was not significant ($F(1,35) = 1.5$, $p = .233$). Separate analyses per Emotion revealed a significant effect of Group ($F(1,35) = 5.5$, $p = .024$) for the recognition of fear, indicating that remitted depressed patients were better at recognizing facial expressions of fear compared to controls. Univariate analyses on fear accuracy per intensity level (in five 20% blocks) showed that the effect of Group was significant or borderline significant for all levels, except for the 30-40% intensity level: 10-20% $F(1,35) = 4.2$, $p = .049$; 30-40% $F(1,35) = 0.1$, $p = .788$; 50-60% $F(1,35) = 4.1$, $p = .049$; 70-80% $F(1,35) = 7.2$, $p = .011$; 90-100% $F(1,35) = 4.1$, $p = .051$ (see Figure 2). No significant main and interaction effects were found for the other emotions.

Regarding the reaction time data, a significant effect of Emotion was found ($F(2.7,88.0) = 4.1$, $p = .011$). The main effect of Group was not significant ($F(1,33) = 0.0$, $p = .834$). When analyzed per emotion, no significant effects of Group or Group x Emotion were found.

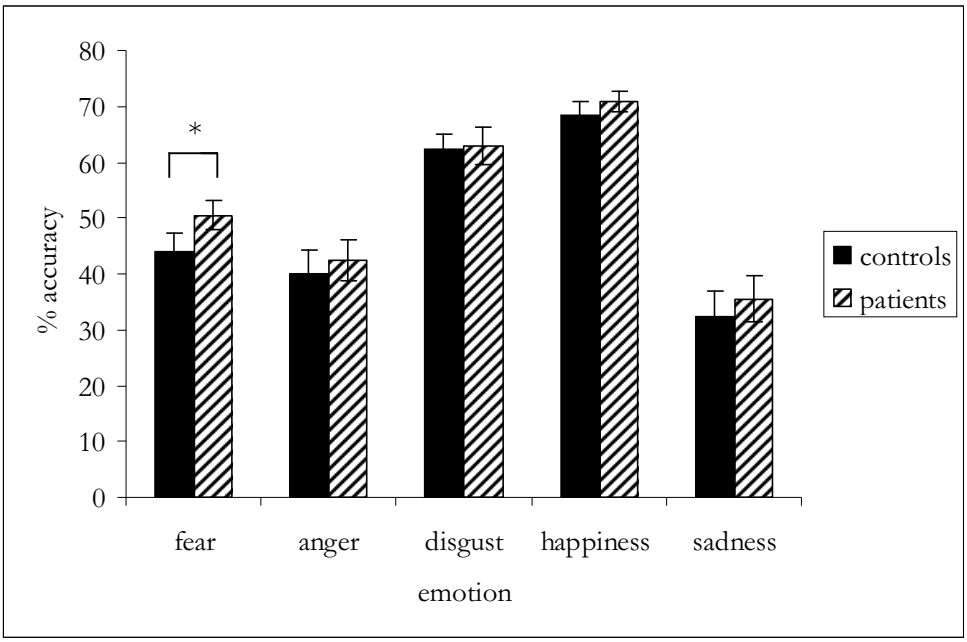
No other significant differences between the groups on cognitive performance were found in study 1.

Table 3a. Cognitive tests of Study 1, presented as means (SD)

	Controls (*n* = 20)	**Patients** (*n* = 19)	***F***	**df**	***p***
Verbal memory (WLT)					
immediate recall # correct	52.0 (9.0)	49.6 (11.0)	0.3	1,34	.581
delayed recall # correct	11.1 (2.2)	10.8 (2.7)	1.3	1,35	.260
Verbal Fluency					
# correct	12.4 (3.6)	9.9 (3.5)	0.03	1,35	.868
IAT Neutral[2]					
RT congruent (ms)	685.7 (107.8)	663.3 (126.4)	2.4	1,35	.134
RT incongruent (ms)	1139.8 (271.2)	1049.0 (273.6)	1.1	1.35	.294
IAT Emotional					
RT congruent (ms)	828.6 (209.2)	897.3 (304.2)	0.1	1,35	.717
RT incongruent (ms)	742.4 (111.8)	847.4 (245.3)	0.1	1,35	.816
Dot-probe					
AB depressive - positive (ms)	-2.3 (20.5)	-1.3 (22.9)	0.0	1,35	.904
AB anxious - neutral (ms)	-1.4 (18.1)	-6.0 (16.5)	0.4	1,35	.524
FERT					
- Accuracy			1.5	1,35	.233
Anger	1.6 (0.8)	1.7 (0.6)	0.5	1,35	.505
Fear	1.8 (0.6)	2.0 (0.5)	5.5	1,35	.024*
Sadness	1.3 (0.8)	1.4 (0.7)	1.3	1,35	.268
Happiness	2.7 (0.4)	2.8 (0.3)	0.2	1,35	.669
Disgust	2.5 (0.5)	2.5 (0.6)	0.0	1,35	.836
- Speed (ms)			0.0	1,33	.834
Anger	1061.1 (344.2)	1205.2 (305.4)	0.1	1,34	.783
Fear	1123.9 (525.6)	1212.1 (464.9)	0.3	1,35	.578
Sadness	1459.6 (495.5)	1514.2 (981.0)	0.3	1,34	.568
Happiness	805.1 (190.5)	870.9 (233.6)	0.0	1,35	.999
Disgust	907.8 (263.1)	1114.9 (691.3)	0.4	1,35	.542

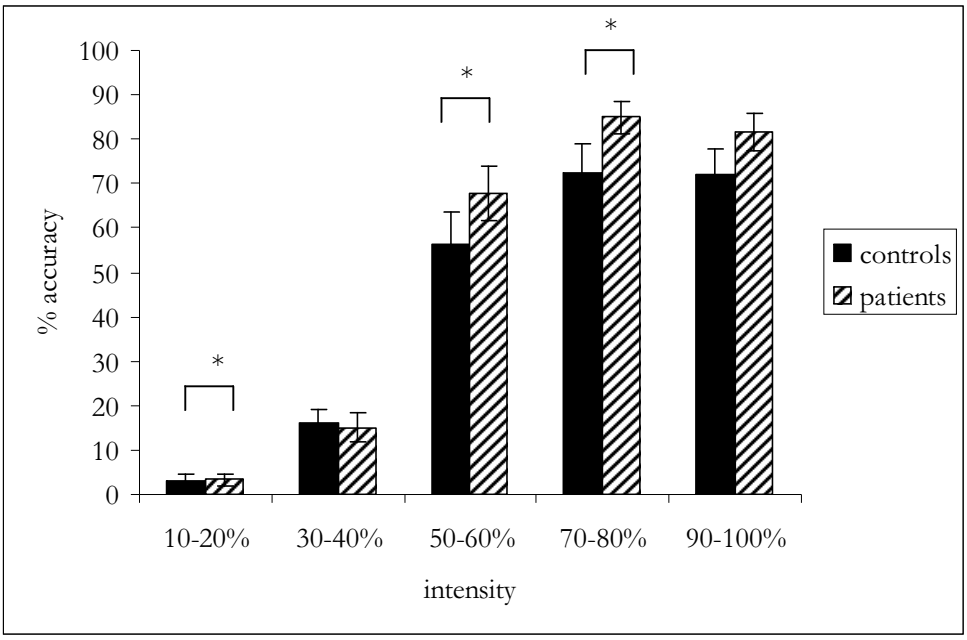
AB = attentional bias, FERT = Facial Expression Recognition Test, IAT = Implicit Attitudes Test, RT = reaction time, WLT = Word Learning Test, * $p < .05$, *F* values present the main effect of Group; [2]: analyses without one outlier are presented. All analyses were performed with Bonferroni corrections.

Figure 1. Facial emotion recognition for controls and remitted depressed patients (Mean ± SEM)



* $p < .05$

Figure 2. Fear accuracy over the different intensity levels (Mean ± SEM)



* $p < .05$

Study 2:

Data screening:

One patient missed all 4- and 5-step problems of the TOL. One control participant missed all 5-step problems of the TOL. Data for another control participant are missing for all positive words on the Emotional Stroop task. Cases with missing data were omitted separately by analysis. Outliers were found on the APRT, Stroop CWT, and Emotional Stroop test. Analyses were conducted with and without statistical outliers, however results were similar. The Verbal Fluency data were successfully log 10 transformed because of a non-normal distribution.

Participants:

Twenty-one controls and twenty remitted depressed patients were included in this study. The control group did not differ from the patient group in terms of gender, age and education level. Past comorbid diagnoses in the remitted depressed patient group were Panic disorder (n = 3, of whom one in partial remission), Social phobia (n = 1) and Anorexia nervosa (n =1).

Self-report

The remitted group had higher BDI-II scores compared to the control group ($F(1,39) = 9.19$, $p = .004$).

Cognition

See Table 3b for the cognitive tests of study 2.

APRT: A significant effect of Group was found for the recognition from long term memory (A'): $F(1,38) = 5.0$, $p = .030$. Patients appeared to

perform worse than controls at recognition of abstract visual information from long term memory.

Discussion

The current results indicate that medicated remitted depressed patients show an increased recognition of facial expressions of fear compared to healthy controls, even after statistical correction for differences in depressive symptoms. Also, patients scored higher on a self-report measure of cognitive reactivity and performed worse than controls at a task measuring recognition of abstract information from long term memory. No other residual cognitive impairments were found on a wide range of tests, despite the fact that the patients still suffered from residual depressive symptoms and were relatively chronic. The BDI-II scores of patients were higher than those of healthy controls, although both groups' scores were within the normal range (Van der Does, 2002b). These findings support the view that most cognitive deficits associated with depression are associated with clinical status, rather than a persisting vulnerability factor (Weiland-Fiedler et al., 2004). Some deficits may be more persistent however, and the higher cognitive reactivity scores suggest that the deficits may have become 'latent'.

A number of studies have shown that cognitive deficits may not be apparent when they are only assessed at 'resting' state (Lau et al., 2004). This implies that negative information processing biases may be rather easily activated by dysphoric mood states – either naturally occurring or induced in the laboratory. This process is called *cognitive reactivity*. Cognitive reactivity is an important vulnerability factor that is linked to depressive relapse (Segal et al., 2006).

Table 3b. Cognitive tests of Study 2, presented as means (SD)

	Controls (n = 21)	**Patients** (n = 20)	***F***	**df**	***p***
Verbal Fluency					
# correct	10.4 (3.9)	12.1 (5.1)	0.1	1,38	.720
Stroop CWT					
Condition I (ms)	567.0 (76.9)	552.5 (72.8)	0.2	1,38	.664
Condition II (ms)	487.5 (62.5)	490.2 (56.0)	0.1	1,38	.784
Condition III (ms)	775.7 (156.4)	792.0 (109.8)	0.0	1,38	.906
Interference (%)	47.3 (23.8)	52.3 (16.7)	0.1	1,38	.774
Emotional Stroop Task					
Negative words (ms)	712.3 (88.2)	749.6 (115.0)	0.0	1,38	.895
Neutral words (ms)	693.7 (91.4)	722.5 (74.3)	0.1	1,38	.741
Positive words (ms)	702.1 (124.1)	705.3 (83.4)	0.1	1,37	.729
Interference negative (%)	3.1 (9.2)	3.7 (9.9)	0.1	1,38	.780
Interference positive (%)	1.7 (10.7)	-2.3 (6.7)	1.1	1,37	.295
Left/right task					
Congruent (ms)	634.9 (94.2)	678.4 (58.9)	0.9	1,38	.353
Incongruent (ms)	652.0 (97.7)	700.4 (54.6)	2.0	1,38	.168
Tower of London					
- % correct			0.3	1,36	.584
2 steps	88.1 (17.5)	84.5 (16.7)			
3 steps	85.2 (19.4)	78.5 (11.8)			
4 steps	72.9 (15.5)	75.8 (21.2)			
5 steps	65.0 (24.0)	54.7 (29.9)			
- RT (ms)			0.1	1,36	.812
2 steps	5337.3 (1190.4)	6733.6 (2001.4)			
3 steps	7359.3 (2424.0)	8101.8 (3388.0)			
4 steps	10869.1 (3101.7)	11902.9 (4482.1)			
5 steps	19407.5 (7191.4)	17908.7 (8352.7)			
APRT					
A' STM (%)	83.0 (9.7)	78.3 (11.7)	1.5	1,38	.226
A' LTM (%)	80.5 (9.9)	74.9 (14.2)	5.0	1,38	.030*
RT STM (ms)	2164.2 (805.6)	2308.0 (802.9)	0.8	1,38	.380
RT LTM (ms)	1976.4 (715.5)	2107.9 (597.3)	0.1	1,38	.808

CWT = Colour Word Test; APRT = Abstract Visual Patterns Task; RT = reaction time; STM = short term memory; LTM = long term memory; *F* values represent the main effect of Group. All analyses were performed with Bonferroni corrections.

The finding of the current study that the difference between remitted depressed patients and controls in DAS scores became non-significant after controlling for residual symptoms is in line with Miranda et al. (1990) who have already shown that dysfunctional attitudes are mood-state dependent for subjects with a history of depression. The group differences on the LEIDS, which aim to measure reactivity of cognitions, remained significant after correction. The current findings therefore suggest that some of the other cognitive deficits might also be more easily triggered in remitted depressed patients than in never-depressed individuals. In line with our findings, Gemar et al. (2001) did not find any baseline differences when they studied implicit attitudes in formerly depressed and never depressed subjects. Only after a sad mood induction, a shift was found toward a negative evaluative bias in the formerly depressed group, again supporting the suggestion that cognitive impairments may become latently present following clinical recovery.

Interestingly, the finding that remitted depressed patients were better in recognizing fear indicates that facial expression recognition may be a scar and a persisting vulnerability factor for relapse to depression. Bhagwagar et al. (2004) also found increased recognition of fear in recovered depressed subjects relative to controls; however administration of a single dose of citalopram normalized this increased fear recognition. In contrast, our patients were already medicated for more than four weeks before entering the study. Bouhuys et al. (1999) found that increased perception of negative emotions is related to relapse, although the recognition of negative emotions decreased from the acute to the remitted phase. The conceptualization of fear recognition as a vulnerability marker was further supported in a study by Masurier et al. (2007) who found faster recognition of facial expressions of fear in female first-degree relatives of depressed patients compared to controls without a

family history of depression. Biases in the processing of emotional information may thus be a stable trait characteristic, even occurring before the onset of a first depressive episode (Leppänen, 2006; review).

Finally, the finding that the remitted depressed patients performed worse on a test measuring recognition from long-term visual memory is in line with previous studies which have shown persisting impairments in memory processes in euthymic patients (Marcos et al., 1994.)

In the current studies, remitted depressed patients were not impaired on tests measuring attentional bias. Studies in recovered depressed subjects mainly used the Stroop Colour Word task to measure attentional bias. Both Paradiso et al. (1997) and Trichard et al. (1995) found persisting impairments in Stroop performance in recovered depressed patients. Attentional bias is thought to be not only a symptom of depression, but also to be important in the development and maintenance of depressive disorders (Williams et al., 1996). Our results do not support this position, since no impairments were found on neutral and emotional Stroop interference as well as on attentional bias measured with the Dot-probe test. However, the literature on attentional bias in depression is contradictory, which may be explained by the differences in stimulus presentation- times (Mathews et al., 1996; Mogg et al., 1995). Studies using the Dot-probe test have found attentional biases in depression using relatively long stimulus presentations (1 sec or more) (Mogg et al., 1995). When stimuli are presented for shorter durations, results are mixed (Bradley et al., 1997; Mathews et al., 1996). Our stimulus presentation time of 500 ms. was probably not optimal to detect group differences.

One factor that might limit interpretation of the data is that patients were treated with serotonergic antidepressants when participating in the study.

Serotonergic antidepressants may have some sedative side effects, but these tend to wear off in the first two weeks of treatment (Amado-Boccara et al., 1995) and the effects on memory and psychomotor performance are of low intensity (Gorenstein et al., 2006; Thompson, 1991). In contrast, SSRIs have been found to positively affect neutral and emotional information processing acutely and after 7 to14 days (Bhagwagar et al., 2004; Harmer et al., 2002; Harmer et al., 2003a; Harmer et al., 2004; Harmer et al., 2006a). However, unmedicated recovered depressed patients also did not show any differences in neutral information processing compared to healthy controls (Booij et al., 2006a), although these groups did differ on cognitive reactivity (Merens et al., 2005). The latter studies used a considerable younger and less chronic sample however. How chronic SSRI use affects emotional processing is still unclear, so it may be possible that some cognitive impairments were remediated by SSRI treatment.

It also has to be considered that the lack of differences between groups in the current study may have been caused by insufficient statistical power. Sample sizes in both studies are relatively small and replication in larger samples is warranted. The fact that both patient groups were not completely asymptomatic only strengthens our conclusion that remitted depressed patients do not suffer from many cognitive impairments. Also, remission status (partial vs. full) did not affect the facial expression recognition data.

Future research may investigate the influence of clinical variables (chronicity, age of onset, treatment modality etc.) on cognitive performance of remitted depressed patients, to clarify possible mediating factors leading to cognitive impairment in depression. Finally, as cognitive function was not assessed during the acute phase of the depressive episode, it cannot be ruled out that we selected groups of remitted depressed patients who showed little

cognitive impairments even in a depressed state. However, this seems very unlikely since cognitive impairments in depression are common (Austin et al., 2001; Elliott, 1998) and both patients groups were relatively chronic.