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Research Article

Cognitive Reserve in Major Depression-Associations with Cognitive Status, Age, Education, Personality, and Depression Severity

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Abstract

Cognitive reserve (CR) is understood as a latent potential underlying the flexible adaptation to mental challenges. By optimizing cognitive performance, it can be used to cope with high task demands. This study examines CR in 40 in-patients with unipolar depression compared to 24 healthy control subjects. The size of CR was assessed by calculating the maximal performance improvement over retesting with a digit symbol substitution task. Furthermore, the relation between CR, cognitive status, age, education, and the personality traits Openness for experience and Neuroticism was explored. CR did not differ significantly between controls and the whole group of depressed patients. However, patients who displayed cognitive deficits in one-time neuropsychological testing (50%) showed a lower CR than controls while patients without deficits showed a marginal higher CR. In patients, CR was positively associated with attention, short term memory, and openness for experience. In controls, CR was relatively independent from cognitive status but showed a negative association with age. Our results support the idea that subgroups of patients can be differentiated through cognitive status as well as CR. Furthermore, the marginal higher CR in patients without cognitive impairment suggests that CR acts as a buffer against the development of cognitive deficits in depression.

Keywords: Cognitive Reserve; Cognitive Plasticity; Depression; Cognition; Personality; Testing-the-limits

Abbreviations

CR: Cognitive Reserve; Ttl: Testing-The-Limits; DSST: Digit Symbol Substitution Test; STM: Short Term Memory; WM: Working Memory; MADR-S: Montgomery Asberg Depression Rating Scale; MMSE: Mini-Mental State Examination; SSRI: Selective Serotonin Reuptake Inhibitors; NASSA: Noradrenergic and Specific Serotonergic Antidepressant; NARI: Selective Noradrenaline Reuptake Inhibitors; D: Depressed patients without cognitive deficits; Ddef: Depressed patients with cognitive deficits

Introduction

Background

Cognitive deficits in depression are well documented. Impairments have been found in many cognitive domains, including attention [1-3], memory [4,5], and executive function [6,7]. However, it has been doubted whether the standard one-time testing reflects the "latent competence" of a subject. This competence is understood as cognitive reserve (CR), which is activated when required to cope for functional consequences of brain pathology [8]. Therefore, people with high CR have a better ability to compensate for pathologies like Alzheimer´s or Parkinson´s disease than people with low CR [9-12]. In healthy individuals CR has been suggested as a protective factor against cognitive decline in normal ageing [13]. CR is also sought to enable individuals at any age to cope with increased task demands by optimizing cognitive performance, possibly by using neural networks high in efficiency or capacity [8]. To measure CR, proxy variables are often used which are hypothesized to reflect cognitive functioning, like education or intelligence (for a discussion, see [14]). Other authors have favored a more dynamic measure of CR by assessing the potential to adapt performance to a challenging cognitive task (e.g. [15]). In the testing-the-limits (TtL) procedure one´s maximal performance improvement due to training or practice is assessed [16-18]. Within this procedure, CR differs from cognitive status as it reflects the latent competence one has available when high performance is needed.

The first objective: The first objective of the present study is to examine CR in depressed patients with a TtL procedure using a simple retest design. As a CR measure, we used the individual performance improvement in the Digit Symbol Substitution Test (DSST, revised Wechsler Intelligence Scale, german version; Aster [19]), which is a simple but multi faced measure incorporating multiple cognitive abilities [20,21]. Since depression is associated with a wide range of structural and functional neuronal abnormalities (e.g. Hickie and Rogers [6,22], not only detriments in cognitive status but also in CR may be found in depression [23,24]. By using performance gain after memory training as a CR measure, Calero and Galiano [25] found no difference in CR between older subjects with and without high scores in a self-rating depression scale. However, generalization of those results is restricted, since subjects with an elevated score might not have been clinical depressed according to DSM-IV criteria [26]. The present study therefore compares clinically diagnosed depressed

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patients with healthy controls. As depression is not necessarily associated with cognitive impairments in one-time-testing [27,3], we additionally compared CR in patients with and without clinically relevant cognitive deficits.

The second objective: The second objective of the present study is to explore a number of variables associated with CR in patients and healthy subjects: age, education, cognitive status, and the personality factors Openness and Neuroticism. As healthy aging is associated with a mild decline in cognitive functions [28], higher age may also be negatively associated with CR [16,18,29]. Since past research has repeatedly shown that the DSST is age sensitive (for a meta-analysis, s. Hoyer [30]), this may be especially prone in a DSST-based CR measure. A positive association with education and cognition has been suggested by Richards and Deary [31] and Scarmeas and Stern [32] as it may help to establish efficient cognitive skills. However, positive associations between general cognitive abilities and CR have only been reported in some (e.g. Singer [29]) but not all [15,21] studies using performance improvement as a CR measure. Past research has shown that the "Big Five" [33] personality factor Openness to experience has a direct positive effect on intelligence through environmental enrichment [34] and is positively related to cognitive abilities like memory and executive functions [35-37]. Neuroticism has frequently reported to be negatively related to cognition (e.g. Chapman [38]). Therefore, Openness (+) and Neuroticism (-) may also be important for the development of CR. However, the relationship between performance improvement and personality has only been studied by few studies, yielding different results [39-41]. Nevertheless, one can assume that a low Neuroticism on the one hand and good cognitive abilities, a high education and a high Openness on the other hand not only favors the development of CR by the accumulation of efficient strategies but are also beneficial in mobilizing CR to improve performance in a current test situation.

In depression, the mobilization of CR may also be affected by the severity of depression as the severity of symptoms can influence the extent of cognitive impairment [42].

Prespecified hypotheses: The following hypotheses have been pre specified in the present study:

- Single DSST trials and CR are positively associated with cognitive status
- Single DSST trials and CR are positively associated with years of education.
- Single DSST trials and CR are negatively associated with age.
- Single DSST trials and CR are positively associated with Openness and negatively associated with Neuroticism.
- Single DSST trials and CR are negatively associated with severity of depression in patients.
- No pre specified hypotheses have been made for group comparisons.

Methods

Study design

Depressed patients and healthy control subjects were tested to assess the individual size of CR, cognitive status, and personality characteristics. Patients were tested on two separate days to avoid fatigue effects. The first day included a routinely administered test battery to comprehensively examine performance in attention, memory, and executive function. The second day implied further study specific measures. Testing in control subjects was executed on a single day including only measures used for the quantitative analysis.

Subjects

Depressed in-patients admitted to the Max Planck Institute of Psychiatry in Munich were originally included when meeting the following inclusion criteria: first episode of unipolar major depression or recurrent depression. Diagnosis of depression was made by the treating psychiatrist according to DSM-IV criteria [26]. Exclusion criteria were other primary psychiatric diagnoses than depression, depression with psychotic symptoms, electroconvulsive therapy within the last three month, present or past neurological illness, present or past substance abuse, unmedicated hypo- or hypertonia, diabetes and thyroid dysfunction.

Healthy control subjects without a history of psychiatric or

Table 1: Cognitive tests used in the routinely administered neuropsychological test battery.

Cognitive domain		Standardized cognitive test
Attention	Processing speed	Zahlenverbindungstest A & B comparable to trail making test [72]
	Selective attention	d2 test of attention [43]
	Alertness	Testbatterie zur Aufmerksamkeitsprüfung (TAP) computerized reaction-time test [73]
Memory	Verbal memory	Wechsler Memory Scale (German version) logical memory [44]
	Verbal short term/working memory	Wechsler Memory Scale (German version) digit span forward and backward [44]
	Verbal learning and recall	Verbaler Lern- und Merkfähigkeitstest comparable to California Verbal Learning Test [74] If the age of the patient exceeded 65 years, word list learning, recall and recognition of the consortium to establish a registry for Alzheimer's disease (CERAD) test battery was rated instead [45].
Executive functions	Problem solving	Wechsler Intelligence Scale (German version) matrices [19]
	Cognitive flexibility	Computerized version of Wisconsin Card Sorting Test [75] Regensburger Wortflüssigkeits-Test (word fluency test; Aschenbrenner [76])

neurological illness were recruited through notices at the Ludwig Maximilian University in Munich and through a control-sample which previously participated in a non-cognitive study at the Max Planck Institute of Psychiatry.

All patients and controls gave written informed consent according to the latest version of the Declaration of Helsinki.

Procedure and Material

Cognitive reserve

CR was measured by a TtL procedure using a retest paradigm with ten consecutive trials of the Digit Symbol Substitution Test (DSST, revised Wechsler Intelligence Scale, german version; Aster [19]) without providing feedback or strategies to improve performance. This simple paradigm was chosen to maximize compliance in spite of the expected reduction of motivation and drive in patients. In each trial, a coding key is presented on the top of the sheet assigning the numbers 1-9 to corresponding symbols. Subjects are asked to use the coding key to note the corresponding symbols under blank fields below a series of digits. The same test was administered ten times in a row with a one minute break in between. To avoid ceiling effects, processing time was limited to 90 sec. The number of correctly written symbols per test served as the outcome measure.

Cognitive status, personality and severity of depression

Table (1) shows the cognitive tests used in the test battery routinely administered at the Max Planck Institute of Psychiatry in Munich. To compare patients with and without cognitive deficits, performance in every test was rated. A clinical relevant deficit was defined as having a test score lower than 1.5 *SD* below the test specific norm in one or more measures. To examine variables associated with CR, we limited the analysis to three cognitive tests as valid measures of short term/ working memory, selective attention, and problem solving.

Selective visual attention: Selective visual attention was measured by the d2 test of attention [43]: Participants were required to cross out the letter d with two dashes out of 14 lines of letters p and d with one to four dashes arranged above and below each letter. The number of correctly crossed out letters minus the number of errors served as the attention score.

Verbal short term and working memory: Verbal short term and working memory was measured by the subtest digit span forward and backward of the revised Wechsler Memory Scale (german version; Härting [44]). Subjects were asked to repeat strings of digits in increasing length either in the same (short term memory; STM) or the reversed order (Working Memory; WM).

Problem solving : Problem solving was measured by the subtest matrix reasoning (matrices) of the Wechsler Adult Intelligence Scale-III (german version; Aster [19]). Subjects were instructed to complete 26 geometric patterns of increasing difficulty by choosing the correct out of five inserts.

Personality: Personality was assessed by a computerized version of the NEO-Fife-Factor-Inventory (NEO-FFI; german version; Borkenau and Ostendorf [46]). Subjects were instructed to indicate on a five-point Likert scale how each of 60 statements suits their personality. The test-score for Neuroticism reflecting nervousness and anxiety and Openness to experience reflecting curiosity and creativity were used for analyses.

Severity of depression: Severity of depression in patients was measured by the Montgomery Asberg Depression Rating Scale (MADR-S; Montgomery and Asberg [47]). The MADR-S is an external rating instrument consisting of ten items representing symptoms of major depressive disorder. The rating was based on a structured interview [48].

Statistical Analysis

As a measure of CR, we used the following formula:

$$CR_i = 1 + (1 + x_1 / x_{\max group}) * [(x_i - x_1) / x_{\max group}]$$

Improvement from the first DSST (x_1) to each of the following nine trials (x_i) is calculated. The formula accounts for possible ceiling effects, which can be expected due to psychomotor restrictions, by compensating for the baseline (x_1) and the maximum score occurring in the respective group ($x_{\max group}$ of patients/controls). The maximal score of the resulting nine scores is used as the CR measure as it reflects the individual maximal performance improvement.

Since most of the data is lacking normal distribution, nonparametric tests are used for statistical analyzing. For analyses between two groups, Mann-Whitney *U* tests are computed. Differences between three groups are calculated with Kruskal-Wallis-Tests using post-hoc Mann-Whitney *U* tests with Bonferroni adjusted *p* values are calculated to detect the location of differences. To examine performance differences in subsequent testing, Wilcoxon signed-rank tests are calculated. To analyze relations between variables, one-tailed Kendall tau-b rank correlation coefficients are computed. To control for variables such as age, years of education, and depression severity, regression residuals of forced entry multiple linear regression analyses are used for further testing. For correlations with CR, the upper (positive relation) or lower (negative relation) levels of bias-corrected and accelerated 90% bootstrap confidence intervals are reported. Bootstrap resampling was set at 2000.

By default, α-levels were set to .05. Bonferroni adjusted *p* values (multiplied by 4) are reported when calculations imply cognitive status (attention, STM, WM, problem solving)

Results

Subjects

Depressed patients: Fifty-four depressed in-patients were originally included in the study. Fourteen patients were excluded

Table 2: Medication in depressed patients (*N* = 37).	
Type of medication	*n*
Sedative Antidepressants (Mirtazapine, Trazodon, tricyclic antidepressants amitriptylin-type)	12
Nonsedative Antidepressants (tricyclic antidepressants imipramin and desipramin type, SSRI, NASSA, NARI, monoamine oxidase inhibitors)	28
Benzodiazepine	7
Neuroleptics	8
Lamotrigin	14
Note. 3 Patients refused medication by the time of testing.	

from analysis due to meeting exclusion criteria at discharge (n = 9), measurement errors (n = 1) or prolonged latency between test sessions (n = 4). The final sample included 40 patients (21 females, 19 males; M age = 44.9, SD = 13.5, range 18-70; M years of education = 12.98, SD = 3.9, range 9-21) either diagnosed with a first depressive episode (moderate: n = 4; severe: n = 9) or recurrent depression (moderate: n = 10; severe: n = 17). All but three patients received medication by the time of testing (table (2)). Severity of depression was assessed by the Montgomery Asberg Depression Rating Scale (MADR-S; Montgomery and Asberg [47]) with a score of 0 indicating absence of symptoms and a score of 60 indicating severe depression. The mean MADR-S sum score was 19.8 (SD = 10.5, range = 3-45). One subject reaching a score of 3 in the MADR-S was not excluded since he was not considered as remitted both by himself and the treating psychiatrist. All patients completed the Mini-Mental State Examination (MMSE; Folstein [49]) as a dementia screening instrument. The mean score was 29.6 (SD = 0.6, range 28-30) indicating normal general cognition in all patients (Table 2).

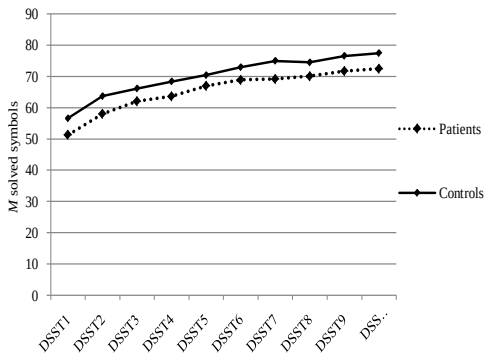

Figure 1: Mean performance in the ten retest trials of the Digit Symbol Substitution Test (DSST) in depressed patients (N = 40) and control subjects (N = 24).

Healthy control subjects: Twenty-four age, gender, and education-matched controls with no history of psychiatric diagnoses were included (13 females, 11 males; M age = 43.7, SD = 16.1, range 20-70; M years of education = 13.1, SD = 4.1, range 8-21). None of the controls reached a score higher than 14 points in the Beck-Depression-Inventory-II (BDI-II; german version; Hautzinger [50]) indicating the absence of mild or more severe depression. None of the controls reported subjective cognitive deficits. The mean score of the MMSE was 29.7 (SD = 0.5, range 29-30).

Performance in the digit symbol substitution test

Figure (1) displays the results of the ten DSST trials in depressed patients and control subjects. In DSST1, patients solved on average 51.35 symbols (SD = 14.74) and increased their performance on

Table 3: Kendall Tau-b rank correlations (one-tailed) with DSST trials 1-10 and cognitive reserve in patients (N = 40).

Depressed patients		1	2	3	4	5	6	7	8	9	10	CR	CI level
Attention (d2)	τ_b	.51**	.45**	.45**	.46**	.48**	.42**	.45**	.47**	.46**	.48**	.26*	.41
	p	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	.04	
STM (digit span forward)	τ_b	.17	.18	.24	.24	.29*	.28*	.33*	.30*	.34**	.40**	.35**	.52
	p	.28	.23	.09	.09	.03	.03	.01	.02	<.01	<.01	<.01	
WM (digit span backward)	τ_b	.31*	.24	.28*	.34**	.33*	.33*	.33*	.26	.26	.27*	.15	.32
	p	.01	.08	.04	<.01	.01	.01	.01	.06	.06	.04	.39	
Problem solving (matrices)	τ_b	.27*	.24	.22	.32*	.27*	.29*	.28*	.27*	.32*	.32*	.16	.35
	p	.04	.07	.10	.01	.04	.03	.03	.04	.01	.01	.30	
Age	τ_b	-.46**	-.31**	-.29**	-.30**	-.24*	-.23*	-.20*	-.21*	-.22*	-.20*	.05	-.14
	p	< .01	<.01	<.01	<.01	.01	.02	.04	.03	.02	.04	.67	
Years of education	τ_b	.05	.05	.07	.16	.15	.11	.16	.13	.13	.17	.12	.36
	p	.35	.35	.27	.10	.10	.19	.09	.13	.15	.07	.15	
MADR-S (severity of depression)	τ_b	-.18	-.23*	-.26*	-.24*	-.29**	-.29**	-.32**	-.33**	-.33**	-.33**	-.19*	-.36
	p	.06	.02	.01	.02	<.01	<.01	<.01	<.01	<.01	<.01	.04	
Openness for experience	τ_b	.11	.20*	.18	.17	.18	.17	.17	.19*	.21*	.17	.20*	.40
	p	.18	.04	.06	.06	.06	.06	.07	.05	.03	.07	.03	
Neuroticism	τ_b	-.02	-.05	-.12	-.08	-.10	-.11	-.09	-.05	-.09	-.10	-.12	-.28
	p	.42	.32	.14	.24	.18	.17	.21	.32	.21	.18	.14	

Note: CR, cognitive reserve; d2, d2 test of attention; CI level, upper (attention, STM, WM, problem solving, years of education, Openness for experience) or lower (age, MADR-S, Neuroticism) 90% bootstrap confidence level for correlations with cognitive reserve; MADR-S, Montgomery Asberg Depression Rating Scale; * p < .05; ** p < .01; p-values for cognitive status (attention, STM, WM problem solving) are Bonferroni adjusted.

Table 4: Kendall Tau-b rank correlations (one-tailed) with DSST trials 1-10 and cognitive reserve in controls (N = 24).

Control subjects		1	2	3	4	5	6	7	8	9	10	CR	CI level
attention (d2)	τ_b	.58**	.56**	.60**	.51**	.46**	.51**	.47**	.42**	.41*	.39*	.11	.40
	p	<.01	<.01	<.01	<.01	.01	<.01	<.01	<.01	.01	.02	.92	
STM (digit span forward)	τ_b	.35*	.36*	.39*	.37*	.37*	.42*	.41*	.43*	.35*	.40*	.20	.45
	p	.04	.04	.02	.04	.03	.01	.02	.01	.04	.02	.38	
WM (digit span backward)	τ_b	.14	.18	.14	.19	.22	.21	.20	.24	.20	.28	.20	48
	p	.77	.50	.74	.46	.32	.37	.42	.26	.40	.16	.39	
Problem solving (matrices)	τ_b	.10	.12	.07	.19	.13	.18	.18	.16	.16	.13	.02	.28
	p	.99	.85	.9	.42	.79	.46	.46	.61	.58	.81	.99	
Age	τ_b	-.34*	-.33*	-.29*	-.37**	-.35**	-.39**	-.36**	-.44**	-.30*	-.34*	-.26*	-.46
	p	.01	.01	.02	<.01	<.01	<.01	<.01	<.01	.02	.01	.04	
Years of education	τ_b	-.28	-.32	-.26	-.33	-.35	-.23	-.28	-.26	-.33	-.34	-.33	-.04
	p	.96	.98	.95	.98	.99	.93	.96	.95	.98	.99	.98	
Openness for experience	τ_b	.05	.02	.08	.12	.05	.08	.09	.01	.03	-.03	.12	.14
	p	.37	.44	.30	.22	.39	.30	.27	.48	.41	.58	.80	
Neuroticism	τ_b	-.08	-.07	-.09	-.10	-.08	-.09	-.09	-.04	-.07	.01	.004	-.31
	p	.30	.33	.28	.24	.30	.28	.28	.60	.32	.52	.51	

Note: CR, cognitive reserve; d2, d2 test of attention; CI level, upper (attention, STM, WM, problem solving, years of education, Openness for experience) or lower (age, Neuroticism) 90% bootstrap confidence level for correlations with cognitive reserve; * p < .05; ** p < .01; p-values for cognitive status (attention, STM, WM problem solving) are Bonferroni adjusted.

Table 5: Cognitive performance in control subjects and depressed patients.

Variable	Control subjects (N = 24)			Depressed patients (N = 40)			Mann-Whitney Test	
	M	Mdn	SD	M	Mdn	SD	U	p
CR	1.36	1.33	0.14	1.33	1.29	0.18	406.0	.31
DSST1	56.63	60	15.08	51.35	52	14.74	368.0	.12
Attention (d2)	167.58	164	33.09	150.51	156	42.45	362.0	.56
STM (digit span forward)	8.17	8	1.99	7.78	8	1.92	420.5	>.99
WM (digit span backward)	7.50	7	2.19	6.95	7	1.80	438.5	>.99
Problem solving (matrices)	20.00	20.5	3.73	18.15	20	4.59	354.5	.32

Note: d2, d2 test of attention; DSST1, Digit Symbol Substitution Test trial 1; CR, cognitive reserve; p-values for cognitive status (attention, STM, WM problem solving) are Bonferroni adjusted.

average by 1.63 *SD* of baseline performance (24.08/14.74 = 1.63 *SD*) to a mean individual maximum of 75.43 symbols (*SD* = 11.34). Control subjects showed a mean initial performance of 56.63 symbols (*SD* = 15.08) in DSST1 and improved their performance on average by 1.55 *SD* (23.38/15.08 = 1.55 *SD*) to a maximum of 80.00 symbols (*SD* = 18.45). Wilcox on signed-rank tests revealed a significant improvement from initial to maximal performance in both, patients (z = 5.51, p < .001) and controls (z = 4.29, p < .001) (Figure 1).

Relations between CR and variables of interest

Table (3) shows the one-tailed Kendall-Tau-b rank correlations in depressed patients. As highlighted in the table, CR was positively related to attention (τ_b = .26, p = .036) and STM (τ_b = .35, p = .004). However, only the relation between attention and CR remained significant when controlling for age, years of education, and severity of depression (τ_b = .42, p = .02). Furthermore, rank correlations revealed a positive relation between CR and Openness to experience (τ_b = .20, p = .036) and a negative relation between CR and severity of depression (τ_b = .19, p = .039). The latter remained even when controlling for age and education (τ_b = .36, p = .014). No further significant correlation was found for cognitive status (WM, problem solving), age, education and personality (Neuroticism).

Table (4) shows the one-tailed rank correlations in control subjects. No significant relation between cognitive status, personality and CR was found (all p <.05). However, rank correlations revealed a negative association between age and CR (τ_b = -.26, p = .041). No significant positive association was found between years of education and CR and the upper level of the 90% bootstrap confidence interval indicates a negative association (-.04).

Relations between single DSST trials and variables of interest

Table (3) shows that in patients, attention, problem solving, and WM were all positively related to DSST1. No significant relation between STM and DSST1 was found but correlation coefficients

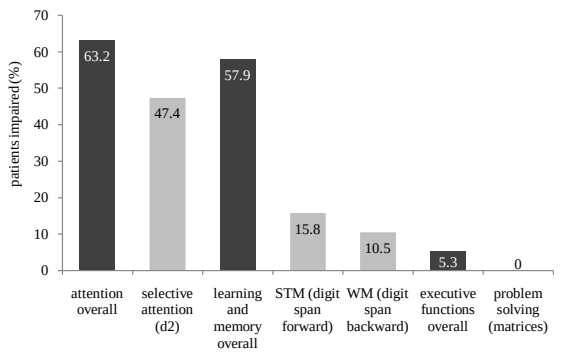

Figure 2: Percentage of depressed patients with impaired performance in attention (including d2 test of attention), memory (including short term memory, STM, and working memory, WM), and executive functions (including problem solving).

marginally increased from DSST1 to DSST10 (z = 1.59, p = .055). In patients, a negative relation was found between age and single DSST trials. However, this relation significantly decreased from DSST1 to DSST10 (z = 1.83, p = .034). No significant correlation between severity of depression and first DSST performance was found. To further analyze the association between severity of depression and cognitive status, we calculated partial correlations with attention, STM, WM and problem solving controlling for age and education. Those revealed only one significant negative association with STM (τ_b = .32, p = .024).

Table (4) shows that in control subjects, attention and STM were positively related to DSST 1-10 while age was negatively related to single DSST trials. No further significant associations were found for single DSST trials and cognitive status (WM, problem solving), education or personality (all p >.05) (Tables 3 and 4).

Group differences in CR, first DSST and cognitive status

To examine group differences between patients and controls in CR, DSST1 and attention, memory and problem solving abilities, Mann-Whitney U tests were calculated. The results are depicted in table (5). Patients increased their performance on average by 24 symbols from baseline to maximum (SD = 11.34), controls by 23 symbols (SD = 7.79). The calculation of CR scores revealed a slightly lower performance of patients (M_{CR} controls - M_{CR} patients = 0.03) when accounting for the higher baseline performance in controls (M_{DSST1} patients = 51.35; M_{DSST1} controls = 56.63). Mann-Whitney U Tests showed that this small group difference in CR is not significant. No further group differences were found (all p >.05) (Table 5).

To examine CR in patients with and without clinical relevant cognitive deficits, the whole group of depressed patients was stratified by their performance in a routinely administered test battery. A cognitive deficit was defined by a score of 1.5 SD below the mean of the age specific norm population in at least one cognitive test. Deficits were present in 19 (47.5%, Ddef) vs. 21 (52.5%, D) patients. As figure (2) depicts, with the exception of problem solving, deficits were found in all assessed cognitive domains. D and Ddef did not differ in age and education and there were no significant differences in the distribution of gender, medication or diagnosis at discharge (all p > .05). However, Ddef showed a marginal higher severity of depression (M = 22.68, SD = 11.37, Mdn = 24) than D (M = 17.10, SD = 9.21, Mdn = 16; Mann-Whitney U = 142.00, p = .06) (Figure 2).

Figure (3) shows the CR score, performance in the first DSST trail and attention, STM, WM and problem solving in controls, D and Ddef, respectively. In the first DSST trial, Ddef showed a numerically lower performance than both, D and controls. In the course of training Ddef increased their performance on average by 16 symbols (SD = 6.93) from baseline to maximum, D by 31 symbols (SD = 9.78), and controls by 23 symbols (SD = 7.79). Kruskal-Wallis-Tests revealed significant group differences in DSST1 and CR (DSST1: H (2) = 11.57, p = .003; CR: H (2) = 26.45, p < .001). Post-Hoc Mann-Whitney Tests showed that this difference was due to a significant lower performance in Ddef than in both, D and control subjects in DSST1 (Ddef vs. D: Mann-Whitney U = 82.5, p = .002; Ddef vs. controls: Mann-Whitney U = 114.00 p = .005) and in CR (Ddef vs. D: Mann-Whitney U = 24.00, p < .001; Ddef vs. controls: Mann-Whitney U = 72.00, p < .001), respectively. Differences in DSST1 between D and control subjects were not significant (Mann-Whitney U = 250.00, p = .960). Surprisingly, there was a marginal higher level in CR in D than in control subjects (Mann-Whitney U = 170.00, p = .062). We reanalyzed the group differences between D and Ddef using regression residuals controlling for depression severity. This confirmed the above pattern showing that Ddef reached lower scores in DSST1 (Mann-Whitney U = 91.5, p = .003) and in CR (Mann-Whitney U = 44.00, p < .001).

As figure (3) depicts, control subjects and D showed a numerically comparable cognitive status with an almost identical performance in attention. Performance in cognitive status is numerically lower in Ddef than in both, controls and D. However, Kruskal-Wallis-Tests revealed that differences in attention (H (2) = 7.29, p = .105), STM (H (2) = 8.16, p = .068), WM (H (2) = 4.01, p = .537), and problem solving (H (2) = 6.88, p = .129) did not reach significance when controlling for the four statistical tests.

Influence of medication

To identify a possible bias due to the use of sedative medication, we explored the association between medication and CR, attention, memory, and problem solving by comparing cognition in patients using sedative (n = 15) or nonsedative drugs (n = 22). Mann-Whitney U tests using regression residuals of the cognitive tests scores corrected for age, education, and severity of depression revealed no significant differences in CR and other cognitive scores (all p > .05) (Figure 3).

Discussion

Key results and interpretation

The present study investigated CR in depressed patients and healthy control subjects using a simple retest design. This design yielded a substantial CR as reflected in performance improvement over retesting [15,51-53].

The first objective: The first objective of the present study was to examine CR in depressed patients and controls. Interestingly, differences in CR between patients and controls did not reach significance. This corresponds to a study by Calero and Galiano [25]

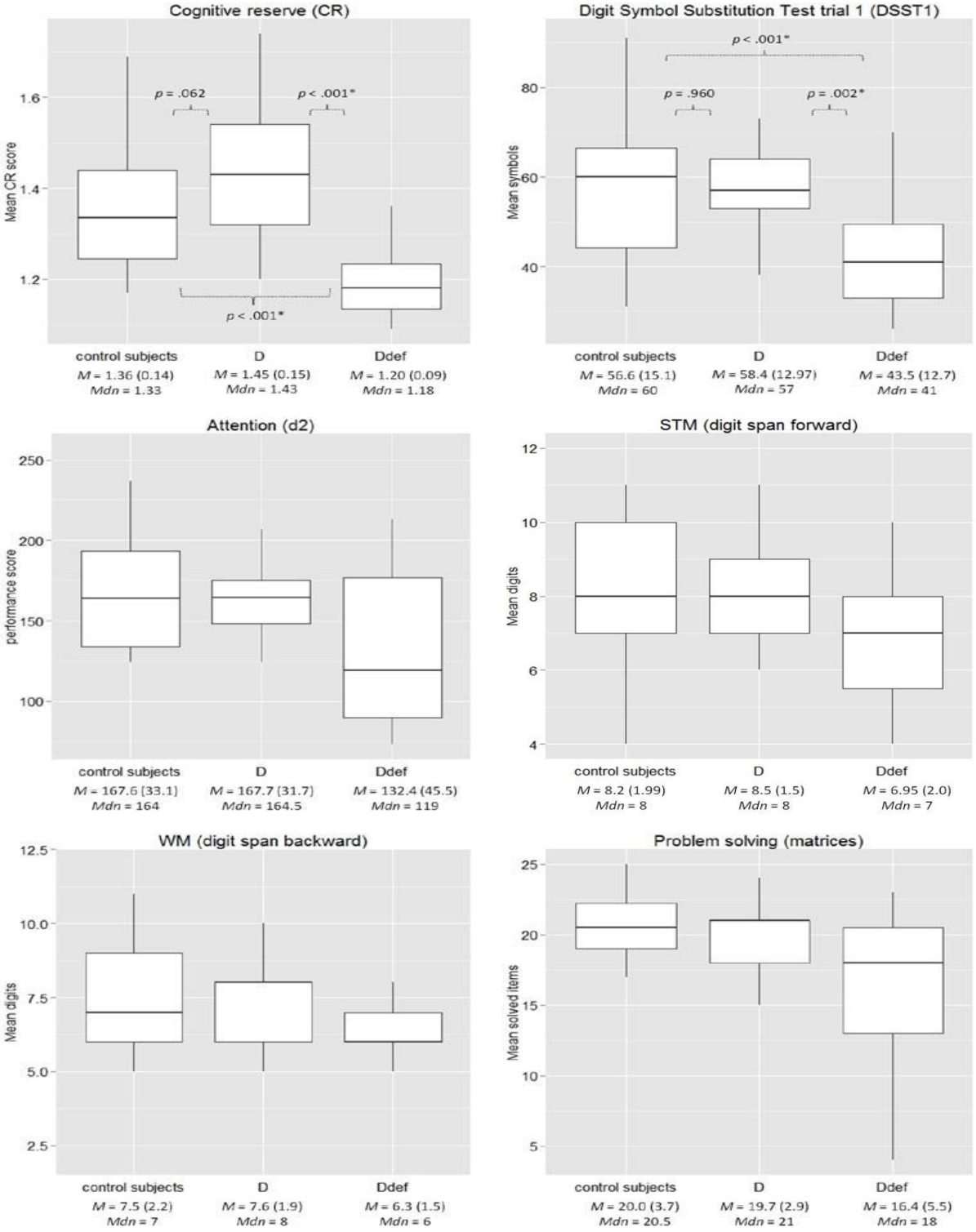

Figure 3: Box plot of cognitive reserve (CR), Digit Symbol Substitution Test trial 1 (DSST1), attention (d2 test of attention), short term memory (STM), working memory (WM), and problem solving (matrices) in controls, depressed patients without cognitive deficits (D) and depressed patients with cognitive deficits (Ddef). Boxes show the median and the middle 50% range. Whiskers show the upper and lower quartile. Means (*M*), Standard deviations (), and Medians (*Mdn*) are stated.

who failed to find a significant reduction of CR in older subjects with high scores in a self-rating depression scale. The present study extends the results to a psychiatric in-sample with a broader age range and clinically diagnosed depression. Therefore, it may be concluded that depression per se does not inevitably lead to a substantial reduction of CR. This also becomes evident when stratifying patients according to cognitive deficits in standard one-time testing. 50% of the patients in our sample display cognitive impairments, with deficits occurring in every cognitive domain. This adds to previous research showing that a subgroup of depressed patients display rather unspecific cognitive deficits [27,54,55]. The comparison between controls and patients with and without cognitive deficits yielded substantial differences in CR: The impaired subgroup had a significantly lower CR than the subgroup without impairment and the controls while the subgroup without impairment did not show a reduced CR compared to controls. This corresponds to the assumption of Reppermund [27] who speculated that subtypes of depression may be described by the predominance of either psychopathological or cognitive deficits. The present study extends this assumption: The reduction of CR in the impaired subgroup suggests not only an impaired cognitive status but also a reduced potential to improve performance when needed. Surprisingly, the subgroup without impairment showed a marginal higher CR than controls while having an almost identical performance in the first DSST (57 vs. 58 symbols) and other cognitive tests. What can be inferred from group differences in CR? Patients without impairment seem to possess an especially high CR. This may act as a buffer against the negative effects of depression on cognition stemming from structural and functional changes in the brain [22,56-58]. Patients with lower CR, as in the impaired group, may be more vulnerable to those effects and their functional consequences.

The second objective: The second objective of the present study was to examine variables associated with CR in depressed patients and healthy subjects. In both groups predictor/criterion relations differed for CR and first DSST performance showing that the construct validity of the task changed in the course of training [59]. Contrary to our expectation, in controls, none of the correlations between cognitive status and CR reached significance. This has also been found in previous studies which examined CR in retest learning [15,21] but it contrasts studies using extensive training programs which suggested an important role of fluid intelligence for CR [29,60]. The result is also in contrast with the frequent use of both, cognitive status and education as proxy measures for CR [8]. The mere lack of significance in the present study does not imply that they are invalid proxies. Inconsistencies in the present and past findings may be due to different sample sizes or age ranges. Furthermore, it is possible that the relations with CR are varying depending on the test and method used to evoke CR. However, the results of the present study highlight the importance of heterogeneous operation alization methods when studying CR. When CR is understood as an efficient and flexible use of cognitive processes [8], dynamic measurements, like the TtL procedure, may reflect this performance-modifiability better than static proxies.

In patients, attention and short term memory (STM) were positively related to CR. It can be assumed that patients with higher STM have a higher ability to memorize item-pairs which leads to a better performance in the course of retesting since the utilization of the coding key decreases [21,61]. Ackerman and Woltz [62] assumed that two strategies can be chosen in coding tests: 1. a constant use of the coding key throughout testing (scanning strategy), 2.a memorization of item-pairs over time (memory strategy). The authors assumed that the scanning strategy is less demanding, but that the memory strategy leads to a higher performance gain: A higher motivation and flexibility is needed to give up the scanning strategy and switch to a memory strategy. As CR is positively related to attention in depressed patients, it can be assumed that patients with a reduced drive and cognitive flexibility spontaneously prefer a scanning strategy which itself depends on attention. As the relation between STM and single DSST trials increases in the course of training, it can be assumed that depressed patients switch to a memory strategy depending on the general STM function. In controls however, the relation between STM and CR did not reach significance. It cannot be inferred from this result, that short term memory abilities are completely irrelevant for performance improvement in the DSST. Nevertheless, one can assume that the memorization of item pairs is a task which is not very demanding, provided that drive and motivation are within a normal range. Therefore, it may be assumed that control subjects spontaneously rely on a memory strategy right from the beginning. In that case a strategy shift might be less pronounced in controls than in patients. Surprisingly, no significant positive association was found between years of education and CR in control subjects and the upper level of the 90% bootstrap confidence interval (-.04) suggests a negative relationship between education and CR in the population. As our CR measure controls for baseline, this is not due to a ceiling effect in higher educated control subjects. As expected, we found a positive association with the personality factor Openness to experience and a negative association with severity of depression in patients. As the DSST is a multi facet measure [20,21], motivation and drive is needed to enhance performance. Therefore, a benefit due to a greater motivation to enhance performance can be expected in patients with a less pronounced symptomatology and with a higher Openness [63,64].

Limitations in the present study: First, the sample size was relatively small. It did not allow us to analyze all variables within one comprehensive model which may be interesting since we found that the association between STM and CR did not remain significant when controlling for age, education, and depression severity. Secondly, all but three patients took medication during study assessments. Past research has indicated that antidepressants can have an impact on cognition [65]. Therefore, the present study cannot rule out a possible influence of antidepressant drugs on CR or cognitive status. However, past research has not always found an influence of medication [66] and the present study did not reveal significant differences in cognition in patients using sedative and non-sedative drugs. Thirdly, we cannot rule out a possible bias due to using different measures for learning and recall depending on patient´s age. However, the analysis focused on the comparison between subgroups with and without cognitive impairment and the results were not used for the quantitative analysis. Using age-specific norms are inevitable to detect clinical relevant deficits in a population with a broad age range.

Generalizability and perspectives for future research

Cognitive deficits in depression have a high clinical relevance since they can have a negative impact on daily living [67,68]. The results of

the present study suggest that also CR is reduced in some, but not all depressed patients. It has to be noted that the generalization of results is limited, as we did not control for variables like age of onset and number of episodes and we did not assess CR in other subgroups of depression such as patients with bipolar disorder (for a discussion, see Porter [69]). However, a reduction of CR in the individual patient may be of relevance for his/her therapy and rehabilitation: As CR reflects the potential to adapt performance to mental challenges, it may be important for coping with demanding job situations or various forms of treatment (for a discussion concerning patients with Schizophrenia, s. Sergi [70], Watzke [71]). The present study also shows that CR in our depressed sample is significantly associated with attention and memory functions. Consequently, it can be speculated that a specialized training of those functions may also be helpful for the mobilization of CR.

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