Psychiatry Research 271 (2019) 343–350

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Neurocognitive performance in patients with depression compared to healthy controls: Association of clinical variables and remission state

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ARTICLE INFO

Keywords:
Major depressive disorder
Cognitive impairment
Neuropsychological performance
Hospitalization

ABSTRACT

Cognitive impairment in Major Depressive Disorder (MDD) has been postulated to persist into remission. However, inconsistent definitions of clinical remission, patterns and influencing factors, isolated cognitive tasks, and the lack of appropriately matched controls (HCs) present significant limitations of previous studies. Furthermore, studies investigating cognition in partially remitted patients are particularly scarce. This study compares the cognition of MDD patients ($N = 65$) and HCs ($N = 65$), matched by one-to-one recruitment strategy for age, sex, and education (ages 19–60). The neuropsychological (NPS) performance was measured via an extensive NPS-test battery and analysed retrospectively, accounting for demographic and clinical variables. Full remission was defined as HAMD cut off ≤7, partial remission as HAMD 8–18. The findings show entire MDD group and partially remitted MDD with significantly poorer NPS performance compared to HCs, while remitted MDD patients did not differ significantly from HCs. This underscores how critical a clear definition of remission is to compare studies on MDD. The clinical variable 'number of hospitalizations' had a significant effect on cognition, whereas current symptom severity did not correlate with performance on any cognitive domain. Higher number of hospitalizations may be associated with higher burden of illness and greater neurobiological "scar effects".

1. Introduction

Cognitive impairment is an important characteristic of Major Depressive Disorder (MDD) (Ravnkilde et al., 2002) and is associated with poor treatment response and deteriorated everyday-functioning (e.g., Rock et al., 2014). However, the extent of cognitive impairment in MDD is disputed, and to date no specific profile has been found (Afridi et al., 2011; Beblo, 2016). Cognitive deficits are mostly described for the domains of *memory, executive function, attention* and *psychomotor speed* (e.g., Lee et al., 2012). Persistence of deficits has been demonstrated to last into remission (e.g., Hasselbalch et al., 2011). Some studies report impairment (*attention* and *executive functions)* and remission-related improvement (*information processing speed* and *memory)* in specific cognitive domains (Douglas and Porter, 2009; Rock et al., 2014). Other studies propose a generalized impairment profile in remission, rather than the existence of selective deficits in specific cognitive domains (Reppermund et al., 2009). Moreover, an unresolved question remains whether cognitive deficits are attributable to mood symptoms, or arise rather out of underlying neurobiological alterations (Murrough et al., 2011). Diverse patterns of cognitive impairment can be found in remission, attributable to (a) state (during episodes of depressed mood, e.g. *psychomotor speed* and *memory performance;* (Lee et al., 2012); (b) trait (persistence into recovery, e.g. *attention* and *executive function*) markers (Douglas and Porter, 2009); and (c) scar features (progressive decline in cognitive function associated with the onset/progression of MDD) (Allott et al., 2016).

Some demographic and clinical variables have been found to be associated with cognitive impairment in MDD, such as onset of disorder, duration of illness, number of hospitalizations, depression severity, subtype of depression (e.g., Elderkin-Thompson et al., 2003; Hasselbalch et al., 2011; Nandrino et al., 2002), age (e.g., Hasselbalch et al., 2011), sex (e.g., Sarosi et al., 2008) and education (e.g., McLaren et al., 2015). Various hypotheses exist regarding altered neurobiological mechanisms in pathogenesis of MDD (e.g., hormonal and structural brain changes as reviewed by aan het Rot et al., 2009, which have been further associated with cognitive impairment (e.g.,

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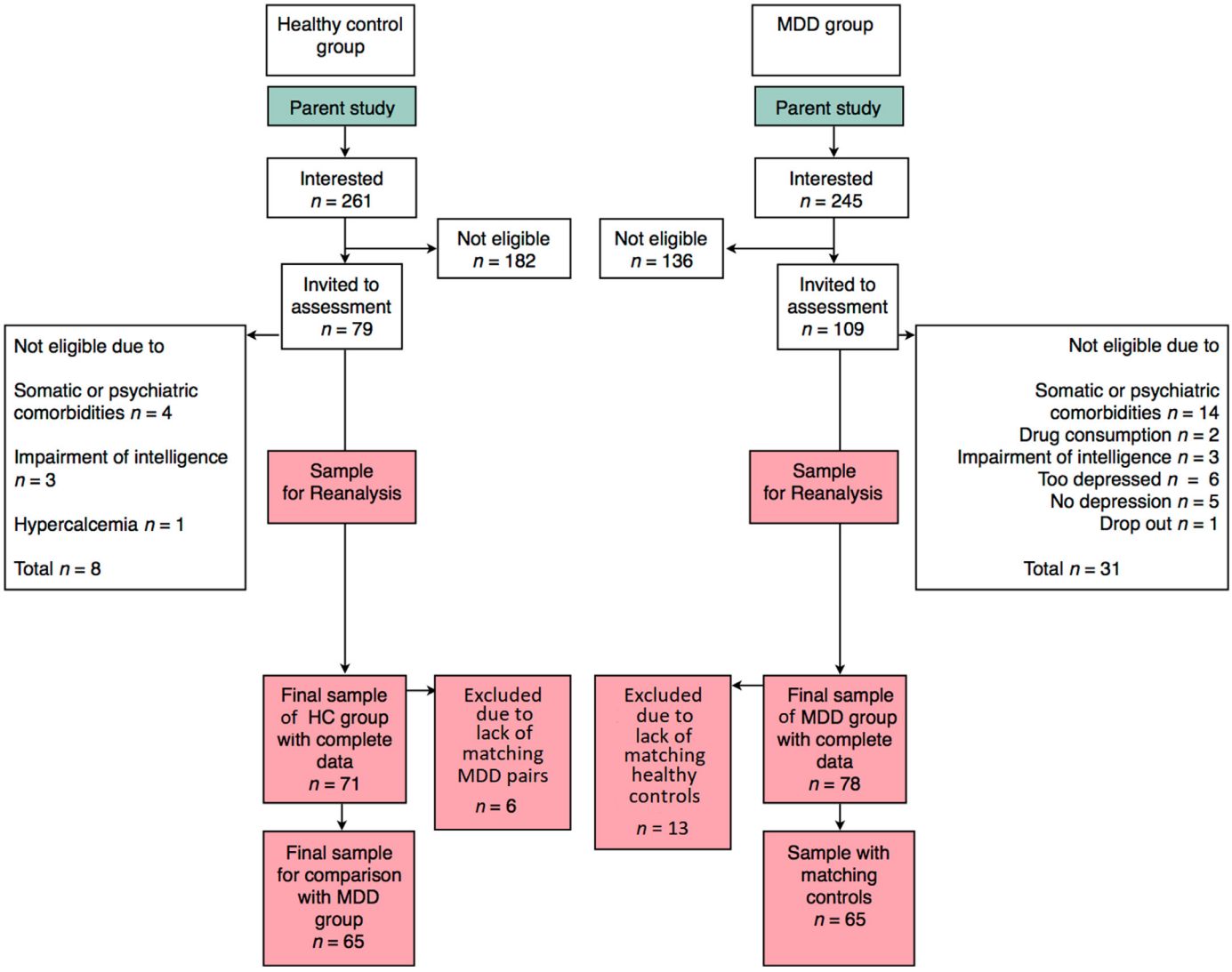
https://doi.org/10.1016/j.psychres.2018.11.047
Received 17 March 2018; Received in revised form 19 November 2018; Accepted 20 November 2018
Available online 20 November 2018
0165-1781/



Flow Chart 1. Participant flow chart with the original study (parent study) and sample for this retrospective re-analysis. *Note.* MDD = Major Depressive Disorder group. HC = healthy control group.

Nissen et al., 2010; Schatzberg, 2015). Cognitive deficits have been reported to be predictive of poor response to antidepressant treatment, and to be associated with a higher risk of relapse (Dunkin et al., 2000; Majer et al., 2004; Story et al., 2008). Persistent cognitive deficits in remitted patients are assumed to contribute to poor psychosocial functioning, to diminished workforce performance (Trivedi and Greer, 2014), and possibly to poorer quality of life (Rock et al., 2014). To address these conditions and develop new treatment strategies, better knowledge about cognitive deficits in MDD is vital.

In this study, we investigated cognitive deficits in (partially) remitted MDD patients, compared with healthy controls (HCs) who were individually matched for age, sex and education by one-to-one recruitment strategy. Most studies that examined cognitive impairment in MDD vs. HCs compared the performance only of acute (e.g., (Baune et al., 2010) or remitted MDD patients (Bora et al., 2013; Hasselbalch et al., 2011; Lee et al., 2012; Rock et al., 2014). The only study with MDD patients in state of remission, from the aforementioned meta-analyses that investigated neuropsychological (NPS) performance in a wide age-range (19–60 years) and examined a large sample size, employed a relatively small number of neuropsychological tests (Preiss et al., 2009). Systematic studies on partially remitted MDD patients are still scarce, despite the obvious clinical relevance of remission-state, the fact that full recovery rates are very low, and the majority of patients who meet criteria of remission still suffer from residual depressive symptoms (e.g., Iovieno et al., 2011). Studies investigating NPS performance in partially remitted patients (age-range 19–60 years) have so far included only a small matched-sample size (Biringer et al., 2007; Elderkin-Thompson et al., 2006; Hammar and Ardal, 2013; Kaneda, 2009; Merens et al., 2008; Ruchsow et al., 2008; Schmid et al., 2011; Strand et al., 2013; Westheide et al., 2007), lacked an individualized matching for multiple demographic categories (Merens et al., 2008), or didn't employ a wide NPS test battery (Elderkin-Thompson et al., 2006; Hammar and Ardal, 2013; Kaneda, 2009; Lee et al., 2013; Ruchsow et al., 2008). However, differentiating between full and partial remission seems to be of importance in acquiring better knowledge about characteristics of cognitive deficits in MDD remission. To our knowledge, this is the first study which overcomes the above pitfalls with a large sample size to investigate differences between (partially) remitted MDD patients compared to matched HCs, based on a one-to-one recruitment and matching strategy. The NPS test battery used in this study tests a wide range of cognitive domains. Moreover, all included domains are well defined and have a short processing time, making the battery suitable for patients with MDD (WTS, (Wiener Testsystem, 2012).

In sum, there is evidence for persistence of cognitive impairment in (partially) remitted MDD patients. However, profile and clinical

Table 1
Sociodemographic and clinical variables for partially remitted and remitted group and healthy control group.

Group	*N*	Age[a]	Sex[b]	Education[c]	Employ-Ment	HAMD	BDI-II	MWT-B	Antidepressant M[e].	Remission duration[i]
MDD (total)	65	38.89 (14.26)	13 M 52F	SS = 7 HE = 58	Yes = 46 No[d] = 19	8.78 (5.1)	15.56 (9.93)	32.08 (2.92)	Yes = 31 No = 34	23 month
Hc (total)	65	38.89 (14.20)	13 M 52F	SS = 7 HE = 58	Yes = 59 No[d] = 6	1.85 (1.99)	2.62 (3.17)	31.45 (2.75)		
MDD (partial rem.)	37	39.49 (13.76)	10 M 27F	SS = 3 HE = 34	Yes = 25 No[d] = 12	12.59 (2.8)	20.21 (7.03)	32.35 (2.68)	Yes = 21[f] No = 16	23 month
MDD (rem)	28	38.11 (15.11)	3 M 25F	SS = 4 HE = 24	Yes = 21 No[d] = 7	3.75 (2.19)	9.75 (10.06)	31.71 (3.23)	Yes = 10[g] No = 18	23 month

Note. *N* = number of cases; HAMD = Hamilton Rating Scale for Depression; BDI-II = Beck Depression Inventory II; MWT-B = Multiple Choice Vocabulary Intelligence Test; MDD = patient group (Major depressive disorder); Hc = Healthy control group.

[a] Age in years.

[b] Sex: M = male, F = female.

[c] Educational level: SS = Secondary school, HE = higher education entrance qualification.

[d] Unemployed and on sick leave.

[e] Antidepressant medication.

[f] SSRI (*n* = 10), SNRI (*n* = 7), NaSSa (*n* = 2), TCA (*n* = 2), St John's Wort (*n* = 2), Agomelatin (*n* = 2), lithium (*n* = 1), antipsychotics (Quetiapine extended release) (*n* = 1).

[g] SSRI (*n* = 7), SNRI (*n* = 2), TCA (*n* = 2), SMS (*n* = 1), SNDRI (*n* = 1).

[i] Mean Remission duration in month.

variables associated with these persistent cognitive deficits are not fully understood, and studies lack a systematic analysis of clinical and demographic variables regarding (partially) remitted patients.

Therefore, the aims of the current study were:

1) to verify and extend previously reported results of persistence of cognitive impairment into (partial) remission of MDD vs. HCs with a large, well-matched controlled sample;
2) to examine effects of clinical variables on the relationship between MDD and NPS performance;
3) at the exploratory level to compare NPS performance of MDD patients vs. HCs when applying a HAMD cut-off for remission state (<7) into two subgroups (fully vs. partially remitted group).

We predict worse cognitive performance in the entire MDD group versus HCs, as well as in the partially remitted MDD group and remitted MDD group.

2. Methods

2.1. Participants

The present inquiry is based on data originally collected within a study investigating the correlation between serum calcium levels and NPS performance in patients with MDD and matched HCs. It analyses the data of Grutzner et al., 2018 from a different angle. MDD patients (*n* = 109) and healthy controls (*n* = 79) were assessed between March 2016 and July 2017 (parent study), of whom a total of 130 individuals entered the final sample for the current analysis (total MDD group: *n* = 65, HC group: *n* = 65), see Flow Chart 1. In contrast to the calcium-study (Grutzner et al., 2018), the present study also includes participants who took calcium and vitamin D supplementations and those who didn't provide a blood sample (see, Flow Chart 1). All participants were outpatients and recruited from contact with doctors and psychotherapists, flyer distribution, advertisements, newspaper articles, etc.

Patients (*n* = 65) received a main diagnosis of depressive disorder (296.35/36 and 296.25/26) without psychotic symptoms according to DSM-IV criteria (Saß et al., 2003) for a singular depressive episode (*n* = 18), a recurrent depressive episode (*n* = 47), or additional dysthymia (300.4) (*n* = 11) in full or partial remission. Diagnosis of MDD was established previously by psychiatrists and confirmed by us with structured clinical interview for DSM-IV (SCID-I) for past MDD (Wittchen et al., 1997) and Mini International Neuropsychiatric Interview (M.I.N.I.) (Ackenheil et al., 1999) for current MDD or comorbidities.

Exclusion criteria to avoid potential effects on cognition other than (partially) remitted MDD diagnosis were: acute depressive symptoms using the 24-item *Hamilton Rating Scale for Depression* (HAMD) scores ≥20 (Guy and Bonato, 1970) (adaption of Hamilton's original version; (Hamilton, 1960); comorbid psychiatric disorders (DSM-IV axis 1) within the previous 6 months; any history of psychotic symptoms; current/past substance abuse (e.g., drugs, alcohol); suspected major brain damage or other neurological diseases; dementia and any diagnosis of intellectual disability; estimated IQ less than 80 according to the *Multiple Choice Vocabulary Intelligence Test* (MWT-B) (Lehrl, 2005); physical illnesses or therapeutic interventions with potential effects on cognition.

The HC group was individually recruited, matched for each MDD participant by sex, age within a +/− 2-year range, and education level. The same inclusion/ exclusion criteria applied, except none of the HCs had any history of psychiatric disorders (screened via M.I.N.I.).

Based on these exclusion criteria, 44 MDD patients and 8 HCs were excluded from further analysis, and additional 6 HCs did not enter analysis because of missing matched pairs. In the MDD group comorbidities before the last 6 months prior to assessment included anorexia (*n* = 5), bulimia (*n* = 1) and anxiety disorders (*n* = 1). From the entire MDD group (*n* = 65) *n* = 13 were proven to have personality disorders assessed by structured clinical interview for personality disorders (SCID-II) (Fydrich et al., 1997), *n* = 28 were full remitters (defined by HAMD cut off ≤7, see Section 2.5.2.), while *n* = 37 were partial remitters (HAMD 8–18, see Section 2.5.2.). For a detailed description of participant characteristics, see Section 3.1 and Table 1.

The study design was approved by the local medical ethics committee (S-106/2012) in accordance with the World Medical Association's Declaration of Helsinki (October 2013). It was ensured that all participants provided written informed consent at the beginning of assessment.

2.2. Questionnaires and interviews

Clinical assessment and NPS testing were conducted individually by one examiner (psychologists or trained researcher under supervision of an experienced clinician). Assessments took place in the morning and lasted about 4–5 hours for MDD group and approximately 3 h for HCs, including a break halfway through the session. For both groups the order of presented tests was held the same. Prior to NPS testing,

assessment started with getting informed consent, drawing the blood sample for the calcium-study, and administering a socio- demographic interview and interviews/tests relevant for exclusion/inclusion criteria: MWT-B (Lehrl, 2005), 24-item HAMD (Guy and Bonato, 1970), SCID-I for past MDD (Wittchen et al., 1997), SCID-II (Fydrich et al., 1997), M.I.N.I. (Ackenheil et al., 1999) and *Beck Depression* Inventory (BDI-II) (Hautzinger et al., 2006) for participants' subjective symptom severity.

2.3. Neuropsychological assessment

NPS assessment started with the computerized test battery CogBat® and WAF-S test of the Vienna test system (WTS, (Wiener Testsystem, 2012). After a short break, paper-pencil tests were conducted. All tests were selected based on previous research on cognitive impairment in MDD and according to recommendations of the German "Gesellschaft für Neuropsychologie" (GNP; engl. Society for Neuropsychology) (Gauggel and Sturm, 2005).

Following cognitive domains were assessed:

1) *Information Processing Speed* via subtest *Trail Making Test A* (Langensteinbach version; TMT-A) of WTS (Wiener Testsystem, 2013) and additional paper-pencil version of *Symbol Coding Task,* taken from the Wechsler intelligence scale for adults (Aster et al., 2009);
2) *Attention* via subtest *Alertness* (*WAF-A), Divided attention (WAF-G)* and *Selective attention (WAF-S*) of WTS;
3) *Working Memory* via subtest *Nback verbal* (NBV) of WTS;
4) *Learning and Memory* – Figural memory via *Figural Memory Test (FGT)* of WTS and Verbal memory via the German version of the *California Verbal Learning Test* (CVLT) (Niemann et al., 2008);
5) *Executive function – Response Inhibition* via subtest *Go-Nogo-INHIB, Cognitive Flexibility* via *Trail Making Test- B* (*TMT-B)* and *Planning ability* via *Tower of London-TOL* (TOL-F) of WTS. For detailed description of tests, see supplementary material S1 in Grutzner et al., 2018. In order to combine the different tests into broader cognitive domains, all raw NPS test parameter scores were transformed into standardized (*z*) scores, using the sample of the parent study as the norm group, and polarised into one direction with higher *z*-scores indicating better NPS performance. Relevant *z*-scores of the individual tests were then further averaged to yield respective cognitive domain *z*-transformed scores (Liao et al., 2017; Yeh et al., 2011). For measuring a generalized cognitive deficit, a composite score was calculated by averaging all domain scores (NPS composite). We preferred this procedure over analysing every single one of our 19 raw test parameter scores (Grutzner et al., 2018) in order to (1) examine broader neurocognitive domains, (2) to reflect underlying theoretical cognitive constructs, rather than single tests, (3) to limit multiple testing issues by formulating directed hypotheses for performances in the most important cognitive domains described in literature.

2.4. Medication

Of all MDD patients, $N = 31$ took antidepressant medication. Among those, $n = 17$ took Selective Serotonin Reuptake Inhibitors (SSRI), $n = 9$ Selective Serotonin-Noradrenalin-Reuptake-Inhibitors (SNRI), $n = 2$ Noradrenergic and Specific Serotonergic Antidepressant (NaSSa), $n = 4$ Tricyclic antidepressants (TCA), $n = 2$ St John's Wort, $n = 2$ Agomelatin, $n = 1$ Serotonin Modulators and Stimulators (SMS), $n = 1$ Selective Norepinephrine and Dopamine Reuptake Inhibitors (SNDRI), $n = 1$ lithium, and $n = 1$ antipsychotics (Quetiapine extended release). For a detailed overview of antidepressant medication among remitted and partially remitted patients, see Table 1.

2.5. Data analysis

2.5.1. MANOVA and regression analysis

Data analyses were performed using SPSS, version 25. The significance threshold was set at $p < 0.05$. Overall performance on neuropsychological testing among MDD vs. HC was compared using multivariate analysis of variance (MANOVA) with neuropsychological performance (five domain scores) as repeated measure factor, and group (whole MDD group vs. HC group) as group factor, followed by univariate ANOVAs. To select appropriate predictor variables for the following regression analyses, correlation (two-tailed Pearson's correlation) was examined between dependent variables – *NPS composite* – and all possibly relevant clinical variables selected on the basis of existing literature (illness duration, number of hospitalizations, number of previous episodes, age of onset, comorbidities, dysthymia and HAMD) (Elderkin-Thompson et al., 2003; Hasselbalch et al., 2011; Nandrino et al., 2002) and demographic variables (age and education) (Hasselbalch et al., 2011; McLaren et al., 2015; Sarosi et al., 2008) for the entire MDD group ($n = 65$), see supplementary material Table S1. Only when *NPS composite* correlated statistical significant, correlation between domain scores and clinical variables was examined (nested testing), applying Bonferroni–Holms correction. Subsequently, backward stepwise regression analysis was employed with *NPS composite* and the domains of *executive function, learning and memory* and *information processing speed* as dependent variables. This was done to examine the unique contribution of each factor from the nested testing approach (age, number of hospitalizations and age of onset) that was significantly correlated with NPS performance to the percentage of variance explained by the model. Since *attention* and *working memory* did not correlate with any of the three clinical variables, no regression analysis was calculated. Influence of medication on cognition was investigated via correlation between *NPS domains* and medication, and in the backward stepwise regression model.

2.5.2. Exploratory analysis

To explore the possible influence of full remission on NPS performance, the total MDD group ($n = 65$) was divided by 24-item HAMD-cut off ≤ 7, as employed in previous studies (Hasselbalch et al., 2012; Rush et al., 2006), into remitted (HAMD ≤ 7, $n = 28$) and partially remitted patients (HAMD 8–18, $n = 37$) (HAMD range in the whole sample: 0–18, mean remission-duration see Table 1). Since most clinical studies have cited the Hamilton's original 1960 or 1967 HAMD-version, yet using new versions without specifying which version they really used, comparability among studies and implementing cut offs is quite difficult (Williams, 2001). In this study, we used the 24-item HAMD version as it covers more areas of symptoms, has a wider variance and was clinically used as rating instrument in the university hospital of Heidelberg where the study was conducted. These considerations had more weight even though HAMD-6 has been found to be superior in terms of scalability and discriminating antidepressants from placebo (Kyle et al., 2016). It has been argued that 17-item HAMD cut off ≤ 7 is set too high and should be lowered (Zimmerman et al., 2012), since many patients still show residual depressive symptoms (Kaneda, 2009). Although cut off score for remission for the 24-item HAMD has been proposed to be < 10 (Kellner et al., 2006; Kyle et al., 2016), we still decided to use a more stringent cut-off score ≤ 7 to eliminate residual depressive symptoms. The HAMD cut-off score for partial remission was set 8–18, as has been done in existing literature (Paykel, 2008). Overall performance on neuropsychological testing among the three groups (remitted versus partially remitted versus healthy controls) was compared using multivariate analysis of variance (MANOVA), followed by Bonferroni post hoc analysis to identify between group differences. Before conducting the MANOVA, group differences for socio-demographic characteristics (age, sex, education) between the three groups (remitted versus partially remitted versus healthy controls) were examined using ANOVAs and chi square tests (for categorical variables).

Table 2
Comparison of clinical variables between partially remitted and remitted patients.

Variable	Partially R. (n = 37) *M, SD (for metric v.) / frequency (for categorial v.)*	Remitted (n = 28) *M, SD (for metric v.) / frequency (for categorial v.)*	Test statistics and p-values[d]
HAMD	12.59 ± 2.81	3.75 ± 2.19	$F(1,63) = 189.655$, $p < 0.001$[e]***
BDI-II	20.21 ± 7.03	9.75 ± 10.06	$F(1,61) = 23.540$, $p < 0.001$[e]***
Previous episodes	3.22 ± 2.26	3.07 ± 3.04	$F(1,62) = 0.046$, $p = 0.831$
Comorbidities[a]	0.11 ± 0.315	0.18 ± 0.390	$F(1,63) = 0.650$, $p = 0.423$
Personality disorder	0.32 ± 0.580	0.11 ± 0.315	$F(1,63) = 3.203$, $p = 0.078$
Number of hospitalizations[b]	1.08 ± 1.34	0.57 ± 0.920	$F(1,63) = 2.977$, $p = 0.089$
Illness duration[c]	10.05 ± 8.41	6.48 ± 8.04	$F(1,62) = 2.922$, $p = 0.092$
Age of onset	27.22 ± 11.66	28.19 ± 12.2	$F(1,62) = 0.104$, $p = 0.749$
Dysthymia	Yes = 10, No = 27	Yes = 1, No = 27	$x^2(1) = 6.237$, $p = 0.013$
Antidepressant medication	Yes = 21, No = 16	Yes = 10, No = 18	$x^2(1) = 2.829$, $p = 0.093$

Note. M = mean; SD = standard deviation. $p \leq 0.05$, two-tailed.
[a] Previous to the last six month before assessment.
[b] Full MDD group: range 0–5, $M = 0.86$, $SD = 1.2$; partial remitted: range 0–5, $M = 1.08$, $SD = 1.34$; remitted: range 0–3, $M = 0.57$, $SD = 0.92$).
[c] From beginning of first diagnose.
[d] Remitted versus partially remitted MDD patients.
[e] Significant with Bonferroni- Holm correction: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Remitted and partially remitted groups (from exploratory re-analysis) were compared for clinical characteristics using univariate one-way ANOVAs (and additional chi-square test for categorical variables).

3. Results

3.1. Demographic and clinical characteristics of the sample

The entire MDD group (remitted and partially remitted MDD patients together) and HC group did not differ significantly with regard to socio-demographic characteristics due to matching strategy. Details of socio-demographic characteristics of the entire MDD group and the HC group are provided in Table 1. The three groups in the exploratory analysis—remitted, partially remitted, and healthy controls—did not differ significantly with regard to socio-demographic characteristics either. Univariate one-way ANOVA and additional chi-square test for the categorical variables found no significant differences between these groups for age, sex, or education (age: $F(2,127) = 0,074$ $p = 0.928$, sex: $x^2(2) = 0.141$, $p = 0.266$, education: $x^2(2) = 0.070$, $p = 0.729$). Table 2 shows clinical characteristics (including medication) for the partially and remitted MDD groups. Furthermore, medication had no statistically significant influence on differences between remitted and partially remitted patients (see Table 2), nor on cognition in the whole MDD group, the partially remitted MDD group, or the remitted MDD group.

3.2. Differences of NPS performance between total MDD vs. HC group

MANOVA revealed a statistically significant difference in neuropsychological performance based on illness state (MDD vs. HCs), [$F(5, 124) = 2.722$, $p = 0.023$; Wilk's $\lambda = 0.901$, partial $\eta 2 = 0.099$ $d = 0.66$]. Illness state had a statistically significant effect on *attention* [$F(1, 128) = 7.14$; $p = 0.009$; partial $\eta 2 = 0.053$ $d = 0.47$], *learning and memory* [$F(1, 128) = 9.37$; $p = 0.003$; partial $\eta 2 = 0.068$ $d = 0.54$] and *working memory* [$F(1, 128) = 3.96$; $p = 0.049$; partial $\eta 2 = 0.03$ $d = 0.35$], with lower performance for the MDD group. Illness state did not have a statistically significant effect on *information processing speed* [$F(1, 128) = 3.9$; $p = 0.05$; partial $\eta 2 = 0.03$ $d = 0.35$] and on *executive function*. Mean z-scores, standard deviations and test statistics for NPS performance of total MDD group and HCs ($n = 65$; $n = 65$) are given in Table 3.

3.3. Impact of clinical variables on NPS performances in MDD

Factors that showed significant correlation with NPS performance in the entire (partially and remitted) MDD group on the nested testing approach were age, number of hospitalizations and age of onset (for detail see supplementary table S1). HAMD measuring symptom severity did not reach significance for correlation (supplementary table S1). Medication had no influence on any target variable. The backward stepwise regression model (with following integrated factors: age, number of hospitalizations and age of onset) for *NPS composite* was significant ($F(2,61) = 13.904$, $p < 0.001$, *adjusted* $R^2 = 0.291$). In the final model only age of onset ($ß = -0.436$, $p < 0.001$) and number of hospitalizations ($ß = -0.316$, $p = 0.004$) remained significant predictors. For *learning and memory* the backward stepwise regression model was significant ($F(1,62) = 15.974$, $p < 0.001$, *adjusted* $R^2 = 0.192$) with age ($ß = -0.453$, $p < 0.001$) as significant contributor in the final model. For *executive function* the backward stepwise regression model was significant ($F(2,61) = 11.314$, $p < 0.001$, *adjusted* $R^2 = 0.247$) with hospitalizations ($ß = -0.298$, $p = 0.010$) and age ($ß = -0.367$, $p = 0.002$) as significant contributors. The backward stepwise regression model for *information processing speed* was significant ($F(2,61) = 25.424$, $p < 0.001$, *adjusted* $R^2 = 0.437$) with age ($ß = -0.582$, $p < 0.001$) and number of hospitalizations ($ß = -0.238$, $p = 0.017$) as significant contributors in the final model. The backward stepwise regression model for *working memory* and *attention* did not reach significance. For detailed information about regression analysis see supplementary *Tables S2-S5*. Range, mean and standard deviation of the number of hospitalizations for the partially remitted, remitted and entire MDD group are given in Table 2. Scatter plots showing trend lines for correlation between NPS performance (*attention, learning and memory, executive function, Information processing speed, working memory and NPS composite*) and *number of hospitalizations* are provided in supplementary material Fig. S2.

3.4. Exploratory analysis: Differences in NPS performance due to remission state

MANOVA showed significant difference between the three groups (remitted vs. partial remitted vs. HCs) on overall cognitive functioning [$F(10, 246) = 2.080$, $p = 0.027$; Wilk's $\lambda = 0.850$, partial $\eta 2 = 0.078$ $d = 0.58$]. Bonferroni post hoc comparisons revealed statistically significant difference for *attention* [$F(2, 127) = 4.176$; $p = 0.018$; partial $\eta 2 = 0.062$ $d = 0.51$], with significantly lower scores ($p = 0.015$) for partial remitted patients compared to HCs (-0.3187, %- CI [$-0.5898, -0.0476$]); for *learning and memory* [$F(2, 127) = 5.015$; $p = 0.008$; partial $\eta 2 = 0.073$ $d = 0.56$], with significantly lower scores ($p = 0.009$) for partial remitted patients compared to HCs (-0.4117, %- CI [$-0.7407, -0.0828$]); and *information processing speed* [F

Table 3
MANOVA for comparison of NPS performance between total MDD group (n = 65) and HCs (n = 65).

Dependent variable	total MDD group (n = 65) *M, SD*	Controls (n = 65) *M, SD*	Independent variable (illness-state)
NPS Performance[b]			[F(5, 124) = 2.722, p = 0.023; Wilk's λ = 0.901, d = 0.66]
Attention	−0.0114 ± 0.587	0.2431 ± 0.495	F(1, 128) = 7.14; p = 0.009; d = 0.47
Learning and memory	−0.0002 ± 0.795	0.3529 ± 0.483	F(1, 128) = 9.37; p = 0.003; d = 0.54
Executive function	0.0572 ± 0.378	0.1651 ± 0.368	F(1,128) = 2.725, p = 0.101 d = 0.29
Information processing speed	0.0663 ± 0.763	0.3129 ± 0.658	F(1, 128) = 3.9; p = 0.05; d = 0.35
Working memory	−0.0194 ± 0.705	0.243 ± 0.797	F(1, 128) = 3.96; p = 0.049; d = 0.35

Note. M = mean; SD = standard deviation.
[b]Overall Model of neuropsychological performance.
*$p \leq 0.05$, two-tailed

(2,127) = 3.592 p = 0.03, partial η2 = 0.054, d = 0.48], with significant lower scores (p = 0.028) for partial remitted patients compared to HCs (−0.3833, %- CI [−0.7360, −0.0306]). Performance in *executive function* and *working memory* did not differ statistically significant for the three different groups. For detail see bar figures in supplementary material Fig. S1.

4. Discussion

The present study aimed to investigate NPS performance in (partially) remitted MDD patients and HCs and examined clinical factors that might contribute to their cognitive performance. Since persistence of cognitive deficits into remission has been described in literature to affect approximately between one-third and one-half of remitted patients (e.g., Jaeger et al., 2006; Reppermund et al., 2009), we expected worse cognitive performance in the entire MDD group versus HCs. Our results confirmed cognitive deficits in the entire MDD group with significantly worse performance in the domains of *attention, learning and memory, working memory* as well as overall neuropsychological performance, compared to individually matched HCs. The post hoc analysis for the separate groups based on remission state (partially remitted and remitted patients) compared to HCs showed the expected significant poorer performance of partially remitted patients compared to HCs in almost all cognitive domains. Our results did not detect significant differences between remitted MDD patients and HCs for NPS performance, even though remitted patients performed worse than HCs. When comparing partially remitted and remitted MDD patients, groups did not differ significantly. Also for this group comparison, it was evident from mean values for NPS performance that partially remitted patients exhibited poorer performance compared to remitted patients, although differences did not reach significance. Nevertheless, comparison with HCs indicate possible differences in cognitive performance in remitted vs. partially remitted state.

Existing discrepancies in literature about persistent cognitive deficits in remitted state, especially in the domain of attention and information processing speed, (Hasselbalch et al., 2012; Majer et al., 2004) and/or improvement of cognitive deficits in full remission (HAMD ≤7) (e.g., Biringer et al., 2005; Roca et al., 2015) might be due to several factors. One reason may be the heterogeneity in defining clinical remission (as shown in the three full, partial and full/partial remission together) “remission-state” groups in this study. Several studies report deficits in assumed ‘full’ remission (or at least not defined partial remission) included samples that might be defined more as ‘partially’ remitted patients: HAMD <9 the last week before discharge (Reppermund et al., 2009); 21-item HADRS ≤10 at discharge (Majer et al., 2004); just recovered after six weeks of treatment with unstable state (Xu et al., 2012). Likewise, studies reporting varying severity of cognitive deficits in remission could have been influenced by the length of reassessment interval in longitudinal designs (e.g., Biringer et al., 2005; Roca et al., 2015).

Another reason for existing discrepancies about persistent cognitive deficits might be the variability of clinical characteristics of the sample (e.g., number and duration of episodes, medication) (Elgamal et al., 2010). Worse performance might be due to higher impact of severity-related factors like longer duration of inpatient hospitalization (Neu et al., 2001). Our results showed clinical factors influencing cognitive performance, since higher number of hospitalizations, and earlier age of onset exerted a negative effect on NPS performance (see supplementary table S1). These results are in line with several other studies (Elgamal et al., 2010; Gorwood et al., 2008; Purcell et al., 1997; Westheide et al., 2007).

Other reasons might be the overall inconsistency in the measurement of symptom severity among studies (McClintock et al., 2010). Interestingly in our sample, severity of residual depressive symptoms, measured by HAMD and BDI-II, was not correlated with any of the NPS performances. These findings are in line with previous studies that found no measures (Elgamal et al., 2010) or only one measure (SWM test- executive function) (Reppermund et al., 2009) to be correlated with severity of symptoms. It may be that relatively low intensity of psychopathological symptoms in partial or full remission do not contribute to cognitive impairment (Reppermund et al., 2009), but may influence cognition at a higher level of symptom severity. Finally, there is a relatively lack of longitudinal studies measuring NPS performance in acute as well as partially and/or fully remitted states in the same individual.

In sum, the heterogeneity in defining clinical remission and the variability of clinical characteristics among samples might contribute to the lack of a definitive neuropsychological profile following MDD remission. As the cognitive profile and influencing factors might be different between remitted and partially remitted patients, an overall equivalent definition of partially remitted and remitted patients is lacking. This, too, might mask the differences in MDD remission throughout existing studies. Therefore, future studies should focus on these differences and employ more stringent remission definitions to acquire a better knowledge.

Further exploratory regression analyses in the entire MDD group revealed the number of hospitalizations as a clinical factor with significant independent contribution to performance on *NPS composite, executive function* and *information processing speed*.

This study indicates in a rather exploratory way that cognitive deficits in MDD and differences in performance between remitted and partially remitted MDD patients could be mediated by factors that contribute to a higher number of hospitalizations rather than by actual residual symptom severity. However, in the acute phase of MDD, current symptom severity may have a greater impact on cognition (Elderkin-Thompson et al., 2003; McDermott and Ebmeier, 2009). Our findings that the number of hospitalizations is associated with worse NPS performance is in agreement with existing literature, which reported patients with past hospitalization to be more impaired in *executive function* (Purcell et al., 1997) and *information processing speed* (Elgamal et al., 2010), compared to non-hospitalized patients or those with fewer hospitalizations. The covariate *number of hospitalizations* could therefore be an indicator for an underlying disease dimension, which may introduce greater scar effects (Allott et al., 2016) and

therefore mediate cognitive deficits in the pathogenesis of MDD. *Number of hospitalizations* was independent from acute symptom severity as measured by HAMD/BDI-II.

Various neurobiological alterations or causes of progressive neurocognitive scarring (Allott et al., 2016) that have been postulated to cause cognitive deficits could also be involved in the factor *number of hospitalizations*. Scarring associates the progressive decline in cognitive function with the onset/progression of MDD, and may represents a greater burden of illness with more severe underlying neurobiological alterations that cause the cognitive deficits rather than the current symptom severity (at least in different remission states) (Allott et al., 2016).

Neurobiological alterations could be, for instance, hypercortisolaemia (e.g., Gomez et al., 2009), low serum levels of brain-derived neurotrophic factor (e.g., Diniz et al., 2014), alterations in long-term synaptic plasticity (Nissen et al., 2010), and/or earlier cognitive decline due to potential early reversed calcium signalling (Grutzner et al., 2018). These various conditions may explain the unspecific impairment profile in MDD (Reppermund et al., 2009).

4.1. Limitations, directions for future research and conclusions

Causality between neurobiological alterations and remission state cannot be determined in this study. The factors that contribute to the variable *number of hospitalizations* could be various, and we are not aware of factors such as certain life events or higher burden of illness. As we cannot measure these possible other factors contributing to the variable *number of hospitalizations*, this has to be considered as a limitation of this study. Other limitations to be taken into account are the cross-sectional design of the study, that 'remission state' has not been the primary outcome variable, the possible contribution of age and sex, multiple comparisons and the risk of masking profile differences by pooling different test to a single domain as well as unknown effects of treatment.

The present study has several strengths such as the large total sample size (MDD group: $n = 65$), the one-to-one recruitment and matching strategy (on age, sex and education) ($n = 65$), and an extensive NPS test battery well-normed and suited for patients with MDD. In sum, the present results add important knowledge about the degree to which cognitive impairment persists into remission, and it outlines clinical variables influencing cognition in MDD. The topic of cognitive deficits in remission is important due to negative impacts on psychosocial functioning and possibly poorer quality of life (Rock et al., 2014) and the evidence that recovering from depression does not necessarily mean normalization of neuropsychological function. However, there is still a lack of knowledge about a definitive neuropsychological profile in remission of MDD. Therefore, more information is needed about cognitive function in remission and clinical variables influencing cognition in MDD. The results show poorer cognition in the entire MDD group, and in particular the partially remitted MDD group, compared to healthy controls, indicating that different MDD groups are affected differently by cognitive deficits. Furthermore, the results indicate that cognitive deficits in remission states do not depend on acute symptom severity, but rather on 'underlying disorder severity' or so called 'scar effects' (Allott et al., 2016) that may be reflected in the number of hospitalizations. If neurocognitive scarring is a mechanism of cognitive deficits in MDD, future research should focus on neuropsychological and biological interventions targeting these pathological mechanisms. Future studies should collect data on clinical variables in a more standardized way and should aim to include homogenous patient groups, taking into account illness-severity-related factors along the course of the disease. Furthermore, future studies should investigate differences between remitted and partially remitted patients in a longitudinal design, employing larger sample size. They should also examine the contribution of biological markers to their illness state, stimulating research on new drugs and neuropsychological treatments, see review on intervention in this area (Listunova et al., 2018), that target various underlying neurobiological alterations of MDD.

Author contributions

D.R.-E., A.S., M.W., M.B. and T.M.G. conceptualized and designed the study; T.M.G. and L.L. collected data; D.R.-E. provided infrastructure and clinical supervision; T.M.G., M.B. and A.S. analyzed the data; T.M.G. wrote the paper; M.B. D.R.-E. and A.S. reviewed the first draft of the manuscript; A.S., D.R.-E., M.B., M.W. and L.L. reviewed the final draft of manuscript. All authors have approved the final article.

Financial support

This work was supported by a grant (number 2016050362) from the Stiftungen Landesbank Baden-Württemberg to Research Group Neurocognition, a grant from the Richard-Winter-Stiftung to Thea Marianne Grützner and a grant from Majic/Majic-Schlez-Stiftung to Anuradha Sharma. Anuradha Sharma was supported by the Physician Scientist Program of the Medical Faculty of the University of Heidelberg during the period of this research. The computerized test battery CogBat® and WAF-S test of the Vienna test system (WTS, (Wiener Testsystem, 2012) was provided by Schuhfried GmbH, Mödling.

Acknowledgments

We greatly appreciate the assistance of Ms. Dilara Köse, Ms. Myriam Guderjan, Ms. Michelle Ohler, Ms. M. Sc.-Psych. Isabelle Rek and Ms. M. Sc.-Psych. Johanna Kienzle with data collection and management. We thank Ms. Kerstin Herwig for managing the organizational and administrative aspects of the project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.047.

References

aan het Rot, M., Mathew, S.J., Charney, D.S., 2009. Neurobiological mechanisms in major depressive disorder. CMAJ 180 (3), 305–313.

Ackenheil, M., Stotz, G., Dietz-Bauer, R., Vossen, A., 1999. M.I.N.I. Mini International Neuropsychiatric Interview. German Version 5.0.0. DSM-IV., München.

Afridi, M.I., Hina, M., Qureshi, I.S., Hussain, M., 2011. Cognitive disturbance comparison among drug-naive depressed cases and healthy controls. J Coll Physicians Surg Pak 21 (6), 351–355.

Allott, K., Fisher, C.A., Amminger, G.P., Goodall, J., Hetrick, S., 2016. Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? Brain Behav 6 (10), e00527.

Aster, M.v., Neubauer, A., Horn, R., 2009. Wechsler-intelligenztest für erwachsene WIE. Pearson Assessment & Information GmbH, Frankfurt am Main.

Baune, B.T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., Mitchell, D., 2010. The role of cognitive impairment in general functioning in major depression. Psychiatry Res 176 (2–3), 183–189.

Beblo, T., 2016. Die Bedeutung kognitiver Beeinträchtigung bei depressiven Patienten. Zeitschrift für Neuropsychologie 27 (2), 69–83.

Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., et al., 2005. Executive function improvement upon remission of recurrent unipolar depression. Eur Arch Psychiatry Clin Neurosci 255 (6), 373–380.

Biringer, E., Mykletun, A., Sundet, K., Kroken, R., Stordal, K.I., Lund, A., 2007. A longitudinal analysis of neurocognitive function in unipolar depression. J Clin Exp Neuropsychol 29 (8), 879–891.

Bora, E., Harrison, B.J., Yucel, M., Pantelis, C., 2013. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol Med 43 (10), 2017–2026.

Diniz, B.S., Teixeira, A.L., Machado-Vieira, R., Talib, L.L., Radanovic, M., Gattaz, W.F., et al., 2014. Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. J Gerontol B Psychol Sci Soc Sci 69 (6), 845–851.

Douglas, K.M., Porter, R.J., 2009. Longitudinal assessment of neuropsychological function in major depression. Aust N Z J Psychiatry 43 (12), 1105–1117.

Dunkin, J.J., Leuchter, A.F., Cook, I.A., Kasl-Godley, J.E., Abrams, M., Rosenberg-Thompson, S., 2000. Executive dysfunction predicts nonresponse to fluoxetine in

major depression. J Affect Disord 60 (1), 13–23.
Elderkin-Thompson, V., Kumar, A., Bilker, W.B., Dunkin, J.J., Mintz, J., Moberg, P.J., et al., 2003. Neuropsychological deficits among patients with late-onset minor and major depression. Arch Clin Neuropsychol 18 (5), 529–549.
Elderkin-Thompson, V., Mintz, J., Haroon, E., Lavretsky, H., Kumar, A., 2006. Executive dysfunction and memory in older patients with major and minor depression. Arch Clin Neuropsychol 21 (7), 669–676.
Elgamal, S., Denburg, S., Marriott, M., MacQueen, G., 2010. Clinical factors that predict cognitive function in patients with major depression. Can J Psychiatry 55 (10), 653–661.
Fydrich, T., Renneberg, B., Schmitz, B., Wittchen, H.-U., 1997. SKID-II. strukturiertes klinisches interview für DSM-IV. Achse II: persönlichkeitsstörungen. Interviewheft. Hogrefe-Verlag GmbH & Co, KG, Göttingen.
Gauggel, S., Sturm, W., 2005. Leitlinien der Gesellschaft für Neuropsychologie (GNP) für neuropsychologische Diagnostik und Therapie. Zeitschrift für Neuropsychologie 16 (4), 175–199.
Gomez, R.G., Posener, J.A., Keller, J., DeBattista, C., Solvason, B., Schatzberg, A.F., 2009. Effects of major depression diagnosis and cortisol levels on indices of neurocognitive function. Psychoneuroendocrinology 34 (7), 1012–1018.
Gorwood, P., Corruble, E., Falissard, B., Goodwin, G.M., 2008. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. Am J Psychiatry 165 (6), 731–739.
Grutzner, T.M., Listunova, L., Fabian, G.A., Kramer, B.A., Flach, D., Weisbrod, M., et al., 2018. Serum calcium levels and neuropsychological performance in depression and matched healthy controls: Reversal of correlation a marker of the aging cognitive clock? Psychoneuroendocrinology 91, 198–205.
Guy, W., Bonato, R.R., 1970. Manual for the ECDEU assessment battery. U.S. Department of Health, Education, and Welfare, National Institute of Mental Health.
Hamilton, M., 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23, 56–62.
Hammar, A., Ardal, G., 2013. Verbal memory functioning in recurrent depression during partial remission and remission-brief report. Front Psychol 4, 652.
Hasselbalch, B.J., Knorr, U., Hasselbalch, S.G., Gade, A., Kessing, L.V., 2012. Cognitive deficits in the remitted state of unipolar depressive disorder. Neuropsychology 26 (5), 642–651.
Hasselbalch, B.J., Knorr, U., Kessing, L.V., 2011. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J Affect Disord 134 (1-3), 20–31.
Hautzinger, M., Keller, F., Kühner, C., 2006. BDI II – Beck Depressions-Inventar – Manual. Harcourt Test Services GmbH, Frankfurt am Main.
Iovieno, N., van Nieuwenhuizen, A., Clain, A., Baer, L., Nierenberg, A.A., 2011. Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse. Depress Anxiety 28 (2), 137–144.
Jaeger, J., Berns, S., Uzelac, S., Davis-Conway, S., 2006. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res 145 (1), 39–48.
Kaneda, Y., 2009. Verbal working memory impairment in patients with current episode of unipolar major depressive disorder and in remission. Clin Neuropharmacol 32 (6), 346–347.
Kellner, C.H., Knapp, R.G., Petrides, G., Rummans, T.A., Husain, M.M., Rasmussen, K., et al., 2006. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 63 (12), 1337–1344.
Kyle, P.R., Lemming, O.M., Timmerby, N., Sondergaard, S., Andreasson, K., Bech, P., 2016. The validity of the different versions of the Hamilton Depression Scale in separating remission rates of placebo and antidepressants in clinical trials of major depression. J Clin Psychopharmacol 36 (5), 453–456.
Lee, R.S., Hermens, D.F., Porter, M.A., Redoblado-Hodge, M.A., 2012. A meta-analysis of cognitive deficits in first-episode major depressive disorder. J Affect Disord 140 (2), 113–124.
Lee, T.W., Liu, H.L., Wai, Y.Y., Ko, H.J., Lee, S.H., 2013. Abnormal neural activity in partially remitted late-onset depression: an fMRI study of one-back working memory task. Psychiatry Res 213 (2), 133–141.
Lehrl, S., 2005. Mehrfachwahl-wortschatz-intelligenztest MWT-B. Spitta Verlag GmbH & Co., KG, Balingen.
Liao, W., Zhang, X., Shu, H., Wang, Z., Liu, D., Zhang, Z., 2017. The characteristic of cognitive dysfunction in remitted late life depression and amnestic mild cognitive impairment. Psychiatry Res 251, 168–175.
Listunova, L., Roth, C., Bartolovic, M., Kienzle, J., Bach, C., Weisbrod, M., et al., 2018. Cognitive impairment along the course of depression: non-pharmacological treatment options. Psychopathology 1–11.
Majer, M., Ising, M., Kunzel, H., Binder, E.B., Holsboer, F., Modell, S., et al., 2004. Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders. Psychol Med 34 (8), 1453–1463.
McClintock, S.M., Husain, M.M., Greer, T.L., Cullum, C.M., 2010. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. Neuropsychology 24 (1), 9–34.
McDermott, L.M., Ebmeier, K.P., 2009. A meta-analysis of depression severity and cognitive function. J Affect Disord 119 (1–3), 1–8.
McLaren, M.E., Szymkowicz, S.M., Kirton, J.W., Dotson, V.M., 2015. Impact of education on memory deficits in subclinical depression. Arch Clin Neuropsychol 30 (5), 387–393.
Merens, W., Booij, L., Van Der Does, A.J., 2008. Residual cognitive impairments in remitted depressed patients. Depress Anxiety 25 (6), E27–E36.
Murrough, J.W., Iacoviello, B., Neumeister, A., Charney, D.S., Iosifescu, D.V., 2011. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem 96 (4), 553–563.
Nandrino, J.L., Pezard, L., Poste, A., Reveillere, C., Beaune, D., 2002. Autobiographical memory in major depression: a comparison between first-episode and recurrent patients. Psychopathology 35 (6), 335–340.
Neu, P., Kiesslinger, U., Schlattmann, P., Reischies, F.M., 2001. Time-related cognitive deficiency in four different types of depression. Psychiatry Res 103 (2–3), 237–247.
Niemann, H., Sturm, W., Thöne-Otto, A.I.T., Willmes, K., 2008. California verbal learning test (CVLT). Deutsche adaptation. Pearson Assessment & Information GmbH, Frankfurt am Main.
Nissen, C., Holz, J., Blechert, J., Feige, B., Riemann, D., Voderholzer, U., et al., 2010. Learning as a model for neural plasticity in major depression. Biol Psychiatry 68 (6), 544–552.
Paykel, E.S., 2008. Partial remission, residual symptoms, and relapse in depression. Dialogues Clin Neurosci 10 (4), 431–437.
Preiss, M., Kucerova, H., Lukavsky, J., Stepankova, H., Sos, P., Kawaciukova, R., 2009. Cognitive deficits in the euthymic phase of unipolar depression. Psychiatry Res 169 (3), 235–239.
Purcell, R., Maruff, P., Kyrios, M., Pantelis, C., 1997. Neuropsychological function in young patients with unipolar major depression. Psychol Med 27 (6), 1277–1285.
Ravnkilde, B., Videbech, P., Clemmensen, K., Egander, A., Rasmussen, N.A., Rosenberg, R., 2002. Cognitive deficits in major depression. Scand J Psychol 43 (3), 239–251.
Reppermund, S., Ising, M., Lucae, S., Zihl, J., 2009. Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. Psychol Med 39 (4), 603–614.
Roca, M., Lopez-Navarro, E., Monzon, S., Vives, M., Garcia-Toro, M., Garcia-Campayo, J., et al., 2015. Cognitive impairment in remitted and non-remitted depressive patients: a follow-up comparison between first and recurrent episodes. Eur Neuropsychopharmacol 25 (11), 1991–1998.
Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 44 (10), 2029–2040.
Ruchsow, M., Groen, G., Kiefer, M., Beschoner, P., Hermle, L., Ebert, D., et al., 2008. Electrophysiological evidence for reduced inhibitory control in depressed patients in partial remission: a Go/Nogo study. Int J Psychophysiol 68 (3), 209–218.
Rush, A.J., Kraemer, H.C., Sackeim, H.A., Fava, M., Trivedi, M.H., Frank, E., et al., 2006. Report by the ACNP task force on response and remission in major depressive disorder. Neuropsychopharmacology 31 (9), 1841–1853.
Sarosi, A., Gonda, X., Balogh, G., Szekely, A., Sasvari, M., Faludi, G., 2008. Gender differences in the neurocognitive components of depression. Neuropsychopharmacol Hung 10 (4), 191–199.
Saß, H., Wittchen, H.-U., Zaudig, M., Houben, I., 2003. Diagnostisches und statistisches manual psychischer störungen -textrevision- DSM-IV-TR. Hogrefe-Verlag GmbH & Co, KG, Göttingen, DE.
Schatzberg, A.F., 2015. Anna-Monika award lecture, DGPPN Kongress, 2013: the role of the hypothalamic-pituitary-adrenal (HPA) axis in the pathogenesis of psychotic major depression. World J Biol Psychiatry 16 (1), 2–11.
Schmid, M., Strand, M., Ardal, G., Lund, A., Hammar, A., 2011. Prolonged impairment in inhibition and semantic fluency in a follow-up study of recurrent major depression. Arch Clin Neuropsychol 26 (7), 677–686.
Story, T.J., Potter, G.G., Attix, D.K., Welsh-Bohmer, K.A., Steffens, D.C., 2008. Neurocognitive correlates of response to treatment in late-life depression. Am J Geriatr Psychiatry 16 (9), 752–759.
Strand, M., Oram, M.W., Hammar, A., 2013. Emotional information processing in major depression remission and partial remission: faces come first. Appl Neuropsychol Adult 20 (2), 110–119.
Trivedi, M.H., Greer, T.L., 2014. Cognitive dysfunction in unipolar depression: implications for treatment. J Affect Disord 152–154, 19–27.
Westheide, J., Wagner, M., Quednow, B.B., Hoppe, C., Cooper-Mahkorn, D., Strater, B., et al., 2007. Neuropsychological performance in partly remitted unipolar depressive patients: focus on executive functioning. Eur Arch Psychiatry Clin Neurosci 257 (7), 389–395.
Wiener Testsystem, 2012. Schuhfried GmbH, Mödling.
Wiener Testsystem, 2013. Manual, Mödling.
Williams, J.B., 2001. Standardizing the Hamilton Depression Rating Scale: past, present, and future. Eur Arch Psychiatry Clin Neurosci 251 (Suppl. 2) Ii6-12.
Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1997. SKID I. strukturiertes klinisches interview für DSM-IV. Achse I: psychische störungen. interviewheft. Hogrefe-Verlag, Göttingen, pp. 7–9.
Xu, G., Lin, K., Rao, D., Dang, Y., Ouyang, H., Guo, Y., et al., 2012. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J Affect Disord 136 (3), 328–339.
Yeh, Y.C., Tsang, H.Y., Lin, P.Y., Kuo, Y.T., Yen, C.F., Chen, C.C., et al., 2011. Subtypes of mild cognitive impairment among the elderly with major depressive disorder in remission. Am J Geriatr Psychiatry 19 (11), 923–931.
Zimmerman, M., Martinez, J., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., et al., 2012. Further evidence that the cutoff to define remission on the 17-item Hamilton Depression Rating Scale should be lowered. Depress Anxiety 29 (2), 159–165.