Paper II

Original investigation

Changes in neurocognitive function associated with remission of unipolar depression: a longitudinal study

Running head: Cognitive changes in depression

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Abstract

Objective: The present study investigated if improvement in neurocognitive functioning follows improvement in depression.

Method: Thirty patients with DSM-IV diagnosis of recurrent major unipolar depression were tested twice, two years apart.

Results: Improvement in verbal memory function followed improvement in depression (r= .34, p=0.037, one-tailed). However, no association between improvement of depression and improvement in attention, visual memory function, or psychomotor speed was found (r= .02, .08, and .04, respectively). Recovered patients (HAM-D ≤ 7, n =17) performed better than in the depressed state in these domains, but poorer than healthy controls (group differences 0.3 to 0.5 SD in favour of the controls, n.s.).

Conclusion: Remission of depression was associated with improvement in verbal memory function, but not in other dimensions of neurocognitive function. There is no support in our study for complete neurocognitive recovery after depression. Longitudinal studies with baseline screenings before onset of any mental disorder are needed.

Key words: major depression; longitudinal; neurocognitive; verbal memory

Introduction

Cross-sectional studies have repeatedly shown that depressed patients perform below the results of normal controls on tests of neurocognitive functioning (1-3). However, the temporal relationship between depressive symptomatology and levels of neurocognitive functioning remains unresolved. Important issues to address include: Does neurocognitive function improve after remission of the depressive symptoms, and if so, to what degree? And is duration of depression associated with persistent changes in neurocognitive function? If changes in neurocognitive function in depression are irreversible, then neurocognitive function could represent a "trait marker", which again may reflect some of the underlying pathobiology of depression.

Several cross-sectional studies have compared neurocognitive functioning in recovered patients with that of depressed patients and healthy controls, and conflicting results have been reported (4-8). There exist a few longitudinal studies investigating whether neurocognitive function improves more in treatment responders than in non-responders. Beblo et al. (1999) reported that treatment responders, in contrast to non-responders, improved their performance significantly on measures of attention and fluency, but not on measures of verbal memory (9). Tarbuck and Paykel (1995) showed that remission of the depressive symptoms was associated with improvement in attention, memory, and verbal fluency (10). However, Reischies and Neu (2000) found no significant difference in change of test performance between a group of remitted patients and a group of healthy controls on measures of attention, verbal memory, visual memory, and verbal fluency (11). Relevant objections to these studies of the hypothesised association between improvement in depressive symptomatology and neurocognitive function may include the short follow-up intervals (1-9 months) and the diagnostic heterogeneity within the samples studied (9-11).

The hypothesised association between improvement in depressive symptomatology and improvement in neurocognitive function has also been studied with continuous (rather than categorical) measures, which is probably a preferred approach, as it excludes misclassification in individuals scoring close to cut-off, and as it captures more of the variance. Again, results have been conflicting. Trichard et al. (1995) found a positive correlation between improvement of depression and improvement of semantic fluency (8). However, Neu et al. (2001) found no correlation between improvement of depression and improvement on measures of attention, fluency, and visual and verbal memory (12). Thus, it is not yet clear if remission of depressive symptoms is associated with improvement of cognitive function in depression.

The neurobiological causes that underlie depression-associated changes in neurocognitive function are not known. Functional brain-imaging studies and positron emission tomography (PET) studies have shown that patterns of blood flow and glucose metabolism are altered during depressive episodes, and that such disturbances improve upon recovery (13-18). It has been hypothesised that prolonged, excessive and dysfunctional secretion of glucocorticoids can cause neuronal loss and subsequent cognitive reduction (19-22). Several studies have suggested that longer duration of depression is associated with volume changes in hippocampus and amygdala (20, 22). On this basis, one would expect that increased duration of depression may be associated with poorer performance on neurocognitive tasks after remission of the depressive symptoms. Support for this hypothesis was reported by Beats et al. (1996), who showed that number of depressive episodes was correlated with response latencies on performance measures in remitted patients (23). However, Neu et al. (2001) found no such correlation (12), and several cross-sectional studies that have investigated

neurocognitive performance in recovered patients have failed to show any association with depression duration or number of depressive episodes with neurocognitive function (11, 24-27). Thus, it remains unclear whether cognitive function deteriorates with increased duration of depression.

Aims of the study

1) to assess if neurocognitive function improves during remission of recurrent unipolar depression, 2) to investigate to what extent neurocognitive function returns to normal after remission of symptoms, and 3) to investigate if duration of depression, or number of depressive episodes, are associated with degree of improvement in neurocognitive function upon remission from depression.

Methods

Sample

Thirty subjects from a sample of 50 patients with a DSM-IV diagnosis of recurrent major unipolar depression (28, 29) were re-examined with psychiatric and neuropsychological measures after a mean test re-test interval of 26.3 months (standard deviation SD=6.1, range 15.3-40.0 months). Inclusion criteria at baseline (T1) was a history of two or more episodes of major depression of recurrent unipolar sub-type, and the patients had to be having a depressive episode as defined by scoring 18 points or above on both the 17-item Hamilton Depression Rating Scale (HAM-D) (30) and the Montgomery Aasberg Depression Rating Scale (MADRS) (31). Twenty-six patients received medication, and no major alterations in medication were performed before testing (Table 1). Benzodiazepines and other tranquilising agents were avoided on the day of examination. At follow-up (T2), depressive symptomatology was re-assessed

employing HAM-D. Evaluation of diagnosis and level of depressive symptomatology was performed by experienced psychiatrists at T1 and T2. Out of the 50 patients included at T1, three were deceased at T2, two were excluded because they had experienced a manic episode, and fifteen subjects did not respond to the invitation to participate in the follow-up examination. There were no significant group differences with regard to sociodemographic or clinical variables, level of functioning (as measured by the Global Assessment of Functioning Scale (GAF)(28)), general intellectual abilities (as measured by the Similarities and the Picture Completion sub-tests from the Wechsler Adult Intelligence Scale-revised (WAIS-R)(32)), or medication (medicated/non-medicated) at T1 between the retested subjects (N=30) and the retest non-attendees (N=20) (for drop-out analysis, see Biringer et al. (2004) (33)). At T2, 17 subjects were recovered from depression (HAM-D cut-off ≤7, sub-group mean HAM-D =2.7 (SD=2.2)), and 13 were non-recovered (HAM-D cut-off ≥8, sub-group mean HAM-D =15.4 (5.8)).

The study was approved by the Regional Committee for Medical Ethics and it was performed in accordance with the Helsinki Declaration of the World Medical Association Assembly. All participants provided written informed consent to participate in the study both at inclusion and at follow-up. The study was funded by the Norwegian Research Council.

-Please insert Table 1 here-

Neurocognitive tests

Seventeen sub-tasks from eight neurocognitive tests were selected from a broader test battery (32, 34-36). Thirteen of these measures have previously been shown to be sensitive to depression (37-39). The tests were administered by trained test technicians.

Tests, selected sub-tasks, abbreviations, and descriptive statistics (raw-scores) of the sub-tasks at T1 and T2 are presented in Table 2.

-Please insert Table 2 here-

Neurocognitive operationalisation

The Stroop C, Stroop W, Stroop C/W, WCST Pres, and CalCAP SRT raw-scores were reverse-scaled so that all variables were scored with higher values indicating good performance. Change-scores and z-scores (standardised scores) of change from T1 to T2 were computed by subtracting T1-scores from T2-scores (Table 2).

Based on a priori theoretical evaluations of the neurocognitive test measures, grouping of the measures into the following conceptually meaningful domains of function was done: attention, verbal memory function, visual memory function, and psychomotor speed. Operationalisation was performed in a large (n=100) sample consisting of the total baseline depressed sample (n=50) and a sample of comparable healthy controls (n=50) examined at T1 (see (37)). The 17 selected sub-tasks were entered as input variables in a PCA with varimax rotation. Four distinct factors with eigenvalues >1 emerged, these factors explained 71% of the variance (Table 3). The PCA supported the a priori four-factor structure. Four summary-scores for neurocognitive function were computed in accordance with the factor structure, and items with weak factor loadings were omitted (Table 3). CVLT Total and CVLT SF were equally correlated with the total factor score, but CVLT Total was excluded from the summary scale because it reduced the inter-scale correlation more than the other CVLT measures when the "alpha if item deleted"-reliability procedure was performed. The correlations between the summary scales and the total factor scores were in the range 0.97 to 1.00, indicating that the summary scales could replace the full factor

scores without substantial loss of information (see Friis et al. (2002) (40)). Internal reliabilities, as assessed by Cronbach's alphas, were: 0.97 for verbal memory function, 0.81 for attention, 0.43 for psychomotor speed, and 0.78 for visual memory function. Intercorrelations between the summary scales were in the range 0.25 to 0.59 (Table 4).

-Please insert Table 3 here-

-Please insert Table 4 here-

Statistical analyses

Pearson's correlation coefficients were computed between the change in HAM-D and the neurocognitive change-scores, in order to evaluate if remission of depressive symptoms was correlated with change in test performance from T1 to T2 (Figure 1).

Group differences in change-scores between recovered and non-recovered patients were evaluated by independent-samples t tests.

In order to assess the degree to which neurocognitive function returned to normal levels after recovery from the depressive symptoms at T2, summary scales of z-scores from raw-scores for the four neurocognitive dimensions were computed at T1 and at T2. Group comparisons with regard to differences on the summary scales were made between the depressed patients and the controls at T1, and between controls at T1 and recovered patients at T2. The latter comparison was done by using a data set consisting of T1 values from the healthy control group (n=50) and T2 values from the re-tested patient sample (n=30).

To investigate if duration of the disorder predicted improvement in neurocognitive function, Pearson's correlation coefficients r were computed between duration of depression or number of depressive episodes as reported at T1, and the neurocognitive summary scales of change from T1 to T2 (Figure 2).

In the analyses that involved group comparisons, skewed variables (raw-variables or summary scales) were log- or power- transformed. Significance was reported from analyses with the transformed variables. Correlation coefficients and group differences in standard deviations of the sample means were reported from the non-transformed variables. The tests were two-tailed with an alpha level of 0.05, except for the analyses performed on change-scores, which were one-tailed (as only positive hypotheses of direction of effect were relevant). Statistical procedures were performed using SPSS 11.5.

Results

Does neurocognitive function improve during remission of recurrent unipolar depression?

Scatterplots with regression lines for the associations of change in HAM-D score with change of the neurocognitive summary scales are presented in Figure 1. Improvement in verbal memory function followed improvement in depression (r=0.34, p=0.037, one-tailed). For the other three neurocognitive domains, no associations were found (r .02 to .08, p>.05). The correlations between change in HAM-D and CVLT SC, and between change in HAM-D and change in CVLT LF were significant (r= .39, p=0.018, one-tailed; and r= .42, p=0.013, one-tailed, respectively).

-Please insert Figure 1 here-

Recovered versus non-recovered subjects

In the categorical analyses with recovered (n=17) and non-recovered (n=13) subject sub-groups (based on HAM-D score at T2), the recovered sub-group improved significantly more on the verbal memory summary scale of change than did non-

recovered subjects (p=0.011, one-tailed). The improvement was significantly larger in the recovered sub-group compared to the non-recovered group on the following measures: PASAT2 (p=0.021,one-tailed), CVLT SC (p=0.005, one-tailed), CVLT LF (p=0.005, one-tailed), CVLT LC (p=0.035, one-tailed), and RCFT Rec (p=0.013, one-tailed). The groups did not differ with regard to change on either of the other single measures, or on the attention-, visual memory-, or psychomotor speed summary scales of change (p=0.465, p=0.336, and p=0.420, respectively, one-tailed).

Does neurocognitive function return to ”normal” after recovery from depression?

At baseline, depressed patients performed more poorly than healthy controls on three of four reported neurocognitive dimensions (Figure 2). Mean group-differences were 0.7 SD for attention (95% CI 0.4 – 1.1), 0.4 SD (95% CI -0.1– 0.7) for verbal memory function, 0.9 SD for visual memory function (95% CI 0.5 – 0.9), and 1.2 SD (95% CI 0.8 – 1.6) for psychomotor speed summary scales. Consistent with our research hypothesis, recovered patients (HAM-D ≤ 7, n=17) performed better than in the depressed state in these three domains, but still performed more poorly than healthy controls (Figure 2). However, only differences in psychomotor speed were statistically significant. The lack of significance in the three other domains may reflect type II errors due to low power in the recovered sub-group (n=17).

-Please insert Figure 2 here-

Is duration of disease associated with degree of improvement in cognitive performance during remission?

Duration of depression and number of depressive episodes were not associated with degree of improvement in neurocognitive function. Non-significant associations were negative, that is, contrary to our research hypotheses (*r,* -0.09 to -0.33, $p>0.05$) .

Discussion

Improvement in neurocognitive functioning was positively correlated with improvement in depression in one of four examined cognitive domains (verbal memory function, $r=.34$, $p=0.037$, one-tailed). No association was observed between improvement of depressive symptomatology and improvement in test performance for the other three examined domains (*r* in the range .02 to .08). Recovered patients (HAM-D≥7) performed in the range 0.3-0.5 SD below healthy controls on the attention, visual memory function, and psychomotor speed summary scales (n.s.). Thus, there is little support in our study for complete neurocognitive recovery after a depressive episode. Several other authors have also reported that remitted patients perform more poorly than controls on measures of attention, memory function, and psychomotor speed (6-8). Paradiso et al. (1997) reported effect sizes for the group differences between remitted unipolar patients and controls on measures of attention, psychomotor speed, and verbal memory in the range of one fourth to one standard deviation of the sample mean in favour of the controls (7). However, rest-symptomatology may have increased the effect sizes for the differences in that study (mean HAM-D in the patient group was 9.2 at re-testing).

Our finding that remission was associated with improvement in verbal memory function was consistent both when we used a linear approach to depressive symptomatology, and when patients were divided into recovered and non-recovered categories according to their HAM-D total score at re-testing ($p=0.011$, one-tailed).

However, the improvement of verbal memory function up to a level comparable to that of healthy controls in our study contrasts with several other studies (7, 9, 11, 12). The shorter test re-test intervals in these studies (mean intervals 3-9 months) may explain the discrepancy between the results of these studies and the present study; such short test intervals may not provide long enough time for subjects to recover completely cognitively.

In our study, duration of illness was not predictive of improvement of neurocognitive during recovery. This is in agreement with Neu et al. (2001) (12), and with findings from cross-sectional studies that have investigated the association between estimates of disease duration and neurocognitive performance in depressed or recovered patients (11, 24-27). These findings suggest that longer duration of disease does not lead to progressive deterioration of neurocognitive function.

Several factors may influence the degree to which neurocognitive function improves during recovery from depression. In other words, there may be multiple explanations for our finding that improvement in neurocognitive function does not correlate more strongly with improvement in depression (Figure 1), and that neurocognitive function does not seem to return entirely to the level of healthy controls after recovery (Figure 2). Possible explanations include: (1) premorbid levels of functioning may have been lower in persons who later developed depression (41, 42), (2) patients may have experienced loss of function caused by hospitalisation or treatment, (3) in depressed patients, there may be pathobiological changes (either being present prior to the first depressive episode, or arising in the course of the disorder), that may affect neurocognitive function in a negative way, (4) patients may have personality traits that influence performance in the test situation negatively (43, 44), and (5)

neuropsychological recovery may be delayed compared to improvement of depression beyond the time frame used in this study.

However, the present study was performed on a homogeneous sample of fairly young patients who had been diagnosed and included in the study according to DSM-IV criteria for unipolar depression with recurrent episodes, with a test re-test interval that was probably long enough (approximately two years) to allow neurocognitive recovery to occur. Effort was made to make a reliable neurocognitive operationalisation, and the operationalisation was based on theoretical considerations about neurocognitive constructs and test qualities, empirically supported by factor analysis and measures of internal consistencies within dimensions.

One limitation in this study is the low statistical power, in particular in the comparisons of recovered patients (n=17) with non-recovered patients (n=13), depressed patients (n=50), and healthy controls (n=50). However, we are careful about drawing conclusions based on results of analyses performed on single test measures. But low power can probably not explain the lack of association between improvements in three neurocognitive domains and improvement in depression. A further limitation in studies like ours, are problems of reliability of measures included for both neurocognitive function and depression. Despite use of reliable measures for depression and strong emphasis on psychometrics in measuring neurocognitive function, we cannot exclude underestimation of associations as a consequence of imperfect reliability. Further limitations could include learning effects when re-testing individuals after two years, and the possibility of selection bias (most subjects were in-patients, and thus subjects with poorer functioning may be overrepresented, compared to those whose level of functioning was less affected).

Conclusion

In our study, remission of depressive symptomatology was associated with improvement of verbal memory function, but not with improvement of attention, visual memory functioning, or psychomotor speed. Our findings thus support the view that there is incomplete neurocognitive recovery following recovery from depression, when neurocognitive recovery is defined as functioning equal to that of healthy controls. However, longitudinal studies that include baseline screenings before the onset of any mental disorder are needed, to elucidate the exact extent to which neurocognitive function may return to premorbid levels after recovery. Future studies should also include sufficient numbers of participants in order to avoid problems caused by low statistical power.

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Table 1. Sample characteristics (*n*=30)

	Mean	SD	Range	*n* T1	*n* T2
Age, years	35.8	8.4	20-50		
Education, years	13.8	3.0	9-19		
Intellectual abilities					
WAIS-R Picture completion					
scaled scores	9.9	2.9	5-17		
WAIS-R Similarities					
scaled scores	10.6	3.3	4-17		
Lifetime number of episodes	3.8	1.2	2-5		
Total disease duration, years	13.6	9.3	1-32		
Sex, male/female				12/18	
Handedness, left/right				28/2	
Hospitalisation (in-patients)				20	0
Work status					
Employed				12	13
Students				4	2
Sick leave or disability pension				14	14
No income				0	1
Medication					
SSRI				21	20
Other antidepressants				7	6
Neuroleptics				7	4
Sedatives				14	9

Table 2. Mean raw-scores at T1 and T2, and mean standardised change scores (scores at T1 subtracted from scores at T2) (*n*=30)

	Mean (SD) T1	Mean (SD) T2	Mean standardised change (T2 minus T1)
Depression			
HAM-D total score	21.8 (3.2)	8.2 (7.6)	1.5
Attention			1.4
Paced Auditory Serial Addition Test			
3-second interstimulus interval (PASAT3)	43.7 (13.1)	47.6 (12.2)	0.3
2-second interstimulus interval (PASAT2)	36.9 (13.0)	40.5 (10.5)	0.3
WAIS-R Digit Span			
Forward (WAIS-R Dsf)	7.1 (2.2)	7.8 (2.3)	0.3
Backward (WAIS-R Dsb)	5.2 (1.5)	6.0 (2.1)	0.5
Wisconsin Card Sorting Test			
Perseverative responses (WCST Pres)[a]	15.7 (11.7)	9.2 (7.4)	0.6
Verbal memory function			1.8
California Verbal Learning Test			
List A Total recall (CVLT Total)[a]	54.5 (11.22)	60.4 (8.96)	0.6
List A Short delayed free recall (CVLT SF)	11.6 (3.2)	13.1 (2.3)	0.5
List A Short delayed cued recall (CVLT SC)	12.3 (2.8)	13.5 (2.4)	0.5
List A Long delayed free recall (CVLT LF)	12.0 (3.2)	13.1 (2.7)	0.4
List A Long delayed cued recall (CVLT LC)	12.4 (3.1)	13.6 (2.3)	0.4
Visual memory function			0.4
Rey Complex Figure Test			
Short delayed recall (RCFT Del)	19.9 (6.5)	20.1 (6.1)	0.0
Delayed recognition (RCFT Rec)	19.9 (3.3)	20.8 (1.5)	0.4
Psychomotor speed			1.7
Stroop Colour and Word Test			
Color (Stroop C)	30.1 (7.6)	27.6 (5.2)	0.4
Word (Stroop W)[b]	20.3 (6.7)	17.3 (4.8)	0.5
Color-word (Stroop C/W)	56.8 (14.0)	51.2 (13.8)	0.4
California Computerized Assessment Package			
Simple reaction time (CalCAP SRT)	362.5 (82.8)	328.3 (74.8)	0.4
Controlled Oral Word Association Test			
Phonetic fluency (COWAT Phon)[a]	23.6 (7.6)	25.8 (9.05)	0.3

[a] Test-measure not included in summary scale

Table 3. Rotated factor loadings of the 17 selected neurocognitive measures T1 (*n*=100)

Selected neurocognitive sub-tasks	Verbal memory	Attention	Psycho-motor speed	Visual memory
California Verbal Learning Test				
List A Total recall[a]	**0.88**	0.14	0.17	0.02
List A Short delayed free recall	**0.89**	0.18	0.22	0.08
List A Short delayed cued recall	**0.92**	0.16	0.09	0.14
List A Long delayed free recall	**0.90**	0.22	0.22	0.12
List A Long delayed cued recall	**0.93**	0.18	0.13	0.08
Paced Auditory Serial Addition Test				
3-second interstimulus interval	0.19	**0.78**	0.20	0.16
2-second interstimulus interval	0.35	**0.74**	0.25	0.09
WAIS-R Digit Span				
Forward	-0.05	**0.71**	0.20	0.02
Backward	0.14	**0.72**	0.15	-0.10
Wisconsin Card Sorting Test				
Perseverative responses[a]	0.25	**0.59**	0.08	0.04
Stroop Colour and Word Test				
Color	0.36	0.35	**0.65**	-0.13
Word	0.12	0.19	**0.83**	0.14
Color-word	0.36	0.46	**0.64**	0.15
California Computerized Assessment Package				
Simple reaction time	0.06	0.10	**0.62**	0.09
Controlled Oral Word Association Test				
Phonetic fluency[a]	0.33	0.32	**0.44**	0.33
Rey Complex Figure Test				
Short delayed recall	0.39	0.36	-0.06	**0.66**
Delayed recognition	0.01	-0.13	0.27	**0.81**
Eigenvalues (sum 12.05)	4.88	3.31	2.49	1.37
Total explained variance (sum 0.71)	0.29	0.19	0.15	0.08

n=100, 50 patients, 50 healthy controls

[a] Test-measure not included in summary scale

Table 4. Inter-correlations between the four neurocognitive dimensions T1 (*n*=100)

	Attention	Verbal memory	Visual memory
Verbal memory	0.43		
Visual memory	0.25	0.39	
Psychomotor speed	0.59	0.49	0.34

All $p>.05$

Figure 1. Scatterplots of the correlations between improvement of HAM-D and improvement on the neuropsychological summary scores from T1 to T2 (*n*=30)

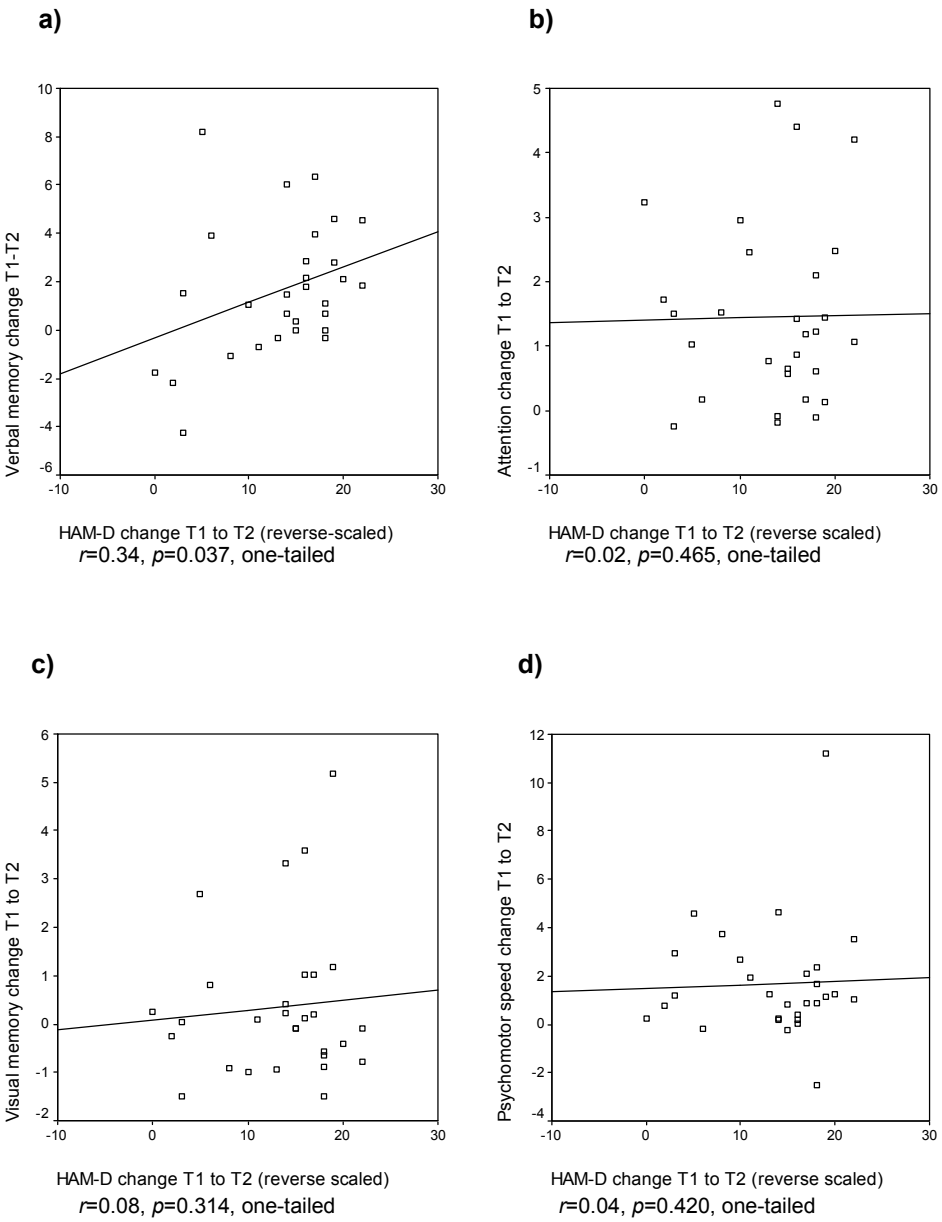
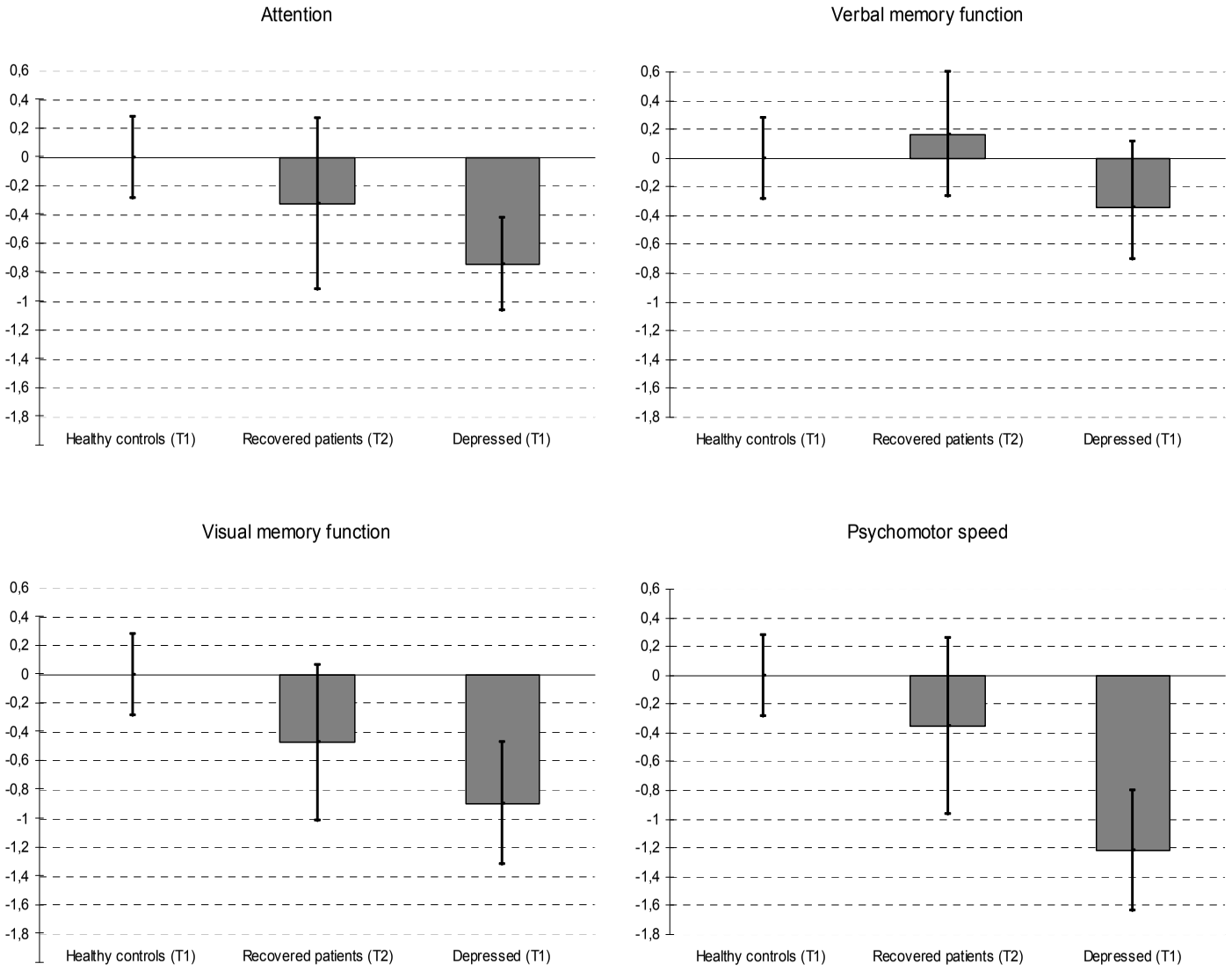


Figure 2. Neurocognitive function in depressed and recovered patients compared to healthy controls
Mean Z-scores (standardised for controls, mean=0 and SD=1) presented with 95% confidence [a].



[a] Healthy controls at T1 [*n*=50], depressed patients (HAM-D range 18-42, mean 22) at T1 [*n*=50], recovered patients at T2 (HAM-D ≤ 7, mean = 2.7) [*n*=17].