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The interrelationship between attentional and executive deficits in major depressive disorder

Jonna Nilsson 1,2, Alan J. Thomas 2, Lucy Stevens 2,3, R. Hamish McAllister-Williams 2, I. Nicol Ferrier 2, Peter Gallagher * 2

1 Aging Research Center, Karolinska Institutet & Stockholm University, Sweden
2 Institute of Neuroscience & Newcastle University Institute for Ageing, Newcastle University, United Kingdom
3 Tees, Esk and Wear Valleys NHS Foundation Trust

*Address for Correspondence:

Dr Peter Gallagher
Institute of Neuroscience & Newcastle University Institute for Ageing,
Henry Wellcome Building, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK
Tel.: +44 (0)191 208 7166 Email: peter.gallagher@ncl.ac.uk

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- Affective disorders
- Depression
- Cognitive functioning
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Significant outcomes
- Deficits in the depressed group were particularly prominent in the domains of attention and executive function.
- The attentional deficit persisted statistical control of variability in executive function whilst the executive deficit did not survive statistical control of variability in attention, indicating that the executive deficit may be secondary to the attentional deficit in major depressive disorder.
- Attention was negatively associated with illness duration.

Limitations
- A data driven approach for composite construction was not possible due to the small sample size, which meant that the findings rest on the theoretical assumption that the included measures tap the intended cognitive domains.
- Data was not available for all participants for all cognitive measures.
- The statistical methods used did not allow for causal inferences to be made.
Abstract

Objective: Cognitive dysfunction is an established feature of major depressive disorder (MDD). However, it remains unclear whether deficits in different cognitive domains are relatively independent or originate from a circumscribed ‘primary deficit’. The present study tested the hypothesis that a deficit in attention represents a primary deficit in depression.

Method: Neuropsychological function was assessed in 30 depressed MDD patients and 34 control participants. Cognitive composites were derived from a minimum of three tests and included attention, executive function, visuospatial memory and verbal memory. A multivariate analysis of variance was used to assess group differences in overall cognitive performance and multiple regression models were used to evaluate the role of attention in deficits in other domains.

Results: The cognitive deficit in the depressed sample was found to be characterized by poorer performance in attention and executive function. When evaluating the interrelationship between the two deficits, the attentional deficit was found to persist when variability in executive function was statistically accounted for whilst the executive deficit was eliminated when attention was accounted for.

Conclusion: The results demonstrated that the attentional deficit could not be explained by deficits in executive function, which provides support for a primary attention deficit in depression.
Background

Cognitive deficits\(^1\) constitute a well-established feature of major depressive disorder (MDD; (1)). Encapsulated in the Statistical Manual of Mental Disorders (5th ed.; DSM–V) as a “diminished ability to think or concentrate, or indecisiveness” (2), they have been empirically demonstrated throughout the course of the illness, from the first episode into remission (3, 4). Their clinical importance has been supported by associations with greater disability in life and work functioning as well as an increased risk of relapse (5, 6). Cognitive deficits in MDD have been found to affect several domains, including executive function, processing speed, attention and memory (7-9).

Whilst cognitive deficits represent an established feature of MDD, the relative impact of and interrelationships amongst deficits in different cognitive domains remains poorly understood (10-13). To merely describe the cognitive deficit profile in depression as ‘broad’ would fail to acknowledge both the hierarchical organisation of human cognitive processes and the complex interplay between these processes. Crucially, the conceptualisation of any observed deficit profile is fundamentally altered if the processes assessed do not operate independently but are instead secondary to reductions in more circumscribed, core functions. As such, deficits in different domains may represent relatively independent processes with distinct neurobiological underpinnings or may be secondary to a primary cognitive deficit in a single domain (14, 15).

The interrelationships amongst deficits in different cognitive domains have been studied most extensively in depressed patients over the age of 60 (late-life depression; (16)). In this group, executive function and processing speed have been identified as the most pronounced of the deficits (17, 18) with contributions to deficits in other domains, such as episodic memory and language skills (14, 19-21). Similar to what has been demonstrated in normal ageing (22), performance in simple speeded tasks has often been found to account for a large proportion of depression-related variance in executive

\(^1\) The term ‘deficit’ is used to refer to reduced cognitive test performance in a patient group relative to a control group. It is acknowledged that a comprehensive clinical assessment would be required to indicate evidence of underlying brain dysfunction and/or functional impairment.
function as well as in overall cognition (14, 15, 20, 23). Such evidence has indicated that a primary deficit might be driving the broader cognitive deficit in late-life depression.

The interrelationships amongst deficits in different cognitive domains have not received the same attention in the younger segment of the adult depressed population (18-65 years). Relative to older adults, younger depressed patients exhibit less severe cognitive deficits, particularly in the domains of processing speed and executive function (24). In a meta-analysis of depressed patients of all ages, Snyder (25) argued that deficits in processing speed tasks could not fully account for the executive deficits. However, this conclusion was predominantly based on numerically smaller effect sizes for measures of processing speed compared to executive measures. Thus, it remains unclear whether the cognitive deficit in younger adult depressed patients is the result of a primary cognitive deficit, similarly to late-life depression, or the result of several relatively independent deficits originating in different cognitive domains.

It is also not known to what extent deficits in different cognitive domains are influenced by various clinical factors in depression (12). A mapping of such influences could provide important information about the likely origins of cognitive deficits in depression (26). For example, if the impact of the severity of the current depressive episode predominates, cognitive performance in depression is likely to be merely a marker of current state. Alternatively, if illness duration over the lifetime predominates, cognitive performance may act as a trait marker of enduring and cumulative effects of depression on brain function. While results relating to clinical factors have been mixed (12), measures of attention and executive function have been put forward as potential trait-like markers in depression (27).

Aims of the study

The present study sought to investigate the hypothesis that a primary deficit in attention underpins the deficits in other affected cognitive domains in MDD. Importantly, for the hypothesis to be supported, the attention composite had to account for deficits in other affected cognitive domains as well as not being fully accounted for by variability in another cognitive domain. In an exploratory effort, the present study also investigated the impact of episode severity and illness duration on performance in different cognitive
domains. Given the sole focus on symptomatic patients, without consideration of treatment response or remission, such analyses were necessarily correlative in nature.

Methodology

Participants

Thirty patients with a confirmed diagnosis of MDD and currently in a major depressive episode, as assessed by the Mini International Neuropsychiatric Interview (MINI; (28)), were recruited via their consultant psychiatrists. All patients had a Hamilton depression (HAM-D) score of 16 or greater, as assessed by the GRID HAM-D (29). Patient exclusion criteria included the presence of any other DSM-IV Axis 1 disorder (other than anxiety disorder considered secondary to a primary diagnosis of depression), present or past electroconvulsive therapy (ECT), a change in psychiatric medication in the last four weeks, dependence or harmful use of alcohol or any other drug in the past 12 months and recent participation in another research study that included similar neurocognitive assessments. A brief illness history was taken from all patients, including age of onset, total illness duration and number of hospitalizations.

Thirty-four healthy volunteers were recruited as a control group. Exclusion criteria for the healthy volunteers comprised any history of psychiatric illness, as assessed by the MINI, any major physical health problem, self-report of one or more first degree relatives with a history of psychiatric illness, dependence or harmful use of alcohol or any other drug in the past 12 months and recent participation in research studies that included similar neurocognitive assessments. Both healthy volunteers and patients had to be right handed, as assessed by the Edinburgh Handedness Inventory (30), and could not have any fMRI contraindications, such as a pacemaker or other metal implants. All participants completed the National Adult Reading Test (NART; (31)) as a measure of premorbid intelligence and the Beck Depression Inventory II (BDI; (32)) as a self-report measure of depressive symptoms.

The study was approved by the local NHS ethics committee (NRES Committee North East - Newcastle & North Tyneside 1) and all participants gave written, informed consent.
Neurocognitive assessment

The neurocognitive assessment was designed to assess the cognitive domains of attention, executive function, visuospatial and verbal memory. All tests were administered according to standard procedure to allow comparison of results with other studies using the same tests (33). Tests were grouped according to the cognitive domain most commonly attributed to the particular test. Ability in each cognitive domain was estimated based on a minimum of three tests to increase the probability that the findings were reflective of the commonality of several tests (e.g. executive function) as opposed to being specific to the methodology (e.g. motor requirements) or scope (e.g. cognitive load) of a particular test (34). The use of composite scores is an established method in cognitive research for minimizing measurement error by a principle of aggregation (35). The attention and executive composites were derived from subtests of the same tasks by a method of subtraction (the subtraction method is used to derive a purer measure of executive function by better separating it from attentional demands; see Statistical Analysis section). Below we describe in detail the measurements that constituted each cognitive domain and how they were derived.

Executive Function

Three tasks were used to assess executive function and attention: the digit span from the WAIS-R (36), the Stroop Neuropsychological Screening Test (37) and the Trail Making Test (38).

The subtests were selected to capture three subcomponents of executive functioning: updating, inhibition and set-shifting (39). The reverse digit span from the WAIS-R (36), in which participants were required to remember and repeat a random series digits in reverse order, was used to assess the updating component. The number of digits in each string increased as the task progressed with two trials for each string length. Memory span was defined as the longest string length at which participants answered correctly on both trials. To separate the executive component from the attentional demand of simply maintaining a string of digits in working memory, forward digit span (see Attention) was subtracted from the reverse digit span. Consequently, the score carried forward to the executive
function composite only constituted the executive aspect of the task, i.e. the ability to reverse a string of digits.

The Stroop Neuropsychological Screening Test (37) was used to assess the inhibition component of executive function. In the incongruent condition of this task, interference is created between word reading and color naming by presenting participants with color words printed in a different color than the word itself denotes (e.g. the word ‘green’ written in red ink). By asking participants to name the color of the ink, the habit of reading the word itself has to be inhibited. The task also included two control condition, one of which required participants to name the color of crosses as quickly as possible. Response times in this control condition were subtracted from response times in the incongruent condition. Consequently, the score carried forward to analysis reflected the ability to inhibit the habit to read the color word, separate from the ability to attend to and name colors.

Finally, Trail Making Part B (38) was used to assess the set shifting component. Participants were required to connect a series of numbers and letters in ascending numerical and alphabetical order respectively, alternating between numbers and letters, as quickly as possible. Time taken to complete the task was measured. In order to distinguish the executive component of shifting between two sets from the attentional demands required to follow a single set, Trail Making Part A (see Attention) was subtracted from Trail Making Part B. Consequently, the score carried forward to the executive function composite only constituted the ability to shift between two set orders, separate from the ability to follow a single set.

Attention

Four tests were used to assess attention. In Trail Making Part A task (38), participants were required to connect a series of numbers in ascending order as quickly as possible. The two control measures in the Stroop Neuropsychological Screening Test were also included in the attention composite, where color naming and reading speed required participants to name the color of crosses and read color words printed in black ink as quickly as possible, respectively (37). All
three tasks are expected to capture attentional abilities whilst not placing significant demands on executive function.

The final task that contributed to the attention composite was the forward digit span from the WAIS-R, in which participants were required to repeat a random series of aurally presented digits (36). Whilst the task required attention to maintain the digit string in working memory, it did not involve any executive manipulation of the material. Memory span was defined in the same way as reverse digit span.

**Visuospatial Memory**

The visuospatial memory composite was derived from three tests: the Visual Patterns Test (VPT; (40)), the object-location memory task (OLM, (41)) and the Newcastle Visuospatial Working Memory task (NSWM, (42)).

The VPT assessed short-term memory for visual patterns. Participants were shown visual matrix patterns for 3-s after which they were required to reproduce each pattern on an empty matrix after a short delay. The matrix patterns progressively increased in size with three trials for each size and difficulty level. The final score on the task constituted the last level at which all three trials were correct.

The OLM task was developed to distinguish between three distinct processing mechanisms relevant to visuospatial memory: object processing, visuospatial location processing and object-to-location binding (41). In this task, participants were presented with a grid containing 10 objects for 30 seconds on a computer monitor. Subsequently, the objects disappeared and reappeared in a random order on a row above the square frame. In the position-only condition, all objects were the same and at recall the objects had to be relocated to their exact positions. In the object-to-location binding condition, all objects were different and at recall objects were relocated to their previous positions, which were indicated by black markers. In the combined condition, the two processes were combined and participants were asked to relocate ten different objects without marked positions. Performance in the position-only and combined conditions was measured in terms
of displacement error. Performance in the object-location binding condition was measured by the number of objects that were correctly placed on their respective marker. Two control conditions were also administered but were not used in the analyses.

In the NSWM participants are required to search visuospatial locations (cups) for a hidden ball. The essential rule of the task was that once a ball had been found in a particular location, it would not appear there again. There was always the same number of balls to be found as there were locations, starting with 4 and progressing to 12. Two types of errors are recorded in the task: between-search errors, which referred to returning to a location in which a ball had already been found, and within-search errors, which constituted returning to a location which had already been found to be empty in the within the same search sequence. Only between-search errors were carried forward to analysis.

Verbal Memory

The Rey Auditory Verbal Learning Test (RAVLT; (43)) was used to assess verbal learning and immediate and delayed verbal memory. Participants were required to repeat a list of 15 aurally presented words immediately after presentation (A1). This procedure was repeated for the same list another four times (A2-A5). Subsequently, participants were presented with a second distractor list, which also had to be repeated immediately after presentation (B), after which they were required to recall the first list again (A6, immediate recall). After an approximate delay of 20 minutes, participants were asked to recall the initial list from memory without another presentation (A7, delayed recall). The subsequent recognition test, where participants were presented with a list with words from the first and second lists and new words and had to determine the source of the words, was not used for analyses. The verbal memory composite was derived from the total number of recalled words (A1 to A5, verbal learning) and from the immediate recall (A6) and delayed recall (A7). However, since the standard delayed recall index at trial A6 and A7 is critically dependent on the number of words initially encoded (i.e., is confounded by words learned at trial A5), the percentage of
words retained from trial A5 at A6/A7 were used to provide a better index of retention per se (A6/A5*100; A7/A5*100).

**Statistical analysis**

Pearson’s correlational coefficients were used to evaluate the validity of the subtraction method for the tests of executive function and attention. Specifically, a weaker correlation between the attentional subtest (x) and the derived measure of executive function (y-x) compared to that between the attentional subtest (x) and the executive subtest (y) would provide support for an improved separation of attentional and executive capabilities through the subtraction method\(^2\). Pearson’s correlational coefficients were also used to investigate the relationships between the cognitive composites.

Composite clustering was performed according to the cognitive domains most commonly attributed to the particular test. The composites were created by calculating an average of the relevant \(z\)-scores for each measure. Supplement (s1) presents the measurements that constituted the composites of executive function, attention, visuospatial memory and verbal memory. When Shapiro-Wilks test showed that the variables did not meet the assumptions of normality, log or square root transformations were applied. Only when the transformations resulted in an improvement of the normality of the variable was the transformed variable used. \(Z\) scores rather than raw scores were used for calculations of the composites, so that scoring schemes across tasks were standardized. These were derived from the raw scores with the formula \((X_{\text{individual}} - \mu_{\text{control}} / \sigma_{\text{controls}})\). The former part of this equation was reversed for tasks in which a high score indicated poorer performance.

A multivariate analysis of covariance (MANCOVA) was conducted to investigate group differences in overall cognitive ability. All cognitive composites were included as dependent variables, group (patient vs. controls) represented the independent variable and age, gender and premorbid IQ were entered as covariates. Subsequently, multiple

\(^2\) For example, the Trail Making Test has Parts A and B. Part B is generally considered a measure of executive function (shifting). However, the same motor/attentional demands required to complete part A are similarly involved in the performance of Part B. Therefore there is typically a moderate-to-strong correlation between Parts A and B. If instead the ‘difference’ is used (i.e. time to complete Part B minus Part A), it leads to a greater dissociation between the motor/attentional component and the ‘purer’ shift component.
regression models were used to test the ability of one composites in accounting for between-group variance in another. To this end, a hierarchical method was used by which the first composite represented the dependent variable and the independent variables were added sequentially in an enter-model, starting with the all the demographic variables (age, gender, premorbid IQ), then the alternate composite and finally group membership (patient vs. control). Similar multiple regression models, restricted to the patient group, were tested to explore the effect of illness characteristics on the cognitive composites.

All reported p values are two-tailed and no corrections have been made for multiple comparisons.

Results

**Demographic and clinical characteristics**

Demographic and clinical characteristics of the depressed group and the control group are presented in Table 1. There were no statistically significant differences between the depressed group and the control group regarding age, gender and premorbid IQ. As a group, the depressed patients were experiencing a moderately severe depressive episode, had experienced several years of the illness and were generally taking antidepressant medication.

{Inset Table 1 about here}

**Neurocognitive performance**

Two control subjects did not have complete data for the OLM and five patients did not have complete data for the RAVLT.

Correlational analyses provided overall support for the validity of the subtraction method. For the Stroop Neuropsychological Screening Test, the derived executive measure (incongruent–colour naming) was unrelated to the attentional subtest (colour naming), $r=0.032$, $p=0.804$, which contrasts with the moderate correlation between the executive subtest (incongruent) and the attentional subtest (colour naming), $r=0.517$, $p<0.001$. For the Trail Making Test, the derived executive measure (Trails B–Trails A) was unrelated to the attentional subtest (Trails A), $r=0.192$, $p=0.129$, which contrasts with the strong correlation between the executive subtest (Trails B) and the attentional subtest (Trails A),
Attention was found to correlate significantly and positively with all other cognitive composites with a particularly strong correlation with executive function. There were also several significant correlations with age, gender and premorbid IQ, providing support for the need to use demographic variables as covariates in further analyses.

A MANCOVA was conducted to investigate group differences in cognitive performance across the composites of attention, executive function, visuospatial memory and verbal memory, whilst controlling for age, gender and premorbid IQ. There was a significant main effect of group, evidencing a broad cognitive deficit in the depressed group ($F_{(4, 49)} = 3.37, p=0.016, \eta^2_p=0.216$). When analyzing the composites separately, only attention ($p=0.001$) and executive function ($p=0.009$) reached significance, with depressed patients performing below the level of controls in both domains (Table 3).

Considering the significant composites identified in the MANCOVA, attention and executive function, the next set of analyses assessed the ability of one of the composites in accounting for between-group variance in the other. Two multiple regression models were therefore tested, the first with attention as the dependent variable and the second with executive function as the dependent variable (Table 4). In Model 1, after accounting for demographic variables and executive function, group membership still accounted for a significant portion of the additional variance in attention ($p=0.014$). In contrast, in
Model 2, after accounting for demographic variables and attention, group membership did not account for any additional variance in executive function ($p=0.196$).

Considering the potentially limited validity of the subtraction method for the digit span test from the WAIS-R, the regression models were repeated with composites that did not include the digit span test (s2). The outcome of the analyses remained the same for both models, as demonstrated in the supplement (s3).

Another set of multiple regression analyses were conducted to investigate the effect of illness duration and illness severity on performance in the four cognitive domains (Table 5). These analyses were restricted to the patient group (not being relevant to the control group). Illness duration was significant in the model implicating attention as the dependent variable, with a longer illness duration being associated with worse performance ($p=0.005$). Illness severity was not a significant variable in any of the four models.

Discussion

The present study found evidence for cognitive deficits in the domains of attention and executive function in a currently depressed sample relative to a matched control group. This is consistent with previous investigations demonstrating a multifaceted cognitive profile in depression, with particular resemblance to the pattern of deficits previously demonstrated in late-life depression (12, 18). Consequently, the hypothesized primary deficit in attention was assessed by evaluating its interrelationship with the deficit in executive function. In support of the hypothesis that a primary deficit in attention underpins deficits in executive function, group membership explained no additional variance in executive function once attention had been accounted for. In contrast, group membership continued to explain a significant portion of the variance in attention, even when executive function had been accounted for in the model.

The results of the present study suggest that the cognitive deficits in depression may be secondary to a primary deficit in attention. This would be in line with the notion that the
cognitive profile in depression can be explained by deficits in more circumscribed, core processes (14). Given the speeded measures contributing to the attention composite in the present study, the results can also be considered consistent with previous findings in late-life depression demonstrating that a deficit in information processing could account for deficits in other affected domains (15). Attention was also the only composite that demonstrated a relationship with a clinical variable, namely illness duration. With no significant relationships with symptom severity, this suggests that the attentional deficit is more likely to be the result of the accumulating burden of illness than of the severity of the current episode. In the context of previous demonstrations of moderate attentional and executive deficits even in remission (1), this finding appears to support the proposal that such deficits represent trait-like effects in depression (27). However, since all patients in the present study were symptomatic at the time of testing, future investigations will be necessary to reach a more definite conclusion in regards to whether the attentional deficit in depression is a state or a trait effect, or a combination of both.

If a primary attentional deficit is indeed underlying the broader cognitive deficit seen in depression, it will be of great importance to identify its neurobiological underpinnings. Whilst such neurobiological causes are likely to originate from multiple sources with complex interactions, a potential candidate is white matter lesions and reduced white matter integrity. White matter has been identified as an important contributor to age-related decline in processing speed and executive function, which both rely heavily on attentional resources (44). White matter abnormalities have also been reported in affective disorders (45-48) and have been found to particularly severe in individuals with a greater burden of depression (49). It is therefore conceivable that white matter abnormalities may represent one important contributor to the attentional deficit demonstrated in the present study (50, 51).

It should be noted the executive and attention composites were derived from the same tasks, which comes with the risk of inflating the relationship between these particular composites. Importantly, however, this overlap in task procedure also allowed for the careful experimental separation between attention and executive function, which represents a strength of the present study. Directly related to this separation, the validity of the ‘subtraction method’ was statistically supported for two out of the three tests used.
and the analysis of the interrelationship between the domains remained unchanged when the analysis included only those tests with supported validity. Also, despite the close relationship between attention and executive function, the results of the present study nevertheless demonstrate that the two composites differed in the extent to which they could account for between-group variability in the alternate domain. Another advantage of the assessment of executive function was that the selection of subtests was based on an established framework of executive function, where each subtest aimed to capture each of the distinct constructs (shifting, inhibition, updating; (52)).

An important limitation of any study using composite scores is how tests are selected for the relevant composites. Given the small sample of the present study, a data driven approach for composite construction was not possible (e.g. principal component analysis). The findings therefore necessarily rest on the assumption that the included measures tap the intended cognitive domains. Another limitation is that complete data was not available for all participants for all tests, which reduced the statistical power for some of the analyses. Limited statistical power also hindered a correction for multiple comparisons, such as the Bonferroni correction, which represents an additional limitation of the study. It is also worth mentioning that since all tests and subtests were administered in a standardized manner and in the same order for all study participants, potential learning and order effects could not be evaluated.

Finally, it is important to acknowledge the limitation of the used statistical methods in establishing a causal of for attention in driving the executive deficit. Such causal inferences could be made possible in future investigations by experimentally manipulating attentional and executive demands and carefully examining its effects on the overall cognitive profile in depression. Future investigations could also consider including additional/alternative measures of attention and executive function in order to examine the process specificity of the interrelationship between deficits in the two domains in depression.

In conclusion, the present study provides evidence for a primary deficit in the attentional domain in a sample of symptomatic MDD patients of working age. The use of cognitive composites and the careful separation of cognitive domains, particularly of attention from
the highly related executive function domain, allowed an evaluation of the interrelationships amongst deficits in the two affected cognitive domains. Future investigations incorporating experimental manipulation of cognitive demand will be necessary to further delineate the role of attention in the cognitive profile in MDD and its neurobiological underpinnings.
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Declaration of interest

None
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| Variable                        | Control (n=34) | Depressed (n=30) | Test statistic | p    |
|--------------------------------|---------------|------------------|----------------|------|
| Demographic characteristics    |               |                  |                |      |
| Age (years)                    | 43            | 46.6             | 1.25           | 0.22 |
| Women                          | 23            | 18               | -0.63          | 0.53 |
| Men                            | 11            | 12               |                |      |
| Premorbid IQ: NART             | 115           | 114              | -0.42          | 0.67 |
| Mood ratings                   |               |                  |                |      |
| HAM-D (17)                     | -             | 22.9             | 16.51          | < 0.001 |
| BDI                            | 1.9           | 35.1             |                |      |
| Clinical characteristics       |               |                  |                |      |
| Age at illness onset (years)   | -             | 28.3             |                |      |
| Duration of illness (years)    | -             | 13.1             |                |      |
| Hospitalisation                | 4             |                  |                |      |
| Medication                     |               |                  |                |      |
| Antidepressants (yes)          | 27            |                  |                |      |
| Benzodiazepines (yes)          | 2             |                  |                |      |
| Antipsychotics (yes)           | 5             |                  |                |      |

Abbreviations: National Adult Reading Test (NART), Hamilton Depression Rating Scale (HAM-D 17), Beck Depression Inventory (BDI)
Table 2

Pearson correlations between demographic variables and the cognitive composites$^a$

| Variable          | Attention $^b$ | Executive Function $^c$ | Visuospatial Memory $^d$ | Verbal Memory $^e$ |
|-------------------|---------------|--------------------------|--------------------------|--------------------|
| Attention         | -             | 0.622**                  | 0.480**                  | 0.470**            |
| Executive Function| -             | -                        | 0.382**                  | 0.231              |
| Visuospatial Memory| -            | -                        | -                        | 0.205              |
| Age               | -0.395**      | -0.356**                 | -0.483**                 | -0.132             |
| Gender $^f$       | 0.418**       | 0.307*                   | 0.143                    | 0.374**            |
| Premorbid IQ      | 0.202         | 0.099                    | 0.018                    | 0.279*             |

$^a$ Bold values indicate statistical significance; * $p<0.05$, ** $p<0.01$
$^b$ Trail-Making A, Forward Digit Span, Stroop Reading Speed, Stroop Colour Naming
$^c$ Trail-Making B, Reverse Digit Span, Stroop Interference Score
$^d$ Newcastle Visuospatial Working Memory, Visual Patterns Test, Object Location Memory Task (position-only, object-location binding, combined conditions)
$^e$ RAVLT (A1-A5, percentage retained at A6, percentage retained at A7)
$^f$ Males coded as 1 and females as 2
Table 3

Results on MANCOVA tests comparing Z-score performance in the patient group and the control group in the four cognitive domains

| Domain                | Mean  | SD   | $F_{(1,52)}$ | $p$   | $\eta^2_p$ |
|-----------------------|-------|------|--------------|-------|------------|
| Attention             | -0.853| 0.862| 11.744       | **0.001** | 0.184      |
| Executive Function    | -0.525| 0.649| 7.446        | **0.009** | 0.125      |
| Visuospatial Memory   | -0.407| 0.679| 2.774        | 0.102  | 0.051      |
| Verbal Memory         | -0.557| 1.067| 1.949        | 0.169  | 0.036      |

*Results are given for the 25 patients and 32 controls for whom data was available for all four composites*
Table 4.

Results of multiple regression analyses examining the ability of executive function to account for between-group variance in attention (Model 1) and vice versa (Model 2). The independent variables were added sequentially to the models.

| Dependent variable | Independent variables                | R²  | R² change | F for R² change | p     |
|--------------------|-------------------------------------|-----|-----------|-----------------|-------|
| Model 1: Attention | Age, gender, premorbid IQ           | 0.334 | 0.334 | 10.503 | <0.001 |
|                    | + Executive function                | 0.505 | 0.161 | 19.161 | <0.001 |
|                    | + Group: Patient vs. Control        | 0.554 | 0.049 | 6.382  | 0.014  |
| Model 2: Executive Function | Age, gender, premorbid IQ | 0.221 | 0.221 | 5.351  | 0.002  |
|                    | + Attention                         | 0.404 | 0.193 | 19.161 | <0.001 |
|                    | + Group: Patient vs. Control        | 0.422 | 0.017 | 1.709  | 0.196  |

*Premorbid IQ as measures by the National Adult Reading Test*
|                                | $\beta$ | $t$  | $p$  | $R^2$ | $F$  | $p$  |
|--------------------------------|---------|------|------|-------|------|------|
| **Attention**                  |         |      |      | 0.445 | 3.689| 0.013|
| Age                           | 0.007   | 0.041| 0.968|       |      |      |
| Gender                        | 0.632   | 3.253| 0.004|       |      |      |
| Premorbid IQ                  | 0.423   | 2.456| 0.022|       |      |      |
| Illness duration (years)      | -0.604  | -3.086| 0.005|       |      |      |
| HAM-D (17)                    | -0.337  | -1.704| 0.102|       |      |      |
| **Executive Function**        | 0.382   | 2.848| 0.038|       |      |      |
| Age                           | -0.287  | -1.530| 0.140|       |      |      |
| Gender                        | 0.177   | 0.863| 0.397|       |      |      |
| Premorbid IQ                  | 0.066   | 0.362| 0.721|       |      |      |
| Illness duration (years)      | -0.372  | -1.801| 0.085|       |      |      |
| HAM-D (17)                    | 0.108   | 0.515| 0.611|       |      |      |
| **Visuospatial Memory**       | 0.407   | 3.161| 0.026|       |      |      |
| Age                           | -0.430  | -2.340| 0.028|       |      |      |
| Gender                        | 0.438   | 2.184| 0.039|       |      |      |
| Premorbid IQ                  | 0.180   | 1.010| 0.323|       |      |      |
| Illness duration (years)      | -0.285  | -1.408| 0.172|       |      |      |
| HAM-D (17)                    | -0.232  | -1.136| 0.268|       |      |      |
| **Verbal Memory**             | 0.185   | 0.815| 0.555|       |      |      |
| Age                           | 0.091   | 0.371| 0.717|       |      |      |
| Gender                        | 0.281   | 1.098| 0.287|       |      |      |
| Premorbid IQ                  | 0.303   | 1.259| 0.224|       |      |      |
| Illness duration (years)      | -0.029  | -0.105| 0.918|       |      |      |
| HAM-D (17)                    | 0.123   | 0.501| 0.622|       |      |      |

*Bold values indicate statistical significance*
Table s1

*Measures constituting the four cognitive composites used for analyses.*

| Domain               | Measures used for composite                                                                 |
|----------------------|---------------------------------------------------------------------------------------------|
| Executive Function   | Reverse Digit Span (span) - Forward Digit Span (span)                                         |
|                      | Stroop Incongruent (ms) - Stroop Colour Reading (ms; square root)                            |
|                      | Trail Making B (ms) - Trail Making A (ms; square root)                                       |
| Attention            | Forward Digit Span (span)                                                                    |
|                      | Trail Making A (ms)                                                                        |
|                      | Stroop Reading Speed (ms; log)                                                               |
|                      | Stroop Colour Naming (ms)                                                                   |
| Visuospatial Memory  | Visual Patterns Test (level)                                                                 |
|                      | OLM Position Only (displacement error; log)                                                 |
|                      | OLM Object-Location Binding (error)                                                          |
|                      | OLM Combined (displacement error)                                                            |
|                      | NSWM 3D (between-search error)                                                               |
| Verbal Memory        | RAVLT Verbal Learning (words recalled for A1-A5)                                            |
|                      | RAVLT Immediate Recall (% recalled at A6 from A5)                                           |
|                      | RAVLT Delayed Recall (% recalled at A7 from A5)                                             |

Abbreviations: Object Location Memory (OLM), Newcastle Visuospatial Working Memory (NSWM), Rey Auditory Verbal Learning Test (RAVLT)
Table s2

Measures constituting the composites for Executive Function and Attention with the digit span test from the WAIS-R excluded.

| Domain         | Measures used for composite                                      |
|----------------|----------------------------------------------------------------|
| Executive Function | Stroop Incongruent (ms) - Stroop Colour Reading (ms; square root) |
|                 | Trail Making B (ms) - Trail Making A (ms; square root)           |
| Attention       | Trail Making A (ms)                                                |
|                 | Stroop Reading Speed (ms; log)                                      |
|                 | Stroop Colour Naming (ms)                                           |
Table s3.

Results of multiple regression analyses examining the ability of executive function to account for between-group variance in attention (Model 1) and vice versa (Model 2), without inclusion of the subtests from the digit span test from the WAIS-R for the composites. The independent variables were added sequentially to the models.

| Dependent variable | Independent variables                      | R²     | R² change | F for R² change | p    |
|--------------------|--------------------------------------------|--------|-----------|-----------------|------|
| Model 1: Attention | Age, gender, premorbid IQ<sup>a</sup>      | 0.312  | 0.312     | 9.051           | <0.001|
|                    | + Executive function                       | 0.436  | 0.124     | 12.967          | 0.001|
|                    | + Group: Patient vs. Control               | 0.484  | 0.048     | 5.421           | 0.023|
| Model 2: Executive Function | Age, gender, premorbid IQ<sup>a</sup> | 0.203  | 0.203     | 5.093           | 0.003|
|                    | + Attention                                | 0.347  | 0.144     | 12.967          | 0.001|
|                    | + Group: Patient vs. Control               | 0.596  | 0.009     | 0.777           | 0.382|

<sup>a</sup> Premorbid IQ as measured by the National Adult Reading Test