The pattern and course of cognitive impairment in late life depression

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Abstract

Background: Cognitive deficits persist despite clinical recovery in subjects with late life depression, but more needs to be known about their longer term outcome and factors affecting their course. To investigate this, we followed the pattern of cognitive impairments over time and examined the effects of current mood, remission status, age of depression onset and antidepressant treatment on these deficits.

Methods: Sixty-seven subjects aged 60 or over with DSM-IV major depressive disorder and 36 healthy comparison subjects underwent tests of global cognition, memory, executive functioning and processing speed at baseline, 6 and 18 months, with some subjects tested again after 4 years. Z-scores were compared between groups, with analyses of clinical factors which may have influenced cognitive performance in depressed subjects.

Results: Half of the patients exhibited a generalized cognitive impairment that persisted after 18 months (OR = 5.2, p = .011). Patients performed worse across all cognitive domains at all time points, without substantial variability due to current mood, remission status or antidepressant treatment. Late age of onset was significantly associated with decline in memory and executive functioning. Impaired processing speed may be a partial mediator of some deficits, but was insufficient to explain differences between patients and controls. Four year follow-up data suggest impairments persist, but do not further decline.

Conclusion: Cognitive deficits in late life depression persist up to 4 years, affect multiple domains and are related to trait rather than state effects. Differences in severity and course between early and late onset depression suggest different pathogenic processes.

Key words: depression, late life, age of onset, neuropsychology, course

Introduction

Cognitive deficits are a core feature of depression in adults of all ages, consistently found in the domains of memory, executive functioning and processing speed (Thomas and O'Brien, 2008). Previously such deficits were thought to be transient, in its most severe forms called 'depressive pseudodementia' (Bulbena and Berrios, 1986), but mounting evidence shows cognitive deficits persist despite remission of depressive symptoms (Abas et al., 1990; Beats et al., 1996; Nebes et al., 2000; Devanand et al., 2003; Portella et al., 2003; Adler et al., 2004; Neu et al., 2005; Bhalla et al., 2006; Lee et al., 2007). These persisting deficits may be related to underlying neurobiological changes, including brain atrophy and an increased prevalence of white matter hyperintensities (Schweitzer et al., 2001; Herrmann et al., 2008).

Although cognitive impairment is nowadays believed to be stable for the group of patients as a whole, recent studies have been short term (not exceeding 12 months) and longer term outcome has not been determined. There might also be differences between patients with specific clinical characteristics. For example, younger patients show a similar cognitive profile, but impairment is generally found to be more severe in older individuals (Gualtieri and Johnson, 2008; Thomas et al., 2008) and might be related to a late onset of depressive disorder (≥ 60 years) in particular (Herrmann et al., 2007). While modest improvement of cognition may occur in patients who were selected based on good response to antidepressant (AD) treatment (Butters et al., 2000; Gallassi et al., 2006; Mandelli et al., 2006), it is largely unknown whether current AD treatment impacts on patients' cognition compared to healthy subjects. Furthermore, controversy still remains as to whether cognitive impairment affects all cognitive domains or whether apparently multi-modal deficits in fact reflect a deficit in a single core neuropsychological function. Although the most suitable candidate, processing speed, has indeed been found to be a strong mediator of other cognitive deficits (Nebes et al., 2000; Butters et al., 2004), its effect might be greater for executive functioning than for episodic memory (Delaloye et al., 2008).

To address these questions we examined the pattern of cognitive deficits in healthy subjects and individuals with late-life major depression over time. We report differences between patients due to current symptom severity, remission status, age

of depression onset and antidepressant treatment. We hypothesized that i) current symptom severity would only marginally affect cognitive deficits, ii) remitted patients would therefore show some amelioration of deficits but remain impaired, iii) later age of onset would be associated with more severe deficits without differences in the domains affected and iv) that those treated with antidepressants would not differ from those not treated. In addition, we addressed the question whether processing speed mediates deficits in other cognitive domains.

Methods

Case ascertainment

Sixty-seven patients aged 60 and over who fulfilled DSM IV criteria for major depression were recruited from clinical old age psychiatry services covering geographically based catchment areas and included referrals from day hospitals, inpatient units and outpatient clinics. A control group (n=36) of similar aged older people (also all over 60 years of age) with no past history of depression or current depression were recruited from community sources such as The Royal British Legion and spouses of patients attending the same hospital units. The baseline neuropsychological profile of this group has been previously reported (O'Brien et al., 2004). We excluded both subjects and controls with a history of prior cognitive impairment, history or evidence of stroke or transient ischemic attack, severe or unstable physical illness (e.g. insulin dependent diabetes mellitus, untreated hypothyroidism, uncontrolled heart failure, cancer) or a Cambridge Cognitive Examination (CAMCOG) (Roth et al., 1999) score of < 75 (patients) or < 80 (controls). Additional exclusion criteria were: history or current substance/alcohol abuse; long term use (> 2 months) of steroids during lifetime; use of steroid or other medication within the last 3 months thought to interfere with HPA axis; ECT in last 3 months; use of medication thought to affect cognition (e.g. non-hypnotic benzodiazepines, antipsychotics or anticholinergic medication); presence of other neurological diagnosis. Use of newer antidepressants (e.g. SSRI's and venlafaxine) and lithium was permitted, and only seven patients were taking tricyclic antidepressants (1 dothiepin, 6 lofepramine). The study was approved by the local ethics committee and all patients and controls gave written informed consent.

Assessment

All depressed cases underwent a comprehensive psychiatric assessment including history, mental state, physical examination and a test of general cognitive functioning (CAMCOG). The CAMCOG is part of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth et al., 1999) and assesses general cognitive functioning and is frequently used in research and clinical practice.

Depression was diagnosed according to DSM-IV criteria (American Psychiatric Association) and symptom severity was rated using the MADRS (Montgomery and Asberg, 1979). In the present study, remission was defined as a MADRS score ≤ 9 (Hawley et al., 2002; Zimmerman et al., 2004). Demographic information (including past and current medical and psychiatric history, medication taken, family history, education and social class) and psychiatric history of past episodes of depression were collected from multiple sources to validate or enrich information from face-to-face interviews with subjects and informants (e.g. case notes, GP records and informant accounts to determine number of previous episodes, age of onset and total lifetime duration of depression). An extensive neuropsychological test battery was administered to controls and all patients who consented to it.

Neuropsychological assessment

The test battery was primarily designed to measure memory, processing speed and executive function as they represent core neuropsychological deficits in late life depression (Thomas and O'Brien, 2008). Tests used in the present study included both traditional pen and paper and computerised tasks:

a) The Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964), a test of episodic memory. The three measures immediate recall, delayed recall and delayed recognition (number of correct items) were used.
b) The FAS verbal fluency test (Lezak et al., 2004), a task sensitive to frontal lobe impairment.
c) The Trail Making Test (TMT) (Lezak et al., 2004), a test of mental flexibility and divided attention.
d) The Stroop Colour Word Test (SCWT) (Stroop, 1935), a test for response inhibition and selective attention.
e) A computerised continuous performance task (VIGIL) (Cegalis and Bowlin, 1991). Over 8 minutes, subjects have to press a button to a complex target

stimulus (letter K when preceded by the letter A), presented 100 times within a total of 480 stimuli (displayed serially in a pseudo-random fashion). Errors of omission and commission can be used as a measure of vigilance and inhibition but in the present study only response latencies (in msec) were used as a measure of processing speed.

Definition of generalized cognitive impairment (GCI)

There is no universally accepted definition of a suitable cut-off to denote significant cognitive impairment and 1, 1.5 and 2 standard deviations (SD) have all been used. In their definition of ageing associated cognitive decline Levy et al (1994) chose 1 SD. The narrower, and more universally accepted, concept of mild cognitive impairment (Petersen et al., 1999) used 1.5 SD. consistent with this, we defined GCI as a score of more than 1.5 standard deviations below the healthy control groups' mean on the CAMCOG at each assessment.

Follow-up

Patients and controls were re-assessed 6 and 18 months and again 4 years after baseline. At each time point, a psychiatric assessment, administration of rating scales and neuropsychological tests were repeated. At 6 months, 93 (90%) participants of the baseline sample were re-assessed and 78 (76%) at 18 months. At 4 year, only 36 (35%) individuals, including 15 patients, were available for follow-up. Our analysis therefore focuses on the 6 and 18 months follow-up data but because longer term follow-up cognitive data on such patients is rarely available we have included the four year data too. While all patients had undergone clinical examination and CAMCOG testing at baseline, only 34 out of 67 of them were tested with the extended neuropsychological battery. While more could be tested at 6 (51 out of 57) and 18 (41 out of 45) months, this means that samples at different time points were not perfectly comparable. We thus decided to look at the associations cross-sectionally only.

Statistical analysis

For ease of comparison, neuropsychological test scores were standardized using the control group's mean and standard deviation at baseline. An overall memory z-score was created by adding up the three z-scores of the AVLT (immediate recall, delayed

recall, delayed recognition) and this 'compound score' was again standardized to a z-score using the control group's mean and standard deviation at baseline. Similarly, an overall executive functioning z-score was created by adding up the z-scores of verbal fluency, Trail Making Test difference A-B and SCWT correct responses. By this, we had three cognitive domains with higher scores indicating better performance: memory, executive functioning and processing speed (VIGIL latencies). The risk of having GCI at follow-up was assessed with logistic regression analyses yielding odds ratio's (OR) and 95% confidence intervals (CI). We then used multiple linear regression analyses to test associations within cognitive domains. The impact of key clinical variables was investigated by comparing remitters and non-remitters, early onset and late onset, and AD users and non-users to healthy controls. In patients we also tested whether current MADRS scores (symptom severity), continuous age of onset and lifetime duration of AD intake predicted neuropsychological performance. All comparisons were adjusted for age, gender and years of education. The alpha-level for statistical significance was fixed at $p \leq 0.05$. All tests were performed with STATA 9.2 (StataCorp, 2006).

Results

Descriptive analyses

Patients and their comparison subjects were well matched for age ($p = .609$) and gender ($p = .633$), but patients had higher MADRS scores ($t = -12.2$, $df = 101$, $p < .001$) and fewer years of formal education ($t = 2.06$, $df = 101$, $p = .042$) (Table 1).

<<< PLEASE INSERT TABLE 1 HERE >>>

Loss to follow-up

At 18 months, 22 (21%) participants were lost-to follow-up (LTFU), all within the patient group. Of these, 19 refused participation and 3 had died. Three control subjects had no data on CAMCOG or other neuropsychological testing. Among patients, being LTFU was not related to age ($t = 0.10$, $df = 65$, $p = .919$), gender ($\chi^2 = 0.07$, $df = 65$, $p = .797$), years of education ($t = -0.27$, $df = 65$, $p = .785$), ,age of onset ($t = -0.04$, $df = 65$, $p = .972$), MADRS score (baseline: $t = -1.47$, $df = 65$, $p = .147$; 6 months: $t = 0.34$, $df = 55$, $p = .739$), remission status (baseline: $\chi^2 = 0.53$, $df = 65$, $p = .466$; 6 months: $\chi^2 = 1.04$, $df = 55$, $p = .308$), baseline antidepressant use ($\chi^2 = 0.04$,

df = 65, p = .836) or weeks on medication (baseline: t = 0.10, df = 64, p = .919; 6 months: t = 1.10, df = 43, p = .277). In addition, there were no significant differences between groups in total CAMCOG (baseline: t = 0.18, df = 64, p = .857; 6 months: t = 1.74, df = 55, p = .087), memory (baseline: t = 1.12, df = 32, p =.270; 6 months: t = 1.11, df = 49, p = .274), executive functions (baseline: t = 1.19, df = 35, p = .241; 6 months: t = 1.87, df = 49, p = .067) and processing speed (baseline: t = 0.83, df = 28, p = .414; 6 months: t = 0.72, df = 44, p = .478). However, all patients LTFU were on medication at 6 months follow up, resulting in a significant difference with patients not LTFU (χ^2 = 4.03, df = 55, p = .045).

Depression and persistent generalized cognitive impairment (GCI)

One patient with missing CAMCOG scores was excluded from this analysis. Of the remaining 66 patients, 33 (50%) showed GCI defined as 1.5 standard deviations below the control group's CAMCOG mean (Figure 1). Having GCI at baseline was highly predictive of having persistent GCI at 6 months (OR = 6.0, 95%CI = 1.86;19.40, p = .003) and at 18 months (OR = 5.2, 95%CI = 1.41;19.18, p = .011). The risk increment remained robust after adjustment for age, gender, years of education, age of onset, remission status and current antidepressant use (6 months: OR = 5.85, 95%CI = 1.43;23.97, p = .014; 18 months: OR = 5.91, 95%CI = 1.12;31.23, p = .036).

<<< PLEASE INSERT FIGURE 1 HERE >>>

Single-domain or multiple-domain cognitive impairment

Next, we wanted to test whether cognitive impairment is domain-specific or affects multiple cognitive domains. Separate linear regression analyses adjusted for age, gender and years of education showed that patients did significantly worse at all time points and in all domains (Table 2). Figure 2 illustrates this by showing little deviation from parallel running lines representing both groups' unadjusted mean z-scores up to 18 months.

<<< PLEASE INSERT TABLE 2 HERE >>>

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Do deficits in processing speed drive the impairment in patients?

In order to test the mediating role of processing speed, analyses were repeated but controlled for VIGIL latency z-scores. Adjusted for group, age, gender and education, processing speed was positively and significantly associated with memory (baseline: b = 0.31, 95%CI = 0.12;0.50, p = .002; 6 months: b = 0.43, 95%CI = 0.19;0.67, p = .001; 18 months: b = 0.34, 95%CI = 0.08;0.60, p = .012) and executive functioning (baseline: b = 0.42, 0.19;0.65, p = .001; 6 months: b = 0.40, 95%CI = 0.13;0.68, p = .004; 18 months: b = 0.46, 95%CI = 0.23;0.70 p < .001). As can be seen in Table 2, adding processing speed to the regression model explained another 6-8% of the variance in memory scores. For executive functioning, this rose to 7-16%. Yet, differences between groups remained significant in both domains at all time points.

Stability of cognitive impairment: depression severity

Next, we tested whether cognitive impairments, despite being relatively stable for the group of patients as a whole, showed some variability due to differential associations with a number of *a priori* identified clinical factors. In order to test the influence of symptom severity in patients, we tested whether MADRS scores at the relevant follow-up point predicted cognition and found that they did not: memory (baseline: b = 0.02, 95%CI = -0.06;0.11, p = .587; 6 months: b = -0.01, 95%CI = -0.05;0.03, p = .593; 18 months: b = -0.02, 95%CI = -0.06;0.03, p = .415), executive functioning (baseline: b = 0.01, 95%CI = -0.08;0.10, p = .814; 6 months: b = -0.00, 95%CI = -0.04;0.04, p = .870; 18 months: b = -0.02, 95%CI = -0.07;0.03, p = .444), processing speed (baseline: b = 0.08, 95%CI = -0.03;0.18, p = .153; 6 months: b = -0.02, 95%CI = -0.06;0.01, p = .179; 18 months: b = -0.02, 95%CI = -0.06;0.02, p = .366).

Stability of cognitive impairment: remitted versus persistently depressed patients

Whether remission of depression went together with an amelioration of cognitive deficits was analysed in a sub-sample from which patients already in remission at baseline (MADRS < 10, n = 9) had been removed. At 6 months, 21 out of 48 (44%) available formerly depressed subjects were in remission, with another 14 out of 38 (37%) available patients in remission at 18 months. At both follow-ups, remitting patients performed closer to healthy controls than depressed patients but both groups were still considerably impaired in memory and executive functioning (Table

3). For processing speed, both groups showed impairment at 6 months, but no significant difference with healthy controls at the 18 months follow-up.

Stability of cognitive impairment: early versus late onset depression

When defined on a continuous scale, age of onset was not significantly associated with executive functioning (baseline: b = 0.00, 95%CI = -0.03;0.03, p = .915; 6 months: b = -0.01, 95%CI = -0.03;0.01, p = .423; 18 months: b = -0.02, 95%CI = -0.05;0.01, p = .226) or processing speed (baseline: b = 0.02, 95%CI = -0.01;0.05, p = .227; 6 months: b = -0.00, 95%CI = -0.02;0.02, p = .955; 18 months: b = 0.00, 95%CI = -0.02;0.03, p = .796), but increasing age of onset was negatively related to episodic memory (baseline: b = -0.03, 95%CI = -0.06;-0.00, p = .049; 6 months: b = -0.03, 95%CI = -0.05;-0.01, p = .010; 18 months: b = -0.03, 95%CI = -0.05;-0.00, p = .043). Thirty (45%) had an onset before age 60 (early onset depression, EOD) and 37 (55%) thereafter (late onset depression, LOD). Both groups were impaired relative to controls at all time points in memory and executive functioning and at baseline and 6 months testing of processing speed, but processing speed was not significantly impaired in either onset group at the 18 months follow-up (Table 3). Mean z-score differences with controls (as displayed in Table 3) suggest some improvement in EOD for all domains, while LOD showed signs of deterioration in memory and executive functioning relative to controls. Paired t-tests on the longitudinal association between 6 and 18 months cognition confirmed this by showing improved memory scores in controls (t = -3.24, df = 31, p = .003) and EOD (t = -2.63, df = 18, p = .017), but not LOD (t = -1.50, df = 19, p = .150) and stable executive functioning scores in controls (t = 0.22, df = 31, p = .828) and EOD (t = -1.70, df = 18, p = .106), yet decline in LOD (t = 2.33, df = 19, p = .031).

Stability of cognitive impairment: influence of antidepressant use

Both the acute effects of current AD use at time of testing (yes, no) and possible long-term effects due to (cumulative) lifetime duration of AD intake (in weeks) were analysed. Duration of lifetime AD intake was not significantly associated with memory (b = 0.001, 95%CI = -0.001;0.004, p = .299; 6 months: b = 0.001, 95%CI = -0.002;0.003, p = .486; 18 months: b = 0.001, 95%CI = -0.002;0.003, p = .533), executive functioning (b = 0.000, 95%CI = -0.003;0.003, p = .942; 6 months: b = -0.002, 95%CI = -0.003;0.002, p = .863; 18 months: b = 0.002, 95%CI = -0.001;0.007,

p = .178) or processing speed (b = -0.001, 95%CI = -0.004;0.002, p = .503; 6 months: b = 0.001, 95%CI = -0.001;0.003, p = .247; 18 months: b = 0.000, 95%CI = -0.002;0.002, p = .958). At baseline, 57 (85%) patients were on medication. Of those available at follow-up, 46 (81%) were on AD at 6 months while 11 (19%) were not, and 34 (79%) were on AD at 18 months while 9 (21%) were not. Both, current AD users and non-user, displayed significant memory impairment at all time points and impaired executive functioning and processing speed at baseline and 6 months (Table 3). Overall, non-users had lower mean z-scores in all domains at baseline and 6 months, yet at 18 months, they did not differ significantly from controls in executive functioning and processing speed.

<<< PLEASE INSERT TABLE 3 HERE >>>

Exploratory analyses of 4 year follow-up data

LTFU from baseline to 4 year follow-up was high with 67 (65%) of baseline participants dropping out of the study (52 (78%) patients, 15 (41%) of controls). Reasons for LTFU were refusal (n = 41, 61%), death (n = 10, 15%), being too late for follow-up (n = 6, 9%), physical health (n = 6, 9%), and other (n = 4, 6%). One patient had developed possible dementia. Being LTFU at 4 years was independent of age (t = -1.41, df = 101, p = .160), gender (χ^2 = 2.27, df = 101, p = .132), remission status at 18 months (χ^2 = 0.83, df = 43, p = .362) and baseline executive functioning (p = .112) and processing speed scores (p = .589), but was significantly associated with fewer years of education (t = -2.06, df = 101, p = .042) and worse baseline episodic memory (t = -2.72, df = 68, p = .008). In addition, patients with a later onset (t = -2.53, df = 65, p = .014) were more likely to be LTFU. Taken together, this pattern reflects the higher attrition in the patient group as opposed to controls.

Of the 15 patients followed-up, 6 had a GCI at baseline and 3 of them had persistent GCI after 4 years, but statistical testing failed to reach significance (OR = 8.0, 95%CI = 0.58;110.27, p = .120). A rather wide 95% confidence interval indicated that this was probably due to small sample size, and it is notable that the OR was similar in magnitude to that found at 6 and 18 months. Regarding domain specific impairment, t-tests suggest a pattern that is consistent with the 6 and 18 months follow-up, but tests lacked power and were therefore not always conclusive. Thus, patients' impairment seemed to persist relative to controls in executive functioning (t = 3.00, df

= 34, p = .005), and processing speed (t = 2.36, df = 29, p = .025), with a trend into the same direction for episodic memory (t = 1.90, df = 34, p = .065).

Discussion

Main findings

We found that cognitive impairment in depressed subjects persists in many subjects, affects multiple cognitive domains and is not significantly influenced by illness factors such as current mood, remission status or current antidepressant (AD) use. Persistence was only partially explained by information processing speed. Patients with a later age of onset displayed worse episodic memory functioning.

The 18 months findings augment earlier reports of shorter follow-up duration (Adler et al., 2004; Bhalla et al., 2006; Lee et al., 2007) and studies in younger cohorts (Weiland-Fiedler et al., 2004; Airaksinen et al., 2006; Reppermund et al., 2007) showing that cognitive deficits are highly persistent in depressive disorder. Furthermore our findings show that incident cognitive impairment can develop in people with prevalent depression while (some) amelioration of deficits occurs in some individuals with initial deficits. Yet, the most common outcome is that of no change at all: persistent impairment or persistent absence of it.

State or trait effects?

Patients' impairments in single cognitive domains were independent of current symptom severity and not related to state effects such as current mood. Likewise, remitting patients showed similar cognitive impairments as depressed patients, albeit milder. Persistent deficits have been reported frequently (Abas et al., 1990; Beats et al., 1996; Nebes et al., 2000; Devanand et al., 2003; Portella et al., 2003; Adler et al., 2004; Neu et al., 2005; Bhalla et al., 2006; Lee et al., 2007) and are a core feature of the disorder itself. We found mixed results for the influence of AD treatment on cognition, but overall, there were only small differences between those who were and were not on medication. If anything, patients taking AD's performed slightly better in all cognitive domains at baseline and 6 months, which does not imply that medication affected cognition negatively in this sample. Inconsistent with this was that those who did not take AD's did not differ from controls at 18 months follow-up testing of executive functioning and processing speed. While at least for executive functioning

this might have been due to lack of power (the mean score of the eight patients tested and currently not on AD was still one standard deviation below controls), the lack of a consistent effect of AD treatment can be seen as evidence that it was not a major factor mediating cognitive deficits in our sample. In addition, lifetime antidepressant treatment had no major effects on cognitive functioning at any time point. Taken together, these findings imply a trait effect on neurocognition, most probably caused by structural cerebral changes which have been consistently reported in depression, especially LOD (Schweitzer et al., 2001, Herrmann et al., 2008).

The role of processing speed

Consistent with the literature, impairment was found to affect multiple cognitive domains, including episodic memory, executive functioning and processing speed (Thomas and O'Brien, 2008). Like in earlier reports, deficient processing speed made major contributions to cognitive deficits in other domains (Nebes et al., 2000; Butters et al., 2004). In the present study however, its effect on executive functioning deficits was greater than on memory deficits, confirming one earlier report (Delaloye et al., 2008). However, it was insufficient to fully explain differences between patients and controls, indicating other deficits exist in parallel. These may stem from structural brain changes, including hippocampal atrophy (Sapolsky, 2000; Steffens et al., 2000; O'Brien et al., 2004; Hickie et al., 2005), frontal lobe atrophy/volume reduction (Schweitzer et al., 2001; Almeida et al., 2003; Lavretsky et al., 2004) and (mainly frontal) deep white matter lesions (Herrmann et al., 2008), which, in their diversity, do not suggest single-domain impairment.

Biological explanations for cognitive impairment in late life depression

Current explanations of potential mechanisms for these brain changes focus on cerebrovascular pathology (Alexopoulos et al., 1997) and glucocorticoid action (Sapolsky et al., 1986). The “vascular hypothesis” (Alexopoulos, 2006) is based on the consistent finding of white matter hyperintensities (Herrmann et al., 2008), especially in the form of ischemic lesions (Thomas et al., 2002). In normal ageing (Turken et al., 2008) and multiple sclerosis (Amato et al., 2008) such lesions are associated with reduced processing speed, but have also been related to executive functioning deficits in late life depression (Sheline et al., 2008). The “glucocorticoid

cascade hypothesis", based on animal models (O'Brien, 1997; Sapolsky, 2000; McEwen, 2005), proposes the dysregulation of the hypothalamic-pituitary-adrenal axis leads to brain atrophy but direct evidence in humans has been inconsistent (O'Brien et al., 2004).

Age of onset of depression

Apparently incompatible with the glucocorticoid cascade hypothesis, subjects with an early onset (and thus a longer illness duration) did not display greater memory deficits or increasing memory deficits over time, which may point to different pathogenic pathways between both onset groups. LOD is more strongly related to cerebrovascular changes than EOD (Schweitzer et al., 2001; Herrmann et al., 2008), and they demonstrate greater hippocampal volume reduction (Lloyd et al., 2004; Hickie et al., 2005). These changes might be superimposed on any pathophysiological changes that are shared with EOD (e.g. glucocorticoid action) and so explain the greater cognitive deficits seen in LOD.

Long term course of late life depression

During the medium-term course (baseline to 18 months), we found little evidence of further progression of deficits. Patients' change in test scores paralleled that seen in controls, which implies that both profited equally from learning effects and increasing task familiarity. Patients with late onset depression tended to show worsening of memory and executive functioning relative to controls, either due to absence of improvement or true decline, which was not observed in early onset patients. The exploratory analyses of the four year data suggest patients remain impaired long-term, but again without evidence of further decline and only one patient developed dementia during the study. As patients with more severe impairment tended to drop out of the study, this might however give a too favorable picture of the true course.

Methodological considerations

The present study has several strengths including an age and gender matched healthy comparison group tested at the same time points, a relatively long follow-up duration and the administration of a comprehensive neuropsychological test battery tapping into core cognitive domains. However, some methodological shortcomings have also to be considered. First, this study was observational. Hence we did not

manipulate antidepressant regime. Other studies found improvement of cognition with AD use, mainly in subgroups of good responding patients (Butters et al., 2000; Gallassi et al., 2006; Mandelli et al., 2006). Cognitive functioning might therefore still be a suitable target for AD treatment, especially since they displayed somewhat better cognitive functioning in the present study, too, although staying impaired. Second, more subjects could be tested with the extended neuropsychological test battery at follow-up than at baseline, and thus groups at different time points are not perfectly comparable. Therefore we focussed primarily on the cross-sectional analyses and tested longitudinal changes between age of onset groups only from 6 to 18 months yet not from baseline. In addition, in contrast to some other reports, we did not control for estimated IQ, but instead used years of education to adjust for premorbid level of functioning. Lost-to follow-up at 18 months among patients was within normal range and unrelated to differences in variables of interest to the present study, with the exception of a higher dropout among antidepressant users. Still, 75% of those seen at 18 months were on medication and it therefore seems unlikely that bias occurred due to selective drop-out. However, coefficients suggest that loss-to follow-up was preceded by worse cognition at previous assessments. This would explain the apparent convergence of patients and controls at the 18 months assessment (see Table 2). Finally, we reported the four year data because of the paucity of longer term studies in the literature, but at this point we observed high and seemingly non-random drop-out among patients, so we advise to interpret these results with due caution. Further studies of comparable follow-up length (and beyond) are clearly needed to verify these findings.

Conclusion

The present study shows that cognitive deficits in late life depression tend to persist up to at least 4 years without further deterioration, affect multiple domains and appear to be related to trait rather than state effects. Differences in the severity and course of cognitive deficits due to age of onset imply different pathogenic processes between early and late onset depression.

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TABLES AND FIGURES

Table 1. Baseline demographic characteristics for depressed and control subjects.

	Patients *N = 67*	**Controls** *N = 36*	**P**
Age, years, mean(SD)	74.1(6.7)	73.4(6.9)	ns
Gender, % female	53 (79)	27 (75)	ns
Education, years, mean(SD)	9.6 (2.1)	10.5 (2.1)	.042
MADRS, mean(SD)	23.6 (10.4)	2.2 (2.2)	< .001
Age of onset, mean(range)	57.4 (17-85)	-	-
Illness duration, weeks, mean(range)	52.9 (2-268)	-	-
Episodes, n, mean(range)	3.1 (1-15)	-	-
In remission, n(%)	9 (13)	-	-
With melancholic features, n(%)	27 (47)	-	-
Severely depressed, DSM-IV, n(%)	22 (33)	-	-
With psychotic symptoms, n(%)	9 (16)	-	-
Antidepressants, n(%)[a]			
None	11 (16)	-	-
SSRI's	36 (54)	-	-
SNRI's	12 (18)	-	-
Tricyclics	7 (10)	-	-
MAO inhibitors	3 (4)	-	-
Pre-baseline electroconvulsive treatment, n(%)	21 (31)	-	-

[a] Percentages do not add up to 100 because two depressed subjects were taking SSRI (citalopram) and tricyclic (one dothiepin, one lofepramine) antidepressant medication.

Figure 1. Diagram showing numbers of depressed patients with and without generalized cognitive impairment (GCI) at each assessment. Arrows indicate how many patients were lost-to follow-up (LTFU), remained with or without GCI, or made transitions between GCI groups from baseline to follow up. The odds ratio (OR) and p-value for having GCI at follow-up given GCI at baseline is also shown.

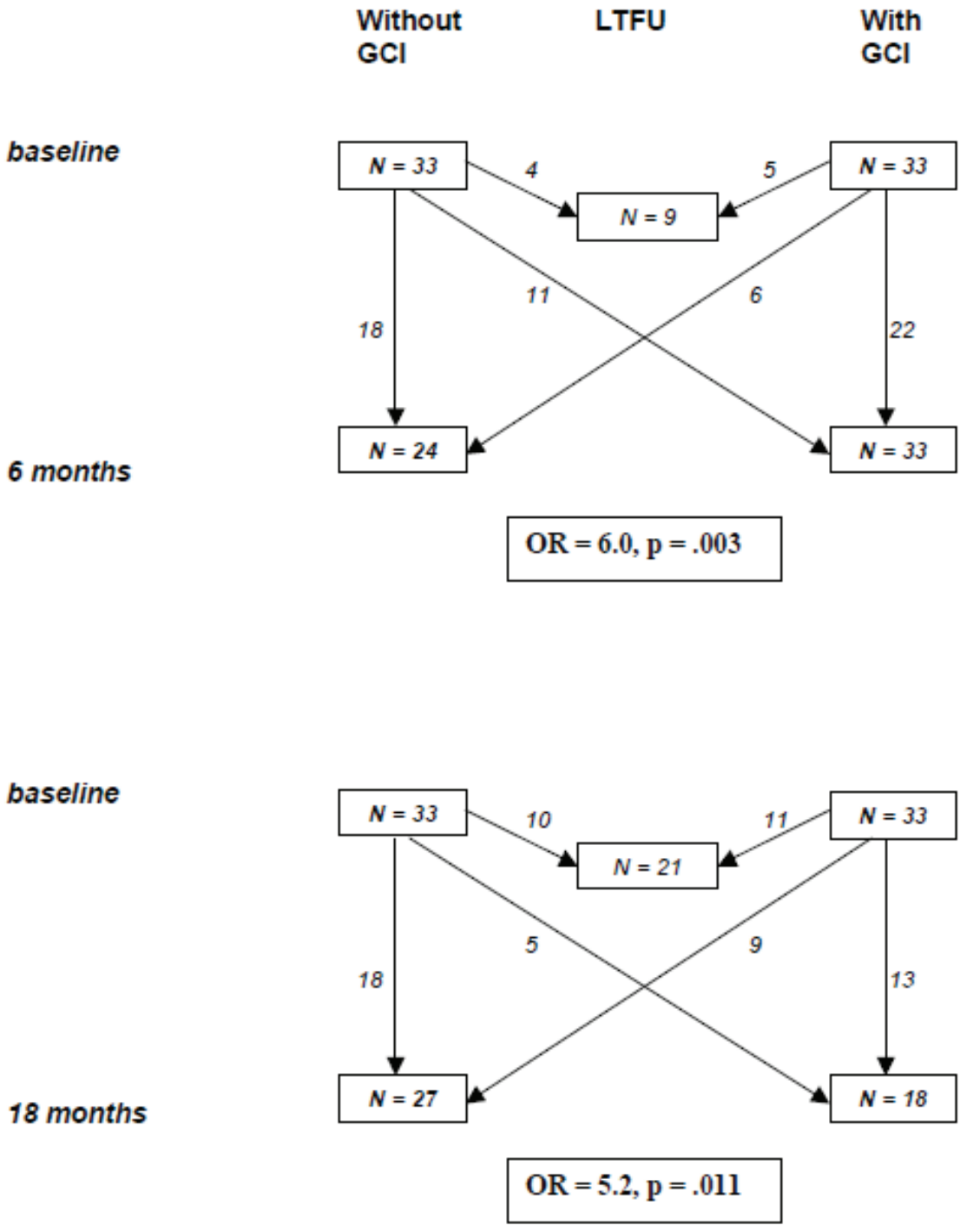

Table 2. Difference in mean z-scores of individual cognitive domains between depressed subjects and controls at baseline and follow-up.

		Controls versus Depressed			Adjusted for processing speed		
		Z-score diff.	95%CI	R^2	Z-score diff.	95%CI	R^2
Episodic memory	baseline	-1.50***	-2.04;-0.97	0.44	-1.18***	-1.73;-0.62	0.52
	6 months	-1.46***	-2.03;-0.89	0.32	-0.86**	-1.46;-0.25	0.40
	18 months	-1.41***	-2.05;-0.76	0.28	-1.09**	-1.77;-0.42	0.34
Executive functioning	baseline	-1.40***	-2.00;-0.80	0.33	-0.85*	-1.50;-0.19	0.42
	6 months	-1.48***	-2.04;-0.91	0.34	-0.90**	-1.49;-0.32	0.41
	18 months	-1.15***	-1.83;-0.48	0.29	-0.67*	-1.28;-0.06	0.45
Processing speed	baseline	-1.13***	-1.80;-0.46	0.17	-	-	-
	6 months	-1.09***	-1.59;-0.59	0.25	-	-	-
	18 months	-0.74*	-1.38;-0.10	0.18	-	-	-

*** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$

Figure 2. Plotted unadjusted z-score means illustrating cognitive trajectories over time for control and depressed subjects in individual cognitive domains.

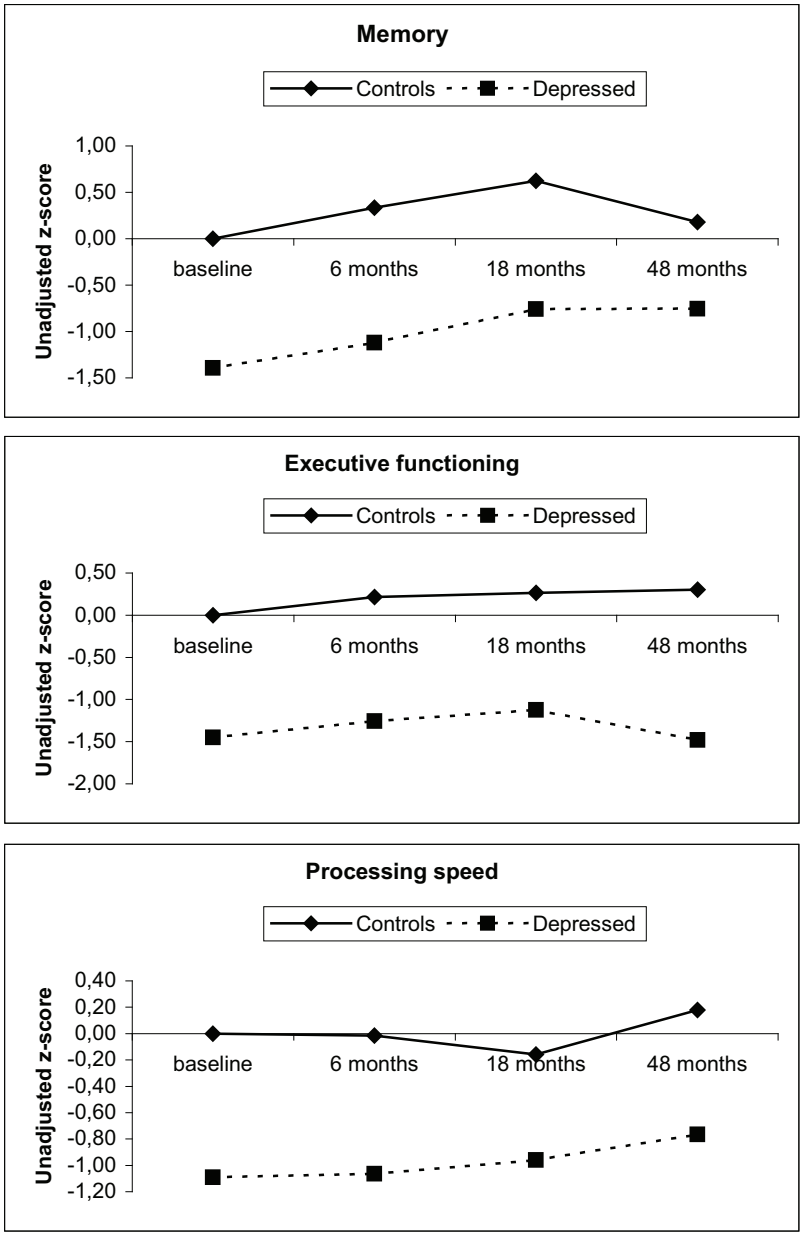

Table 3. Association between categorical measures of remission status, age of onset and antidepressant use on cognition[a].

		Remission[b]				Onset ≥ 60 years				AD use[c]			
		Yes	95%CI	No	95%CI	Yes	95%CI	No	95%CI	Yes	95%CI	No	95%CI
Episodic memory	baseline	-	-	-	-	-1.68***	-2.29;-1.08	-1.18**	-1.91;-0.44	-1.42***	-1.97;-0.88	-2.19***	-3.36;-1.01
	6 months	-1.25***	-1.98;-0.53	-1.75***	-2.43;-1.07	-1.73***	-2.37;-1.09	-1.07**	-1.79;-0.36	-1.39***	-1.99;-0.79	-1.71***	-2.65;-0.77
	18 months	-1.18**	-1.90;-0.45	-1.70***	-2.62;-0.77	-1.77***	-2.53;-1.00	-1.05**	-1.81;-0.29	-1.25***	-1.93;-0.56	-1.93***	-2.99;-0.88
Executive funct.	baseline	-	-	-	-	-1.25***	-1.94;-0.56	-1.64***	-2.44;-0.83	-1.37***	-1.99;-0.75	-1.68*	-3.05;-0.30
	6 months	-1.48***	-2.23;-0.73	-1.69***	-2.39;-0.98	-1.47***	-2.12;-0.82	-1.49***	-2.21;-0.77	-1.46***	-2.06;-0.86	-1.55***	-2.49;-0.62
	18 months	-1.05*	-1.85;-0.23	-1.40**	-2.42;-0.39	-1.51***	-2.31;-0.70	-0.81*	-1.61;-0.00	-1.11**	-1.82;-0.40	-1.03	-2.12;0.06
Processing speed	baseline	-	-	-	-	-1.05**	-1.82;-0.28	-1.29*	-2.28;-0.30	-1.03**	-1.73;-0.34	-1.80*	-3.22;-0.37
	6 months	-0.70*	-1.33;-0.08	-1.49***	-2.10;-0.88	-1.18***	-1.77;-0.59	-0.98**	-1.60;-0.35	-1.03***	-1.57;-0.50	-1.28**	-2.11;-0.46
	18 months	-0.62	-1.35;0.10	-0.85	-1.84;0.14	-0.78	-1.59;0.03	-0.70	-1.46;0.06	-0.82*	-1.50;-0.14	-0.24	-1.28;0.81

*** p ≤ .001, ** p ≤ .01, * p ≤ .05

[a] Values represent unadjusted z-score differences with healthy comparison subjects.

[b] Patients in remission at baseline were excluded in this analysis

[c] Current antidepressant use at time of testing