A STUDY OF DEPRESSED PATIENTS WITH SUBJECTIVE MEMORY COMPLAINTS : A VOLUMETRIC MRI STUDY OF THE HIPPOCAMPUS AND THE AMYGDALA

Armin von Gunten

MD (University of Lausanne, Switzerland),

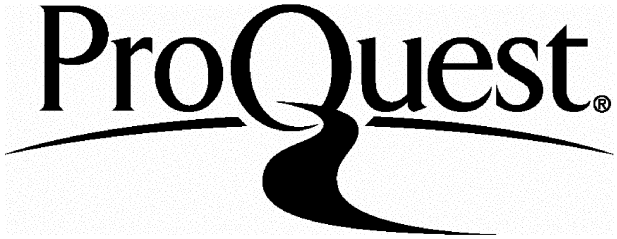
FMH psychiatry and psychotherapy (Foederatio Medicorum Helveticorum, Switzerland)

Thesis submitted to the University of London for the degree of MPhil, 2003

Institute of Neurology

Queen Square

London WC1N 3BG



Abstract

Subjective memory complaints are common in depression and not closely related to performance on memory tests. The possibility that hippocampal and amygdalar abnormalities may be related to subjective memory problems in these patients has not been explored. This study investigates volumetric changes in the hippocampus and the amygdala in depressed, non-demented patients with persistent cognitive complaints.

Methods. Fourteen non-demented patients who fulfilled ICD-10 criteria for depression and who persistently complained of "memory" difficulties were studied. They had been tested neuropsychologically when first referred to the National Hospital for Neurology and Neurosurgery on average three and a half years before this study. Volumetric magnetic resonance imaging (MRI) was performed in 1998 and neuropsychological testing repeated. Fourteen healthy volunteers with no history of psychiatric illness matched for age and gender were used as controls for MRI data. Volumetric measurements of amygdala and hippocampus were performed blind to side and group membership.

Results. Five patients had intellectual or memory underfunctioning when first tested, but all had improved or returned to normal by the time of the study. The volume of the left amygdala was significantly smaller in patients compared to controls. In the five patients with initial neuropsychological impairment the volume of the left hippocampus tended to be smaller than in the unimpaired. Seven patients still complained of memory difficulties at the time of the study and this was unrelated to objective neuropsychological performance.

Conclusions. The study suggests that subjective memory complaints in depression are not a harbinger of dementia. The reduction of amygdalar volume observed in these patients is more likely to be related to depression and subjective memory complaints than to cognitive impairment, but may be relevant to the both. Changes in hippocampal volume may be more closely related to the subtle cognitive impairment observed and to subjective memory loss.

Table of contents

Contributors to the thesis

Personal contribution

For this study, I

1) interviewed all the patients and caregivers
2) administered all the clinical instruments
3) prepared the protocol to measure hippocampal/amygdalar volume
4) performed all the volumetric measurements
5) did the statistical analysis
6) wrote up the thesis

Contributors

1) Prof M Ron was the supervisor of this study
2) Dr L Cipolotti advised on the analysis of the neuropsychological data
3) Dr N Fox put the MRI scans of healthy controls at my disposal and helped with the design of the volumetric protocol
4) Ms M Hall performed the psychometric tests
5) Prof G du Boulay did the qualitative analysis of the MRI scans

Professor M Ron approves that I have contributed to this thesis as stated above

Marta Ron

Professor M Ron *London, the* 21/3/2003

List of tables and appendices

(Tables are in the text)

Acknowledgements

I am indebted to my wife Catherine and my children, Cyril and Solène, who have courageously faced the time I spent far from home.

I am extremely grateful to the late Professor Jean Wertheimer for making my time in London possible, and to Professor Maria Ron for accepting me as a postgraduate student in her department and for her competent and amiable guidance.

My thanks also to Dr Lisa Cipolotti who agreed to be the co-supervisor of this thesis, and to Dr Nick Fox, both of whom contributed crucially to this study.

I also thank Dr Ludger Tebartz van Elst, Miriam Hall, Robert Hart, Professor George du Boulay, David MacManus, and Dr Richard Harvey who all helped greatly.

INTRODUCTION

Depression is the most frequent psychiatric disturbance. Community surveys have found lifetime prevalence rates for major depressive episodes to be as high as 17%, even though in half of these cases the intensity may be mild. The prevalence depends on the population examined: 5% of people in primary care settings and up to 30% in institutional settings. The WHO expects depression to have the second highest prevalence rate of all human diseases by 2020. Its current socio-economic impact is already as high as that of other common diseases such as rheumatoid arthritis.

Depression is a syndrome which encompasses different diagnostic categories as defined by ICD-10 (bipolar affective disorder, depressive episodes, recurrent depression, persistent affective disorders including dysthymia and cyclothymia, other and not otherwise specified affective disorders) or DSM-IV (depressive disorders including major depressive disorder and dysthymia, bipolar disorders, mood disorder due to medical conditions or substance-induced mood disorder, and mood disorder not otherwise specified).

The depressive syndrome comprises symptoms or subjective features including sadness, hopelessness and despair, anxiety, anhedonia or lack of pleasure, feelings of guilt, ideas about death and suicidal ideation, loss of appetite, fatigue as well as memory or other cognitive complaints. Signs or objective features include tearfulness, paucity of facial expression, psychomotor retardation, social withdrawal, mood-congruent delusions, suicidal or auto-aggressive behaviour, weight loss, sleep disturbances as well as cognitive impairment.

Subjective cognitive impairment is a frequent symptom of depression. However, subjective memory impairment is thought to be a poor predictor of objective memory deficits. Objective cognitive impairment is often observed and in the depressed elderly its prevalence may be as high as 30% (Ebly et al. 1995). Memory changes are the most frequent cognitive impairment in the depressed, but mild disturbance of executive functions and language, praxis, and gnosis can be found. The outcome of both subjective and objective cognitive impairment is uncertain. However, it is becoming increasingly evident that some patients still complain of and/or exhibit cognitive deficits after affective symptoms have recovered.

The aetiology of depression is likely to be multi-factorial and its pathogenesis is complex and the same is likely to apply to the cognitive impairment that accompanies it. In recent years, increasing interest has been focused on structural brain abnormalities in depressed patients. Growing evidence stemming from neuroimaging studies suggests that in at least some patients depression might be secondary to either global or focal brain abnormalities. Focal brain changes have been found in medial temporal structures. However, little is known about the role the amygdala may play in depression nor do we understand the role of the hippocampus and the amygdala in causing or maintaining both the subjective and cognitive deficits. In short, it is unclear which clinical features of depression correspond to the various brain changes observed.

Intrigued by a group of depressed patients with persistent cognitive complaints who did not fulfil the diagnostic criteria for dementia, I set out to explore the possible link between structural brain changes in the amygdala and hippocampus and subjective and objective memory changes in a group of carefully selected patients using volumetric MRI techniques.

To set the context of this study, a review of objective and subjective memory deficits and of structural brain abnormalities in depression is included.

LITERATURE REVIEW

Memory abnormalities in depression

Chapter 1

The pattern of memory impairment in depression

Cognitive changes are a common part of the depressive syndrome. This has long been recognized, but systematic investigations only date back 30 years. It is sometimes said that disorders of mood are usually associated with cognitive impairment (Emery & Oxman 1992), but only very few studies have addressed the topic of the prevalence of cognitive deficits in depression. Prevalence rates of cognitive impairment between 30% (Ebly et al. 1995) and 70% (Abas et al. 1990) have been reported in the elderly depressed. Although cognitive impairment in depression may increase with age, recent studies report that memory and other cognitive deficits are also common in younger depressed patients (Austin et al. 1992a, Burt et al. 1995), but their frequency remains uncertain.

In this review, the term cognition will be used to refer to a series of functions including memory, attention, executive functions, language, gnosis and praxis.

The most frequently reported neuropsychological findings in depressed patients are impaired memory and attention deficits. Clinical studies focus

mostly, and experimental work exclusively, on memory. Language, gnosis and praxis are less commonly investigated and usually considered intact. This review focuses on memory and attention impairment in depression. The various components of memory and the specific problems described in depression will be reviewed in turn.

Memory components

The distinction between declarative or explicit and procedural or implicit memory is generally accepted. Declarative memory refers to our conscious knowledge about ourselves and the world. It is further subdivided into episodic and semantic memory. Procedural memory refers to sensory-motor skills, conditioning and priming to which we have no conscious access.

Declarative or explicit memory

Declarative or explicit memory comprises episodic and semantic memory. Episodic memory refers to learning new information and to information characterized by its temporo-spatial or contextual attributes such as much of our knowledge about ourselves. Knowledge about the world, facts, concepts, words and so on is called semantic memory.

Before a stimulus can be retrieved and used it must first be laid down in memory stores. These processes can be understood as a chain of information processing steps. A percept (or sensory input) is kept in a very short-term memory system usually referred to as sensory register. Since information is treated in a modality-specific way, an iconic sensory register for visual stimuli and an echoic one for auditory stimuli are usually distinguished. The percept is kept in the sensory register for a few hundred milliseconds and then it either fades or is further processed. This first step is very short-term memory.

The representation in the sensory register can be forwarded to a short-term memory system called working memory which can hold information over a few seconds, just long enough to enable us to keep track of the information we manipulate during the performance of cognitive tasks.
From working memory, the representation of a stimulus can be encoded in long-term memory stores, when we learn new information, and is held there forever or forgotten again. From long-term memory stores, information can be retrieved freely or via associations such as those from the category the target stimulus belongs to. Recognition is the retrieval of the correct item among a series of non-target stimuli or distractors.

Very short-term memory.

The sensory registers, either iconic or echoic, store sensory input for a few hundred milliseconds (ms). Very short-term memory can be tested by backward masking : a stimulus (e.g. the letter T) is projected tachistoscopically on a screen for a few ms. If a second stimulus (e.g. a series of Xs projected simultaneously) is projected immediately after the letter T, the letter T will be masked by the subsequent stimulus (Xs). As the time gap between the first and the second stimulus increases to the order of about 150 ms, normal subjects are usually able to remember having seen both stimuli. Patients with affective disorder show some evidence of prolonged masking and thus impaired processing at the very first step of memory formation (Rund & Landro 1990). However, in another study (Saccuzzo & Braff 1981), young hospitalized good-prognosis and poor-prognosis schizophrenics, depressed neurotic and bipolar manic patients were compared with normal controls. A tachistoscopic single-letter presentation and backward masking was used. Minimal stimulus duration for correct identification of the stimulus was significantly worse in schizophrenics, but depressed and hypomanic patients did not differ from the performances of normal controls.

Working memory.

Working memory as assessed by the Brown-Peterson task, which requires the subject to perform a cognitive task and then to count backwards to prevent rehearsal, was not altered in a study (Brown et al. 1994) of an elderly depressed patient group (mean age 60 years) as compared with normal controls. The same finding has been reported using digit span in younger patients (Austin et al. 1992a) and in patients with severe major depression (Ilsley et al. 1995). However, digit span was significantly shorter in severely depressed patients compared with normal controls in Danion et al.'s study (1991). Another study (Beats et al. 1996) analyzed visual working memory using an computerized version of the Corsi test (where the subject is asked to remember a sequence of blocks on a board) and found no difference between elderly patients suffering form major depression and normal controls.

More interesting are studies trying to dissect the various working memory components. Channon et al. (1993) tried to dissect working memory in the depressed according to Baddley and Hitch's model : the articulatory loop and the visuo-spatial sketch pad were unimpaired as indicated by normal performances on the block digit span, trail making and letter cancellation tasks. However, some tasks thought to require the participation of the central executive were found to be impaired. Thus, patients with major depression reproduced fewer items than normal controls in the backward digit span task. Furthermore, on the PASAT, an auditory serial addition test where subjects had to add pairs of digits so that each new digit was added to the immediately preceding one, the depressed group scored worse than controls although this fell short of significance.

In summary, with the exception of one study, all findings point to an intact working memory in patients with depression, although subtle deficits affecting specific components of working memory may be present.

Episodic memory.

Incidental learning. Most information in working memory is quickly extinguished, but information can be forwarded to long-term memory stores, even if it has not been actively rehearsed, though the extent of normal incidental learning has not been clearly determined. There are no studies on depression explicitly addressing this issue, but one study (Sternberg & Jarvik 1976) using a one-trial verbal learning task, where stimuli were presented to the individual, but not immediately recalled and thus probably not enhanced, found identical results in depressed patients and normal controls when tested after a delay.

Learning, immediate free recall and delayed free recall. In cognitive assessments, learning is usually tested by repeated active rehearsal of test material over several trials. Learning new material may be affected by depression. Brand et al. (1992) demonstrated, using a 15-word learning task, that the immediate recall of the words presented was impaired in severely depressed patients after 3 and 5 trials, whereas both delayed recall (after a delay of 20 minutes) and recognition were normal. However, when these variables were tested after one learning trial only, immediate and delayed recall were both impaired. Retrieval therefore seems to be particularly impaired in the beginning of a learning task. In another group of severely depressed patients (Sternberg & Jarvik 1976), immediate recall of verbal and visual material was found to be decreased in depressed patients as compared with normal controls and so was delayed recall but only if the stimuli were previously rehearsed by immediate recall. This finding is similar to the one in Brand et al.'s study quoted above. Other investigators (Brown et al. 1994, Austin et al. 1992a) have observed a worse performance, but a similar rate of verbal learning in depressed patients as compared to normal controls. It seems therefore that learning mechanisms are essentially preserved in depression, but their overall capacity is reduced in particular at the beginning of a learning task.

Free recall and recognition. Brown et al. (1994) divided 29 depressed patients in a cognitively unimpaired, a cognitively intermediate and a cognitively impaired group and compared them with 16 normal controls. The mean age of this sample was almost 60 years. Cognitively unimpaired patients had worse performances than normal controls in delayed verbal recall and to a lesser extent in recognition and short-term memory. Immediate recall of prose material, however, was relatively unimpaired as was the rate of learning. When the three depressed subgroups were compared, the data suggested a gradient in their performance, but no qualitatively distinct impairment separated these subgroups. In addition to the Brown study, other groups (Austin et al. 1992a, Golinkoff & Sweeney 1989) have also found recall and recognition to be affected in younger patients. A meta-analysis (Burt et al. 1995) supports the conclusion that both recognition and recall are affected in depression. However, results of other studies contradict this view. Depressed patients in the study of Ilsley et al. (1995) demonstrated deficits in free recall, both immediate and delayed, whereas recognition was normal. In another study (Purcell et al. 1997), non-verbal recognition using a delayed matching to sample task, a spatial recognition task and a pattern recognition task were normal. This finding is noteworthy, since the selective recall deficit suggests that material has been encoded, but that search and retrieval processes may be impaired in depression.

Visual and verbal memory. Depressed patients seem to perform equally well in verbal and visual tests although deciding whether such tests are of comparable difficulty may be problematic. Reischies (1988) examined 55 severely depressed patients and 18 normal controls (mean age 60 years) using a verbal memory task, in which the patients had to recall the maximum number of chunks in a text, and a visual memory task where the patients were asked to remember an itinerary on a map. He found deficits of comparable severity in both verbal and non-verbal memory tasks. Burt et al. (1995) performed a meta-analysis on a large number of studies on cognition in depression and tried to determine the effect of depression on verbal

versus visual memory. The results were contradictory as to recall, whereas in recognition there seemed to be a greater depression effect for verbal than for visual stimuli.

Forgetting. Memory decays quickly in the beginning and speed of forgetting becomes slower over time. Only a few studies on depression address this topic explicitly. Austin et al. (1992a) examined 20 neurotic and 20 endogenous depressives and compared them with 20 normal controls. As a measure of forgetting, they used the difference between 'trial 5 recall' and 'delayed recall' using a five trial auditory verbal learning test. The patients were impaired both on delayed recall and recognition, but not on forgetting. In another study (Sternberg & Jarvik 1976), memory performance of 26 severely depressed patients was compared both with that of normal controls and with euthymic affective patients. They studied forgetting on two verbal and one visual one-trial memory tests and using a global score based on all three tests ; they failed to find significant differences.

Procedural or implicit memory

Procedural or implicit memory is comprised of sensori-motor skills, conditioning and priming. Only priming - the unconscious association of a stimulus with a similar one that has previously occurred - has been studied in depression.

Priming.

Priming is the only form of implicit memory to have been studied in depression. Priming can be demonstrated using word-completion tasks. Patients are given a list of words to read. When asked to complete word-stems, subjects use significantly more words from the previous list than non-related words. This phenomenon is referred to as priming. Based on such a task, impaired explicit memory (free recall task) and preserved implicit memory have been found (Danion et al. 1991) in 18 severely depressed patients with major unipolar disease as compared to normal

controls. Similarly, Ilsley et al. (1995) using a word-stem completion task found their 15 patients with severe major depression to be unimpaired in this test. Neither Bazin et al. (1994) nor Golinkoff and Sweeney (1989) found their patients with major depression to be impaired in implicit memory, the latter using a frequency-of-occurrence-of-words judgment which is another task to test implicit memory.

Psychomotor speed and reaction time

Reischies (1988) found psychomotor speed to be significantly slower in moderately depressed unipolar and bipolar patients with a mean age of 60 years than in normal matched controls. Psychomotor speed in this study was assessed by measuring the time subjects required to complete the Trail Making Test A in which 25 numbers must be successively linked. In another setting (Ilsley et al. 1995), speed in performing the Digit Symbol Substitution Test of the WAIS-R was significantly slower in 15 severely depressed patients as compared with normal controls. These patients were younger (mean age 47 years) than those in Reischies study. In Tarbuck and Paykel's study (1995), an age effect in depressed patients was found insofar as simple reaction time, choice reaction time and speed on a letter cancellation task revealed that older severely depressed patients (mean age approximately 70 years) were significantly slower than a younger group (mean age 41 years) matched for gender, number of previous episodes of affective illness, estimated verbal IQ, and severity of depression as measured using the Hamilton depression scale and the MADRS (Montgomery Asberg Depression Rating Scale). However, no normal control group was assessed in this study. Abas et al. (1990) used a delayed-matching-to-sample test in which the subject was required to identify the stimulus, out of four choice patterns, which exactly matched a sample stimulus. The choice stimuli appeared only after the sample stimulus had disappeared with time delays of 0, 4, 8 or 16 seconds. The computer set-up allowed to measure the subject's response latency between the appearance

of the choice stimuli and their touching the target stimulus on the screen. In the normal controls, the latency increased as the task became more demanding that is after the 8- and 16-second delay. The depressed group, however, was consistently slower to respond but irrespectively of the level of demand of the task.

These studies do not separate the contribution of the motor and cognitive components of the tasks used to measure psychomotor slowing in depressed patients. Purcell et al. (1997), using the tower of London test, found young unipolar depressed patients to be impaired on motor but not cognitive speed. In this task, the subjects are required to copy an arrangement of coloured balls in the least number of moves. However, the study of Beats et al. (1996) used the same task and found that the depressed patients had global slowing affecting both motor and cognitive processing speed, but response accuracy was unimpaired. Thus, age may be related to slow psychomotor processing.

The relationship of psychomotor speed and severity of depression was assessed by Austin et al. (1992a) using the Trail Making Tests A and B and the Digit Symbol Substitution Test. Speed was found to be slower in an 'endogenous' or psychotic subgroup of 40 depressed patients (21 to 67 years of age) than in the 'neurotic' subgroup, even though the latter were slower than normal controls. This finding was interpreted as reflecting « decreased psychomotor speed in more severely depressed patients ».

Effortful tasks

Several studies have tried to determine whether the memory difficulties observed in depressed subjects are related to the effort required to perform the tasks. Watts et al. (1990) tested immediate recall in 18 subjects with major depression and normal controls using lists of semantically related words. The lists were presented either in a random way or with a medium or high level of semantic categorization. Normal controls and depressed patients were able to benefit from an organized presentation, but normal

subjects were able to do so more than depressed patients. The difference between the depressed and control groups was greater at a medium level of semantic categorization. This finding could be explained, at least in part, as a ceiling or floor effect or as an artefact produced by the comparatively greater difficulty of a given task. However, motivational aspects and the perception of task difficulty may have been relevant.

In another study, Weingartner et al. (1981) tested ten patients with moderately severe depression, with a mean age of 44 years, on cued and un-cued recall. In the first experiment, subjects were asked to give a word with a similar sound to the one they were asked to recall (acoustic cueing) or a word with a related meaning (semantic cueing). According to the authors, semantic cueing requires more elaborate encoding operations than acoustic processing. Free recall was worse than cued recall in both normal controls and depressed patients. Both groups performed the same on acoustically cued words, but the depressed patients did worse on semantically cued words. Thus, the depressed patients had difficulty in the task that required the use of more elaborate encoding mechanisms. In the second experiment, subjects were asked to organize word lists into categories and to recall them. Depressed patients used more categories and remembered significantly fewer unrelated words than controls. In the third experiment, subjects had to recall word lists with different organizational levels beginning with a random list and progressing to 8, 4, and 2-category word lists. Depressed patients performed consistently worse than controls, except in the condition in which the word lists were highly organized with evident clustering. The authors concluded that deeper semantic encoding was impaired in depression, but that recall was helped by a high degree of organization. In short, depressed patients were less effective in organizing test material than normal subjects. Using a sorting task, Silberman et al. (1983) came to a similar conclusion, namely that depressed patients (1) failed to use encoding operations that would help later recall and (2) that they improved when the test material was presented to them in an organized way.

As an example of more generally impaired motivation in depression, Cohen et al. (1982) examined 11 young patients with either unipolar or bipolar depression, either in a euthymic state (3), in a moderately depressed state (3) or in a severely depressed state (5) and compared them with five normal controls. When asked to squeeze a dynamometer, the depressed subjects maintained a 50%-of-maximal-strength pressure over a shorter time than the normal individuals. Furthermore, they recalled fewer trigrams than normal people with recall being worse when the delay between presentation and retrieval increased. In general, the deficits worsened with the severity of depression. The authors reckoned that the parallel decrement of both the motor and cognitive functions was best interpreted as a "single deficit in the areas of the central motivational state".

Other studies have found little support for the notion that depressed patients find greater difficulty in performing effortful tasks. Austin et al. (1992a) interpreted the finding that recall and recognition were both affected in their depressive groups as an argument against the effortful hypothesis because delayed free recall is a harder task than recognition. Similarly, Burt et al. (1995), in a meta-analysis of depression and memory impairment, found no convincing evidence that effortful tasks were more impaired in depression.

Summary

Cognitive impairment is often present in depressive disorders. Memory dysfunction seems to be the most frequent cognitive impairment. The various components of memory may not all be disrupted to the same degree and some aspects of memory are likely to be normal in depressed patients. These include :

- the sensory registers except in depressed subjects with psychotic features
- working memory as long as the task does not rely more heavily on its executive components
- incidental learning
- forgetting
- priming.

Other components of memory more often impaired in depressed patients are :

- consolidation of memory especially after initial rehearsal
- search and retrieval mechanisms appear to be more impaired than encoding
- visual memory may possibly be more impaired than verbal memory
- tasks requiring sustained effort or executive capacities may also be more impaired.

Overall, the clinical experience shows that memory is frequently impaired in patients with depression. The different memory components are not uniformly impaired. However, the literature review shows equivocal results and this may point to a considerable variation of the cognitive symptoms in the individual patient rather than to a uniform pattern of memory impairment.

Chapter 2

Memory impairment, demographic and clinical features

Cognition as a function of depressive subtypes

Mention has already been made to the fact that cognitive changes are not limited to a specific type of affective disorder, although it remains possible that specific types of affective disorder may be accompanied by specific patterns of cognitive changes. A review of the literature can only go some way towards clarifying this issue as comparison between different studies is often extremely difficult. Over the years, different diagnostic classifications have been used and the variety of neuropsychological tests employed by these studies is endless. In addition, many studies have included patients with bipolar and unipolar depression, increasing the difficulty even further.

Memory in depressed unipolar and bipolar patients

Wolfe et al. (1987) compared word learning (Rey auditory verbal learning test) and verbal fluency in depressed unipolar and bipolar patients, in normal controls and Huntington disease patients (HD). Bipolar patients performed slightly better on tests of memory than HD patients who in turn were significantly more impaired than unipolar patients. In tests of word recognition, unipolar patients performed qualitatively the same as HD patients with both groups giving many false negative answers. Bipolar patients had a more severe illness than unipolar patients as measured by twice the number of hospital admissions and a longer duration of depression and this may have influenced the results. Burt et al.'s (1995) meta-analysis

(1995) found a stronger association between deficits in memory recall and bipolar than unipolar depression.

Memory in euthymic unipolar and bipolar patients

One study (Krabbendam et al. 2000) examined 22 bipolar patients in remission (mean age of 47 years) and found them to be impaired on short and long-term recall of the Auditory Verbal Learning Test. Paradiso et al. (1997) compared a small group of euthymic patients with recurrent unipolar disease with euthymic bipolar patients. Though their overall illness duration was shorter, unipolar patients performed worse than the bipolar patients on the Trail Making A and B Tests, the Stroop Colour Test, immediate memory test and the digit symbol subtest of the WAIS. Bipolar patients performed the same as healthy controls. The authors interpreted the results as due to impairment in executive functions.

Executive and other functions in decompensated unipolar and bipolar patients

In Wolfe et al.'s study (1987), bipolar patients performed slightly better on verbal fluency than HD patients who in turn were significantly more impaired than unipolar patients. In another study (Savard et al. 1980), severely depressed bipolar and unipolar patients (age range 20 to 50 years) were examined using the category subtest of the Halstead-Reitan battery. Bipolar patients, especially those over 40 years of age, were significantly more impaired than unipolar patients who performed the same as normal controls. Yet another study comparing young bipolar patients with a mixed affective state and depressed unipolar subjects on a series of neuropsychological tests including the WAIS, the Trail Making Test B, and the WCST found no significant differences between the two groups. Manic bipolar patients were identical to depressed bipolars and this held true for psychotic bipolars and non-psychotic bipolars (Goldberg et al. 1993). Robertson and Taylor (1985) compared middle-aged male remand prisoners

with manic-depressive illness, unipolar endogenous or reactive depression using visuo-spatial tasks (WAIS picture completion, block design, picture arrangement subscale ; simple to complex visual retention test) and verbal tasks (WAIS vocabulary, similarities and digit span subtests). The group as a whole performed worse on all tests except the vocabulary and similarities subtest of the WAIS than psychiatrically normal prisoners. Men with reactive depression had the most generalized picture of right-hemisphere disturbance, but they performed better on complex tasks such as picture completion or a visual retention task with items difficult to discriminate, while bipolar and unipolar patients had worse performances on some visual tasks. Interpretation of the data is difficult as patients in the manic-depressive group were in very different mood states when tested.

Executive and other functions in euthymic unipolar versus bipolar patients

Paradiso et al. (1997) found unipolar patients to perform worse than the bipolar patients on the Trail Making A and B Tests, the Stroop Colour Test, and the Digit Symbol subtest of the WAIS whereas bipolar patients performed the same as healthy controls. In another study (Krabbendam et al. 2000), bipolar patients in remission were impaired on letter tracking of the Concept Shifting Test and number and letter shifting of the Letter Digit Substitution Test as compared with healthy controls.

Further distinctions

Austin et al. (1992a) subdivided 40 middle-aged patients with major depression into a neurotic and an endogenous group according to a cut-off score of 6 on the Newcastle scale. Auditory verbal learning, recall and recognition were equally impaired in both groups, but endogenous depressives were more impaired on Digit Symbol Substitution and on the Trail Making Test because of slowing of their psychomotor speed.

In another study (Ilsley et al. 1995), 15 inpatients with major depressive disorder, with and without evidence of hallucinations or delusions, were studied; no differences between the groups were disclosed on neuropsychological examination comprising the Digit Span, the Rivermead Behavioural Memory Test, verbal fluency, the 'silly sentences' test as well as a test of verbal implicit learning and subsequent recall.
Although these studies found differences between cognitive deficits in clinical subtypes, they cannot unequivocally support the hypothesis that these differences are qualitative, but they may be one of degree.

Cognition in depression as a function of age

The studies reviewed so far show that both young and old patients with depression may have cognitive impairment. Overall, the pattern of cognitive impairment in the younger age group seems to be comparable to that in the elderly. A more important distinction may be between early and late-onset of depression.

Tarbuck and Paykel (1995) compared old severely depressed patients (mean age of 70 years) with a younger group (mean age of 41 years) matched by severity of depression. On most cognitive tests, the older group performed worse than the younger one. This effect was particularly marked for speed of performance as measured by simple reaction time, choice reaction time and speed on a letter cancellation task. The possible assumption from this study that worse cognitive performance may be secondary to age-related slowness and not specific to depression is, however, contradicted by the study of Palsson et al. (2000) who examined the neuropsychological functioning in a cohort of 85-year old community-dwelling patients with major depression and in healthy controls. The latter performed better than the depressed patients, a difference that was not due solely to the depressed patients' slowness since their performance was also decreased in tests which were not time-limited. In another study of patients with major depression

(Brauer Boone et al. 1994), three different age groups (46-59, 60-69, and 70-85 years) were investigated on a wide range of standard neuropsychological functions. In the two younger age groups, mild to moderate depression resulted in deficits of nonverbal memory, performance IQ and selected executive skills such as word fluency and WCST category performance as compared with normal controls. However, subjects belonging to the oldest group performed the same as normal controls. In other words, no depression effect was observed in the oldest age group.

Age of onset

A variety of studies hint at brain imaging differences (Coffey et al. 1989, Greenwald et al. 1997) and cerebrovascular risk factors (Greenwald et al. 1997) that may be different in late-onset and early-onset depression as suggested by Alexopoulos et al. (1992). Cognitive differences may also exist between early-onset and late-onset depression. Thus, one study (Salloway et al. 1996) examined severely affected patients with late-onset depression and found them to be more impaired than early-onset patients on most measures assessed (verbal fluency, motor programming, verbal learning and recall as well as visual reproduction) although the latter had higher depression scores on the Modified Hamilton Depression Rating Scale. The patients were matched for years of education and age, whereas mean age of onset of depression was 35.8 years in the early-onset group and 72.4 years in the late-onset group. Furthermore, the late-onset group had significantly more periventricular and deep white matter hyperintensities in magnetic resonance imaging (MRI). The overall length of depression of these patients was not estimated, but it is likely to be shorter in the late-onset group. More severe brain pathology in the late-onset patients may account for more pronounced cognitive impairment as compared with the early-onset group. Furthermore, one preliminary study (Lavretsky et al. 1999) has found that patients in whom the size of white matter MRI hyperintensities increased over time developed a chronic unremitting course of depression. The association between brain changes and chronicity of late-

life depression may point to the possibility that brain changes predispose to depression in the elderly and influence its outcome.

Cognition as a function of depressive severity

The best strategy to study the influence of depressive severity on the cognitive syndrome of depression is to test the same patient at various times when the severity of depression varies. Few studies have done this partly due to methodological problems of which the practice effect is only one. Moffoot et al. (1994) avoided practice effects by using parallel forms of all neuropsychological tasks administered. They tested 20 patients suffering from major melancholic depression (mean age of 45 years) with marked diurnal mood variation once in the morning and once in the evening and compared them with normal controls. A self-rating mood scale (Befindlichkeitsskala) was also administered and a blood sample taken to analyze total cortisol and ACTH levels. The depressed patients showed deficits of attention, working and episodic memory, psychomotor and recognition speed as well as of grip strength at the time of maximum depression. Their performance was markedly improved in the evening in parallel with mood improvement. However, their performance remained inferior to that of the controls at all times, although this was mostly not significant. Another study (Cohen et al. 1982) examined a small group of eleven young people (mean age 33.2 years) with either unipolar (9) or bipolar (2) depression, either in a euthymic state (3 patients), in a moderately depressed state (3 patients) or in a severely depressed state (5 patients). Five normal controls were used for comparison. Subjects were instructed to squeeze a dynamometer and to recall trigrams - that varied over trials to avoid practice effects - at intervals varying between 0 and 18 seconds. Greater severity of depression as measured by self-rating (Beck Depression Inventory) and caregiver scales (Bunney-Hamburg nurse rating scale and Hamilton Depression scale) was paralleled by both weaker motor and worse recall performance.

Other studies have looked at differences in patients with different degrees of severity of depression. One study (Smith et al. 1994) examined 36 young patients (mean age 44.3 years) with single-episode or recurrent major depressive disorder varying from mild to severe without psychotic features. Performance on word learning, recognition, and verbal fluency correlated negatively with severity of depression. However, it is not clear how homogeneous these patients were as to age and to educational level.

Illness duration may influence cognitive performance. However, Purcell et al. (1997) found no correlation between age of onset or duration of illness and cognitive performance in a group of twenty young (mean age 37.5 years) patients with unipolar depression. Cognitive impairment on set-shifting did not depend on the severity of the current depressive episode as scored on the HAM-D scale. Similary, another study (Brown et al. 1994) found no significant relationship between cognitive functioning (as tested by CAMCOG, WAIS verbal performance, Boston Naming Test etc.) and depression severity according to the Hamilton Depression Scale in 29 moderately to severely depressed unipolar (26) and bipolar (3) patients. Another study (Silberman et al. 1983) assessed executive performance using a task similar to the Wisconsin Card Sorting Test and found severity of depression and cognitive impairment to be positively correlated in some tasks but not in others. Thus, the more severely depressed patients had poorer focusing abilities than the less severely depressed ones (focusing being the capacity to narrow down the set of possible solutions), but the number of correct hypotheses generated – though lower than the one in the control group – did not depend on the severity of depression. Thus, some but not all cognitive tasks may be sensitive to the severity of depression.
Although studies trying to correlate cognitive performance and severity of depression have not all carefully controlled for confounding parameters such as educational level and illness duration, the overall picture seems to point to a rather weak correlation between the two variables.

Summary

- Cognitive impairment does not appear to be limited to a specific type of affective disorder, but it may be related to the depressive subtype. Differences in cognitive impairment have been found in small studies between patients with unipolar and bipolar disease, but the results are equivocal. However, even if depressive subtypes are related to the pattern of cognitive impairment, similarities between subtypes may outweigh the differences.
- Age seems to influence cognitive functioning in depressed patients to the same extent that it modulates cognition in normal individuals. Age of onset of depression may be a more important factor in determining cognitive impairment as demonstrated by studies showing more severe cognitive impairment in late-onset depression than in age-matched patients with early-onset depression.
- The degree of cognitive impairment of depression is not strongly related to the overall severity of the affective syndrome. Nevertheless, in individual patients, cognitive impairment parallels daily mood fluctuations.

Chapter 3

Memory impairment in depression and other psychiatric illness : a comparison

Depression, in particular its melancholic or retarded form, shares many behavioural features (e.g. psychomotor retardation, slowness, stooped posture, rigidity, lack of facial expression, sleep disturbance) with other disorders involving ***fronto-striatal*** circuits such as Parkinson's disease or Huntington's disease where depression is also common (Cummings & Benson 1992). In these disorders, deficits in cognitive and motor speed (Austin & Mitchell 1995), memory and executive functions are also present (Habib et al. 1991). Despite these similarities, there are cognitive differences between depression and the fronto-striatal disorders. Memory function was evaluated in a group of depressed patients with unipolar and bipolar depression, patients with Huntington's disease (HD), patients with Alzheimer's disease (AD), and normal controls. A discriminant function analysis taking into account verbal learning and memory differentiated well HD, AD, and normal subjects, but 28.6% of the depressed patients were classified as HD patients, 49.0% were classified as normal, none were classified as AD patients, and 22.4% were difficult to classify. These findings provide support for the hypothesis of fronto-subcortical dysfunction, but only for a subgroup of depressed patients as suggested by Massman et al. (1992).

Depression may share some features of cognitive dysfunction with fronto-striatal disorders but differs in others. Beats et al. (1996) compare moderately depressed patients over 60 years of age with patients with Parkinson's disease (PD). The depressed patients showed milder cognitive impairment over a broad range of functions whereas PD patients had frontal lobe type impairment and relative sparing of memory. Depressive patients exhibited slowing of both motor and cognitive processing, more so than the

patients with PD. Furthermore, the accuracy of the depressed on tests of pattern and spatial recognition was impaired as in patients with AD, whereas PD patients, and those with frontal lobe damage, were impaired on spatial but not on pattern recognition tests. In short, cognitive deficits in depressed patients were not limited to frontal functions but they were also seen in tests (recognition memory) sensitive to temporal lobe damage. Furthermore, these authors observed that performance dropped only after the subjects perceived failure which may be a depression-specific mechanism of cognitive impairment and which will, later in this text, be referred to as over-sensitivity to negative feedback.

Some cognitive deficits appear to be common in depression and ***schizophrenia***. Thus, memory is also impaired in schizophrenic patients. According to Tamlyn et al. {in (McKenna 1997)}, who analyzed memory in five schizophrenics, the impairment was restricted to long-term memory whereas working memory was spared. Thus, the characteristic pattern of memory impairment seems to be a normal immediate recall relative to impaired delayed recall. However, another study (Nathaniel-James 1996) of a group of 25 young schizophrenics with high estimated pre-morbid IQ has reported impaired immediate and delayed verbal recall (California Verbal Learning Test), with immediate recall being poor relative to delayed recall. This observation was interpreted as suggesting a memory deficit secondary to an executive function impairment.

Few studies have attempted direct comparison between patients with schizophrenia and depression. One study (Mitrushina et al. 1996) examined 103 adult psychiatric patients, all psychotic, with mania, depression, schizophrenia, schizoaffective disorder or not otherwise specified psychosis according to the DSM-III-R criteria. The investigators used the Neurobehavioural Cognitive Status Examination, a screening instrument that provides a cognitive profile across ten cognitive domains. Although all patients had psychotic features, two distinct groups were found : an affective and a schizophrenic/schizoaffective group. All groups were impaired on memory tasks with the schizophrenic/schizoaffective group

having the most pronounced impairment. In addition, the latter had deficits in tests of abstraction and judgement and was aided by recognition cues whereas the affective group benefited more from category cues.

Other studies also find differences between depression and schizophrenia. Thus, in one of them (Strauss et al. 1984), a timed letter detection task was used to determine perceptual span which was found to be significantly worse in schizophrenics as compared with depressed patients who performed the same as normal controls. Another study (Goldberg et al. 1993) compared currently ill young uni/bipolar with schizophrenic patients (schizoaffective patients were excluded) matched for estimated premorbid IQ as assessed using a reading test. At the time of the study, schizophrenic patients had lower current full IQs estimated by the WAIS and had been ill more than twice as long. The schizophrenic patients performed consistently worse than the affective patients. Furthermore, visual performance (Wechsler memory scale visual reproduction) remained worse once the IQ was controlled for. Analyzing the possible correlation between cognitive function and psychopathological symptoms as measured using the BPRS, the authors found evidence that symptoms accounted for a much smaller proportion of the variance in cognition in the schizophrenic than in affective patients. This suggests that cognitive impairment is likely to be more persistent in schizophrenia than in affective illness. In another study (Gruzelier et al. 1988), memory impairment was also found to be more common and severe in schizophrenic patients than in currently depressed or manic patients. Similarly, Krabbendam et al. (2000) assessed 22 bipolar patients in remission and 22 schizophrenic patients (mean BPRS 45.2 $\pm$ 10.3) ; they found a similar pattern of cognitive deficits, but patients with schizophrenia were more severely impaired although they were significantly younger.

Another recent study (Verdoux & Liraud 2000) tried to control for severity of illness ; they examined patients shortly before hospital discharge who had never been previously admitted to hospital. All of them were younger than 60 years. The schizophrenic patients (n=20) were more impaired on global memory performances than those with major depression (n=19) and

they had poorer delayed memory abilities than those with bipolar disorder (n=33) and those with major depression. Executive functions (Stroop test, WCST) did not differ between the diagnostic groups. There may have been a ceiling effect blurring real differences. No association was found with duration of illness.

Overall, cognitive impairment seems to be more severe and persistent in schizophrenia than in affective disorders, but similarities and differences can be observed in the pattern of impairment. Comparing schizophrenic with affective patients is, however, challenging due to the different courses and their psychopathology that differs greatly and hampers matching groups.

Summary

Although many questions remain unanswered,

- cognitive impairment in depressed patients resembles that found in fronto-subcortical disorders. This pattern, however, may only be present in a subgroup of depressed patients.
- The cognitive syndrome of depression seems on average less severe than the cognitive syndrome of schizophrenia and less clearly related to illness severity.
- The cognitive syndrome of depression, despite many overlaps, seems distinct from the cognitive syndrome of schizophrenia. Abstraction and judgment may be better preserved in depression. Memory is impaired in both groups, but recognition cues help the schizophrenics whereas the affective group benefited more from category cues. Thus, a single common psychopathological factor seems unlikely.

Chapter 4

Subjective and objective memory impairment in depression : a comparison and possible links

Subjective memory complaints

When patients complain about poor memory they may refer to a variety of things, e.g. difficulty in learning new things, general forgetfulness, forgetting occasional words and lack of concentration. Thus, such complaints can be expected when memory and/or other cognitive functions are impaired and insight is preserved. Thus, they may be associated with aging as well as a great variety of organic brain syndromes and functional psychiatric disorders. However, specific personality traits or life circumstances may also predispose people to monitor their memory/cognition closely and to be alerted by minimal and possibly non-significant changes and to complain about memory loss without any objective evidence of cognitive abnormalities. In Bassett and Fostein's study (1993), age, emotional distress, and the number of current medical illnesses predicted subjective memory complaints. Objective recall was predicted by age, functional disability, years of education, and the number of current illnesses, but not by emotional distress. Thus, subjective memory impairment seems to be more related to cognitive decline due to physical illness than to emotional distress resulting from physical illness.

Surprisingly, few investigators directly asked memory complainers why they thought they had cognitive difficulties. In a survey among 500 elderly people (Commissaris et al. 1993), many subjects ascribed their memory complaints to bad concentration, stress and tension and their medication, and a substantial amount of them worried about incipient dementia.

Frequency of subjective memory complaints

Three major studies have addressed this issue. Tobiansky et al. (1995) studied subjective memory complaints in a community survey of 705 subjects over 65 years of age. Subjective memory impairment as defined by at least three positive answers on a 9-question scale was found in 25% of this sample. There was a significant positive association between the complaints and the presence of dementia or depression. Yet, more than 60% of all complainers had no evidence of either of these disorders. Another community study (Bassett & Folstein 1993) revealed an overall 22% prevalence of memory complaints in a cohort of 810 people of an age range of 18 to 92 years and of which 373 individuals had a major psychiatric diagnosis including affective disorders (47) and dementia (62). In another community-based study (Jonker et al. 1996), non-demented and non-depressed people aged 65 to 85 years were selected. 22% of them reported memory problems compared with 37% of the depressed and 46% of the demented in the same cohort of a total of 4051 participants.

Correlation with age

Bassett and Folstein (1993) found that the frequency of subjective memory complaints increased dramatically with age. Approximately 15% of those 18 to 44 years old had subjective memory complaints and this frequency increased to 88% in those older than 85 years. The agreement between complaints and actual performance was maximal in those individuals under 44 years of age. No relation between the severity of memory complaints and age was found in another study (Derouesne et al. 1989) investigating all attenders to a memory clinic.

Correlation with educational level

How far the pre-morbid IQ or the educational level influences the prevalence of memory complaints remains unclear. However, in Jonker et al.'s study (1996) of 2367 non-demented and non-depressed elderly community residents, those with memory complaints had higher NART (National Adult Reading Test) scores than those without complaints. As previously addressed, the NART is considered a valid measure of premorbid IQ. Thus, memory complaints were more frequent in individuals with higher premorbid IQs. In contrast, in Basset and Folstein's study (1993), the prevalence of memory complaints was higher when the educational level was lower. Furthermore, the agreement between complaints and actual performance was maximal in those with more than 12 years of education. Similarly, another study found that persons with higher verbal intelligence reported less memory complaints (Bolla et al. 1991).

Correlation with gender

The only study (Bassett & Folstein 1993) that addressed the question found no association between gender and frequency of subjective memory problems.

Correlation with cognitive performance

In a large community survey (Grut et al. 1993), 314 subjects screening positive for dementia (MMSE < 23) and a sample of 354 people screening negative for dementia (MMSE > 23) were examined as to their subjective memory complaints. A single question was used in which the person had to state whether a) he/she had no memory complaints, 2) occasional memory disturbances or 3) severe memory loss. Slight complaints increased with increasing MMSE scores except for the persons with the highest MMSE who clearly had no cognitive impairment. Marked subjective memory complaints were most frequent in those with an MMSE between 6 and 10

and became less frequent as the MMSE increased. Patients with the worst performances on the MMSE rarely had any complaints. One study (McGlone et al. 1990) examined 29 demented and 28 non-demented subjects, all of whom had subjective memory or other cognitive complaints, and 35 healthy controls. 19 of the demented individuals were rated as having mild and 10 moderate dementia, but all were living in the community at the time of the assessment. The non-demented group comprised patients with depression, stress/anxiety disorders, benign forgetfulness, cardiovascular disease, headaches and other disorders not further specified. The Memory Observation Questionnaire 2, an extensive memory self-assessment questionnaire, showed that both the demented and non-demented responded similarly, and both groups had more memory complaints than the healthy controls.

Type and severity of dementia are important parameters to consider when subjective cognitive impairment is assessed. In patients with Alzheimer's disease in whom memory loss is an early manifestation subjective complaints would be common early in the disease, eventually ceasing when memory impairment becomes profound, whereas in fronto-temporal dementias, where lack of insight is an early feature, subjective memory loss is less likely to be prominent.

Subjective memory complaints in depression and other psychiatric disorders

Tarbuck and Paykel (1995) compared both objective memory performance and memory self-assessment in 18 younger (mean age 41 years) and 19 older patients (mean age 70 years) all of whom had an episode of severe major depression and who did not receive minor tranquillizers or neuroleptics 48 hours prior to testing. The older group performed worse on most of the cognitive tests employed, but the subjective assessment of their cognitive abilities showed little relationship with their objective dysfunction. During the depressive phase, the younger subjects judged their performance to be poor unlike the older group who did not rate their

cognitive performance as poor, but who continued to complain of memory difficulties when their mood improved. In a population-based sample of 85-year olds with major depression or dysthymia (Palsson et al. 2000), subjective memory complaints rated as absent, mild or moderate/severe did not correlate with the scores of any of the memory, executive and visuo-spatial tests used.

Basset and Folstein (1993) determined the frequency of memory complaints in 373 individuals with a variety of psychiatric diagnoses. Memory complaints decreased in frequency according to the diagnostic group. 60% of schizophrenics and 50% of patients with cognitive disorders complained about their memory. They were followed by those with affective disorders (34%) and those with adjustment and anxiety disorders (both 28%). The authors then determined the agreement between subjective memory complaints and recall performance. In the sample as a whole, those who complained of memory difficulties had poor performances in 29% of the cases as compared with 15% for those who did not complain. Furthermore, only patients belonging to the anxiety and affective disorder categories correctly judged their own performances as compared with the other groups. Other studies have also reported an association between subjective memory complaints and anxiety (Bassett & Folstein 1993, Corcoran & Thompson 1993, Hanninen et al. 1994, Smith et al. 1996), schizophrenia (Bassett & Folstein 1993), and adjustment disorders (Bassett & Folstein 1993).

An example of such an association comes from the study of McPherson et al. (1995) who compared 25 first-degree relatives of Alzheimer disease (AD) patients with controls with no family history of dementia. 12 of the first-degree relatives were related to patients with early-onset Alzheimer's disease and 13 related to patients with late-onset Alzheimer's disease. As a group, relatives of Alzheimer patients did not differ significantly from controls either in the level of complaint or in performance on neuropsychological tests. However, among relatives of patients with early-onset AD, significant correlations were found between performance on memory tests and self-rated changes despite their subtle objective memory problems. Thus, relatives of AD patients within the range of at risk age

monitor their memory performance more diligently than relatives of patients whose illness began at much later ages or those with no AD relatives. Both, a pronounced capacity of detecting small but actual memory changes and an increased vigilance in monitoring their memory may account for these findings. Conversely, Small et al. (1994) failed to find such an association when they examined 43 individuals between 40 and 79 years with age-associated memory impairment (perceived decrease in day-to-day memory functioning and memory test performance at least one standard deviation below the mean established for young adults). They found no difference on subjective memory complaints as assessed with the Memory Functioning Questionnaire between those persons with a family history of Alzheimer's disease and those without such a history.

Outcome of subjective memory complaints

Most studies suggest subjective memory complaints can be persistent, but they differ in their views as to whether the symptom predicts the development of dementia. Tobiansky et al. (1995) reinvestigated their cohort with subjective memory impairment two years after the initial examination. Of those who initially had subjective memory complaints, 79% either reported similar complaints or had lost them two years later ; 13% were depressed, and 7% were demented, one subject had both depression and dementia. 12% of those with neither subjective memory impairment nor dementia or depression in 1988, had developed subjective memory impairment for the first time in 1990. On the 9-point scale, two questions were strongly associated with developing dementia two years later (" forgetting what they have read or heard " and " claiming that their memory posed a significant problem for them ") and one with depression (" being embarrassed by their perceived memory problem "). On the whole, subjective memory impairment was not found to be useful as a population screen for dementia or depression. The authors found that individuals with subjective memory impairment were twice as likely to have depression than those without memory complaints [26% against 12% in 1988 and 23%

against 10% in the 1990-follow-up sample]. Another large community study (Schmand et al. 1997a) re-examined 2114 subjects, with no dementia and a MMSE score of at least 24 at baseline, four years later. Of these individuals, 131 had developed dementia at follow-up and they had more subjective memory complaints at baseline relatively to the non-demented. The authors suggested that subjective memory impairment may be a useful marker for the development of dementia and/or depression. However, this was not confirmed in another study (Flicker et al. 1993). Over a mean interval of 3.4 years, this study followed up 54 individuals who had reported a subjective decline in cognitive capacity in comparison with their performances 5 to 10 years previously. These subjects had no clear evidence of cognitive impairment at baseline and they were at no particular risk of developing dementia more than three years later.

In depressed patients, subjective memory complaints correlated negatively with objective performance as discussed earlier (Bassett & Folstein 1993). Thus, subjective memory complaints depend on depressive status and, hence, we might expect them to disappear once depression is successfully treated. This hypothesis was tested by Plotkin et al. (1985) in 29 outpatients over 55 years of age with major depression. A 12-item self-rated memory scale was administered with a range of scores from 14 to 44 ; a 1-point change in score was considered sufficient to qualify as a change in memory complaints. Of the 16 patients who responded to treatment as defined by at least 55% improvement 12 had fewer complaints, whereas only four of the 13 non-responders had fewer memory complaints at the endpoint than at baseline. Thus, improvement in depressive symptoms was significantly related to a decrease in subjective memory complaints (Plotkin et al. 1985). In Tobiansky et al.'s study (1995), younger depressed patients judged their memory to be poor when they were depressed, but their self-ratings improved significantly after recovery. The older group, who did not rate their cognitive performance as poor during the depressive phase, continued to complain of memory difficulties when their mood improved.

Change in cognitive performance with normal aging

Many elderly people have some degree of cognitive impairment which tends to increase with age. Different terms have been given to cognitive impairment of aging. Benign senescent forgetfulness (BSF) was the first term to be introduced, but age-associated memory impairment (AAMI) is the best known term. There are many other concepts of which one of the more convenient ones may be aging-associated cognitive decline (AACD) and mild cognitive impairment (MCI) which seem preferable because 1) they encompass different cognitive domains (contrary to e.g. AAMI), 2) because they do not include the word dementia (as in Questionable Dementia), and 3) because they presume no aetiology (as in the ICD-10 Mild Cognitive Disorder and in the DSM-IV Mild Neurocognitive Disorder).

These terms are rooted in the idea that changes in cognitive performance with normal aging are qualitatively and quantitatively distinguishable from an incipient dementia (Crook et al. 1986). However, there is increasing support for the hypothesis that cognitive performance is a continuum from normal aging to dementia and that the transition from normal aging to dementia is not abrupt. This idea is supported by epidemiological studies such as Brayne and Calloway's (1988), a community-based study of 410 women aged 70 to 79 years. Likewise, the performance in AACD overlaps extensively with those of healthy and mildly demented people (Brayne & Calloway 1988, Derouesné & Thibault 1995, Storandt & Hill 1989) mainly due to a high variability of cognitive performance in the elderly as suggested by Reischies (1997).

Thuillard and Assal (1991) studied normal cognitive aging using a cross-sectional design: they analysed cognitive performance in normal subjects dividing them in age groups ranging from 20-29, 30-39 etc. the oldest group including those aged 80-89 years. A series of neuropsychological tests were administered covering the whole range of mnestic, linguistic, practo-gnostic

and executive functions. All tests used were sensitive to age, but to a variable degree. Working memory, as measured by digit span, remained stable and decreased by maximally one item between the age of 20 and the age of 80. Episodic memory decreased more markedly with age. General slowing not only of the sensory processing and motor speed, but also of central processing seems to be one of the most consistent findings of aging. Heterogeneous effects of aging on cognition are confirmed by Valdois and Joanette's study (1991). Although echoic and iconic memory, working memory and semantic memory remained relatively stable throughout normal aging, memory and learning start declining around the fifth decade of life, whereas visuo-spatial performances did so after the age of 70 or 80 years.

Similarly, the aging process does not homogeneously affect the various functional components of language. Phonological competence remains stable with age. Older subjects frequently complain about difficulty finding words, because the active use of words is sensitive to aging, but their passive stock of words is not altered as suggested by Valdois and Joanette (1991). According to these authors, sentence comprehension may decline in the very old. Changes in pragmatics occur in that narrative style may become more laboured with longer and more complex sentences and more recherché words with growing age although the variety of themes lessens, as may the informativeness of their discourse.

Individual cognitive differences seem to be marked in the elderly. Valdois and Joanette (1991) studied 81 normal elderly from 55 to 84 years of age using a standardized neuropsychological test battery and found several different groups : one with optimal performance in most of the tests, another with sub-optimal performance in most tasks and two further groups showing double dissociations. Subjects in one of these two groups had weak performances on visual form discrimination/copy of the Rey figure, but good scores in oral comprehension/repetition of a word list, whereas the opposite pattern of performance characterized the other group.

The outcome of cognitive impairment in depression

The outcome of the cognitive syndrome of depression

The cognitive syndrome of depression is commonly said to improve when depression improves. Thus, after 26 days of successful treatment with antidepressant drugs, 26 severely depressed inpatients showed a significant improvement in immediate and delayed recall (Sternberg & Jarvik 1976). Euthymic bipolar men with a mean age of 51 years were found to have a normal verbal fluency (van Gorp et al. 1998) which corresponds to the observation that verbal fluency normalized as depression cleared up as Tarbuck and Paykel (1995) suggested. Improvement has also been observed by Savard et al. (1980) on the performance on the Halstead-Reitan category test, a test of executive function, in adults after recovery from unipolar depression. Alexopoulos et al. (1993) found that even severe cognitive impairment of depression may be reversible. Similarly, a community-based epidemiological study (Palsson et al. 2001) using the MMSE to assess cognitive performance showed that while currently depressed 70 and 74-year-old women with lower educational level had mild cognitive impairment, those euthymic but who had had previous depression did not differ from the comparison group of healthy women who had never had depression.

Other studies have reported persistent cognitive impairment in euthymic patients. Marcos et al. (1994) found deficits in immediate visual memory, delayed logical and visual memory, paired learning and block design in symptom-free patients suffering from a recurrent depressive disorder with melancholia. In another study (Adler et al. 1999) the majority of elderly patients with moderate depression and mild cognitive impairment (MMSE at least 24) still exhibited mild cognitive deficits after a 6-week trial on antidepressants even after improvement of their affective symptomatology. In Savard et al.'s study (1980), severely depressed bipolar and unipolar inpatients between 20 and 50 years of age were examined when arriving at the hospital and 2 weeks after discharge following remission. Bipolar

patients as a group continued to perform in the defective range, whereas unipolar patients, who were slightly younger, returned to normal performance levels. Contrary to this finding, Paradiso et al. (1997) reported that unipolar but not bipolar patients remained cognitively impaired and exhibited a frontal-like syndrome. The reasons for the differences in these two studies remain unclear although variable length of remission, mean age, gender and the cognitive tests used could account for some of these differences. These discrepancies point to the likelihood that the cognitive outcome is heterogeneous and dependent on a series of variables just as is the nature of the cognitive syndrome of depression.

Overall, immediate and delayed (Marcos et al. 1994), verbal (van Gorp et al. 1998) and visual (Marcos et al. 1994) memory, frontal functions (Savard et al. 1980) and response latency (Beats et al. 1996) may remain altered after remission from the affective syndrome. Furthermore, residual cognitive symptoms may be more persistent in the elderly than in the younger patients (Blazer 1989).

Duration of depressive illness

The duration of the depressive illness may be a crucial factor determining persistent cognitive impairment; thus, a possible "aggregate negative effect" of lifetime duration of bipolar illness on memory and frontal systems has been hypothesized by van Gorp et al. (1998). Persistent memory and executive impairment after affective remission was found in another study (McKay et al. 1995) of a mixed group of uni- and bipolar patients with a very severe illness course of whom some remained euthymic only briefly. Both younger and older patients with a less severe and chronic disease had no persistent cognitive impairment. Unfortunately, chronicity was not clearly defined, but it seemed to refer to the absence of longer euthymic periods and an increased number of either depressive or manic episodes.

Timing of cognitive improvement

The timing of cognitive improvement may be rapid after affective recovery (Savard et al. 1980) or delayed as another small study suggests (Stoudmire et al. 1991). In this study, eight severely depressed patients showing significant improvement of their HDRS score after ECT treatment were followed-up at a 6-month, 15-month and 4 year-interval. These patients' cognitive performances were also noticeably better at 6 months and the improvement was sustained over time though a tendency of the performance to decline slightly after 4 years as compared with the 15-month performance was apparent. The cognitive effects of ECT may have contributed to this delayed recovery of cognitive functioning.

Effects of medication on cognitive performance

The possible effects of medication on cognitive performance have been explored in several studies. Although the anticholinergic effect of tricyclic antidepressants is thought to negatively influence memory functioning, in one study (Danion et al. 1991), seven non-medicated depressed patients had similar memory performance to eight depressed patients taking both benzodiazepines and tricyclic or serotonin-reuptake inhibitors. The cognitive improvement that often accompanies affective improvement as a result of drug treatment does not rule out the possibility that residual cognitive changes can be due to side effects of medication. Should further research show this to be the case, then, the duration of post-remission treatment with antidepressants would have to be optimized with cognitive side effects of medication and risk of relapse being the two crucial factors. However, as a general rule, the negative effects of depression on cognition most likely exceed those of medication.

Is depression a risk factor for dementia ?

This question is difficult to answer, since depression may occur in incipient dementia. However, within the setting of a large-scale community survey in southwest France, one study (Dufouil et al. 1996) explicitly addressed the question whether depressive symptomatology is a risk factor for dementia. 1600 out of 2726 non-institutionalized and non-demented elderly people over 65 years of age and living in the community were reassessed 3 years after entry into the study. The MMSE was used and cognitive deterioration was defined as a 5-point drop on re-examination. Depressive symptomatology was assessed with the CES-D (Center for Epidemiologic Studies - Depression scale), a self-assessment scale. The authors were interested in the predictive value of high level depression as defined as a CES-D score above 16 for men and above 22 for women. At 3 years, the incidence of cognitive deterioration did not correlate with the level of depression and, thus, depressive symptomatology did not predict cognitive deterioration. Henderson's epidemiological psychiatry research group (Henderson et al. 1997, Henderson & Jorm 1997) reached a similar conclusion and stated that depressive symptoms at the entry into the study, within the setting of a large community-survey of the elderly, do not predict subsequent cognitive decline or dementia. Similarly, in the epidemiological AMSTEL (Amsterdam Study of the Elderly) project (Schmand et al. 1997a) in the Netherlands, depressive symptoms did not predict future development of dementia, once age, objective and subjective memory deficits were taken into account. However, subsequent data of this study combined with data from the LASA (Longitudinal Aging Study Amsterdam) study (Geerlings et al. 2000) found that depression was associated with an increased risk of AD and cognitive decline, but only in subjects with higher education (>8 years). These subjects had normal cognitive function (GMS and CES-D assessment) at the beginning of the study and 80% of the depressed patients reported no history of early or late-onset depression, the latter being suggestive of an organic origin of depression. Another large community-based epidemiological study (Bassuk et al. 1998) showed that dysphoric

mood predicted future cognitive losses among elderly persons with initially moderate cognitive impairment. However, the study was not able to determine whether the depressive symptoms preceded or followed declining cognitive performance.

The presence of depressed patients with incipient dementia in study samples may, however, explain the high occurrence of dementia found by some follow-up studies of depressed patients. As an example, in an uncontrolled study (Reding et al. 1985) of patients seen at a dementia clinic, half of the patients with depression were reported to have dementia when followed up three years later. Many of them had very subtle neurological changes at the first assessment. Another study (Richards 1995) suggested that medically treated depression increases the relative risk of 1.8 (normal risk is 1) to develop AD one year or more later as compared with those with no previous depression. But again, in these patients, depression may have been the first manifestation of the underlying dementia. Nevertheless, as a group, depressed patients with cognitive deficits may be at a higher risk to develop dementia than those without cognitive impairment. Alexopoulos et al.'s (1993) study mentioned before clearly showed this correlation.

Summary

Change of subjective and objective cognitive ability can be part of normal aging. However,

- subjective memory impairment increases with age and those with subjective memory impairment are more likely to have objective memory deficits than those who have no such complaints
- subjective memory impairment is a frequent symptom of depression
- subjective memory impairment in depression is weakly correlated with objective cognitive impairment and more closely with the severity of depressive symptomatology
- objective cognitive impairment can improve when depression improves however, recent evidence suggests that cognitive deficits may persist in euthymic patients and in some patients depression is the first sign of an incipient dementia.

Chapter 5

Mechanism of memory impairment in depression

There are a number of possible mechanisms that can explain the cognitive changes observed in depression. These mechanisms fall into two categories: 1) those invoking mood-related "cognitive styles" such as hedonic bias, and over-sensitivity to negative feedback and 2) those invoking the presence of organic brain changes that impair cognition either globally or by involving specific brain circuits

Hedonic bias

The affective valence of the test material, whether emotionally positive, neutral or negative, may have an impact on cognitive performance. This is referred to as hedonic bias or mood congruency. Hedonic bias in depressed patients has been investigated mainly in relation to memory and executive functions.

Mood congruent learning has been repeatedly shown in depressed patients. Thus, in one study (Dunbar & Lishman 1984) healthy controls recognized newly learnt material more readily than depressed patients when the material was pleasant and they recognized pleasant material better than neutral and unpleasant material. In sharp contrast, depressed patients recognized unpleasant material more readily than controls and unpleasant material more readily than pleasant material. White et al. (1992) compared moderately depressed patients with a heterogeneous group of non-depressed psychiatric patients using an "articulated thought during simulated situations" method where the subject was shown one positive (compliments, praise and gratitude from an acquaintance whom the subject had helped

with a plumbing emergency), one negative (an acquaintance expressing disappointment about an outdoor party the subject had planned and which was disrupted by bad weather) and one neutral (an acquaintance making polite conversational remarks and discussing innocuous topics) videotaped and scripted situation of 15-30-minute duration. During a subsequent interval of 30 minutes the subject was requested to think aloud. These thoughts were then coded according to thought categories used in cognitive therapy (e.g. arbitrary inference etc.). The investigators found that "depressed subjects significantly exceeded the non-depressed group on total bias in the negative situation, but not in the neutral or positive situations". Other studies (Brittlebank et al. 1993, Moore et al. 1988) found that autobiographical memory in depressed people can also be subjected to hedonic bias. However, at least one study (Ilsley et al. 1995) of severely depressed patients was unable to find evidence of mood-congruent recall. Experimental studies have supported the possibility of hedonic bias using mood induction procedures. Thus, in one study (Gilboa & Gotlib 1997), a mood induction procedure was used in 66 currently non-depressed under-graduate university students of whom a previously depressed group was compared with a previously non-depressed group. They underwent an emotional Stroop task in which they were required to tell the colour in which an emotional word was written rather than to read the word itself. Subsequent incidental recall of the emotional Stroop task items was greater in previously depressed students than in the previously non-depressed. Hence, the memory of the previously depressed students was better and their increase in performance was due to the better remembering of negative words.

There is some evidence that hedonic bias disappears with the remission of depressive symptoms. However, a number of studies (Gilboa & Gotlib 1997, Miranda & Gross 1997, Teasdale & Dent 1987) have suggested that hedonic bias may only be dormant during euthymia and be reactivated by negative mood in subjects at risk for depression. These findings are referred to as cognitive vulnerability or mood-state dependent hypothesis (Miranda & Gross 1997). Some aspects of hedonic bias may be more resistant to

improvement ; this appears to be the case for negative thinking related to one's self as suggested by Blackburn et al. (1986).

Over-sensitivity to negative feedback

It has been postulated that depressed patients may perform normally on cognitive tasks as long as they are not faced with the evidence of failure and that, once failure occurs and the subject becomes aware of it, it will negatively influence the subsequent test performance. This has been termed "over-sensitivity to negative feedback" by Beats et al. (1996). Elliott et al. (1996) examined 28 in- and outpatients meeting criteria for major unipolar depressive disorder between 40 and 70 years of age and 22 control subjects matched for age and estimated pre-morbid IQ. A computerized delayed matching-to sample-task and a new Tower-of-London task (CANTAB battery), an executive function test, were administered. Positive or negative feedback was immediately given at random. Depressed patients were more likely to fail immediately after negative feedback than controls. In a subsequent study of the 28 patients with unipolar depression and four control groups (22 normal subjects, 15 patients with Parkinson's disease, 12 patients with frontal lobe damage, and 12 patients with schizophrenia), the authors (Elliott et al. 1997) further showed, using similar methodology, that response to negative feedback was specific to depression, since neither the normal nor the pathological controls showed this behaviour. They suggested that depressed patients may have a reduced expectation of reward, or that they may perceive they have reduced control over the task or that they may fail to process response-outcome associations over a series of trials.
Over-sensitivity to negative feedback may also outlast remission or recovery from depression even if its severity decreases with symptomatic improvement. Therefore, over-sensitivity to negative feedback may be a trait marker for unipolar depression according to Elliott et al. (1997).

The cognitive reserve hypothesis

The cognitive reserve hypothesis may explain why some depressed patients become cognitively impaired, either globally or in specific cognitive domains. Cognitive capacity can be seen as a reservoir. Lowering of this capacity below a certain threshold will manifest itself clinically. Both diffuse or focal organic changes may reduce the cognitive capacity. The cognitive reserve theory has been an influential hypothesis in dementia research. Thus, low pre-morbid linguistic ability (Snowdon et al. 1996), low brain metabolism in association areas (Alexander et al. 1997), limited education (Dufouil et al. 1996) and low pre-morbid levels of employment (Schmand et al. 1997b) have been considered to be markers of low cognitive reserve and therefore to represent an increased risk for dementia or for its early expression when other factors (i.e. aging, vascular pathology, Alzheimer's disease) are present. However, a recent volumetric MRI study (Jenkins et al. 2000) shows evidence against the cerebral reserve hypothesis in both familial and sporadic Alzheimer's disease.

In analogy to dementia, a patient who becomes depressed may develop cognitive impairment if their pre-morbid cognitive reserve is reduced due to a variety of aetiologies that may be similar to those mentioned above with regard to dementia.

No study has explicitly examined this possibility, but a recent epidemiological study (Palsson et al. 2001) has found that cognitive impairment, as assessed with the MMSE, was present in 70- and 74-year-old women with depression only when they had a lower educational level.

The finding that depression is thought to be a risk factor for later dementia according to various authors (Richards 1995, Stern et al. 1993) can be seen in the light of this theory. Low premorbid cognitive reserve due to incipient dementia could be revealed by depression which in turn could be considered a risk factor for a future dementing illness as suggested by the results of a variety of studies (Dufouil et al. 1996, Henderson et al. 1997, Henderson & Jorm 1997, Schmand et al. 1997a). The cognitive reserve theory predicts

that cognitive impairment is not necessarily a function of the severity of the depressive syndrome as discussed earlier.

Structural brain changes may point to reduced cognitive reserve, and general brain atrophy and ventricular enlargement as well as more focal brain changes can be seen in some depressed patients. The relationship between structural brain abnormalities and depression will be dealt with in the next chapter.

Chapter 6

Structural brain abnormalities in depression

A number of studies have looked at structural brain abnormalities in patients with affective disorders. This chapter will review the available studies on structural brain imaging in patients with primary depression. Structural imaging methods considered comprise computed tomography (CT) and magnetic resonance imaging (MRI).

Normal aging

Increasing age is associated with structural brain changes. Brain atrophy occurs over 50 years of age as demonstrated by increases in sulcal and ventricular size in healthy controls (Coffey 1996, Coffey et al., 1992, Hentschel & Förstl 1997). These changes occur gradually until around 60 years of age and thereafter progress more rapidly (Pearlson 1996). There is, however, a large degree of individual variability and MRI findings were considered abnormal in two thirds of healthy elderly controls and normal in the remaining third (Zubenko et al. 1990).

Regional age-related changes may also occur, especially in the medio-temporal and association cortex (Hentschel & Förstl 1997) as well as in the frontal lobes (Coffey et al. 1992). According to another study (Golomb et al. 1993), 33% of all persons above 55 years who were clinically normal

had hippocampal atrophy that increased with age and was more common in males.

White matter hyper-intensities detected with MRI also increase with age in the normal elderly (Coffey 1996, Coffey et al. 1992).

Structural brain changes in depression

Sulcal widening and ventricular enlargement in depression

Most studies assessing sulcal width and ventricular size have been done in elderly patients with major depression. As early as in 1980, a CT study (Jacoby & Levy 1980) of 41 elderly depressed patients reported enlarged ventricles in a subgroup of patients. This subgroup of 9 patients were older and had their first episode of depression late in life ; they also had more endogeneous features than the rest. At a one-year follow-up (Jacoby et al. 1981), these patients had a higher mortality than those without ventricular enlargement. Another CT study (Alexopoulos et al. 1992) compared patients with early-onset and late-onset depression and patients with dementia and found that the late-onset patients showed ventricular enlargement and cortical sulcal widening similar to that of the demented subjects, suggesting that increase in ventricular size and sulcal width is not simply due to increasing age.

Recent MRI investigations have confirmed the findings of CT studies. Thus, in one study (Rabins et al. 1991), 21 patients 60 years or older with severe major depression according to DSM-III-R criteria were compared with age-matched normal controls and patients with Alzheimer's disease. Depressed subjects had wider sulci and bigger ventricles than normal controls. Although the Alzheimer patients had greater changes than the depressed patients, the differences did not reach statistical significance. Another study (Pantel et al. 1997) showed a significantly smaller whole brain volume, higher CSF volume and a higher ventricle-brain ratio in a

group of 19 patients with late-onset major depression as compared with 13 age-matched controls. In this study, Alzheimer's disease patients had significantly greater changes in all parameters studied than depressed patients and controls. In another study (Zubenko et al. 1990), cortical atrophy was also commoner in depressed patients than in normal controls, although cortical atrophy was two to three times more common among those with dementia than those with major depression. Cortical atrophy was independent of the age of onset of depression, contrary to the suggestion of other studies. A recent quantitative MRI study (Kumar et al. 1997) found no difference of global measures of brain and CSF volumes in patients with late-onset depression as compared to normal controls. This investigation, however, differed from the above quoted study since patients with minor depression only were included.

Bipolar patients may also have ventricular enlargement as suggested by one study (Swayze et al. 1990) of young patients compared to normal controls, although this held true for men only. Furthermore, ventricular enlargement was modest and much less prominent than that seen in the schizophrenic comparison group.

The above studies suggest that ventricular enlargement and/or sulcal widening is a feature of both major depression and bipolar illness in subgroups of patients, especially in the elderly. Age alone is unlikely to account for the presence of these abnormalities, but they may be more severe and frequent in late-onset as opposed to early-onset depression. The explanation for these findings remains uncertain, but several possibilities are suggested by Dolan and Goodwin (1996) : 1) structural changes may indicate an early stage of Alzheimer's disease in which depression is a common feature, 2) they may be due to depression or a combination of both, and 3) they could be seen as a morphological substratum of increasing vulnerability to depression.

Regional changes of brain morphology

Magnetic resonance imaging has high spatial resolution and makes it possible to study *regional* patterns of atrophy in depression. Frontal and/or temporal structures have as a consequence been the focus of attention.

Prefrontal lobe abnormalities.

The frontal lobes account for about a third of the human brain and are implicated in executive functions and in the regulation of emotions. Focal prefrontal abnormalities may be relevant in depression. Coffey et al. (1993) examined 48 severely depressed patients referred for electro-convulsive therapy and compared them to 76 normal age-matched controls who had received more years of education. The volume of the frontal lobe was measured in all the slices (10 to 13 depending on the individual) anterior to and including the optic chiasma. The patients had significantly smaller frontal lobes than normal controls whereas the cerebral volume and that of the temporal regions were similar. Kumar et al. (1997) performed a cross-sectional quantitative MRI study of 18 elderly patients with a mean age of about 70 years with minor depression (low mood and anhedonia and at least one additional depressive symptom from the DSM-IV checklist) of whom two had dysthymia (minor depression of at least two years duration) and compared the results to those of a control group of 31 normal individuals. The groups were matched for age and gender. The patients with minor depression had only slightly smaller absolute values of prefrontal volumes than controls (183.62±33.21 versus 197.0±30.7) and total brain and intra-cranial volumes were similar in both groups. Prefrontal volumes relative to total intra-cranial volumes were significantly smaller in the depressive group.

Pantel et al. (1997) compared 19 patients with unipolar major depression, 13 healthy controls and 27 patients with Alzheimer's disease. The mean age of all three groups was about 70 years. This quantitative study defined the posterior limit of the frontal lobes as corresponding to the last slice which showed both lobes separated. The study showed no significant decrease of

frontal lobe volume in the depressed group, as compared to normal controls, but they had a significantly smaller whole brain volume. Alzheimer patients showed significantly lower volumes than depressed patients and controls with regard to all volumetric parameters.

Although all quoted studies compare depressed patients of a similar age, the results are contradictory. However, the groups had different types of depression and the neuroanatomical delineation of the frontal lobes was strikingly different. In addition, these are small studies unlikely to have sufficient statistical power.

Temporal lobe abnormalities.

Temporal lobe abnormalities, in particular of the hippocampus and the amygdala, have also been described in depression. Hippocampus and amygdala are particularly important to memory and mood regulation.

Qualitative studies. One of the earliest MRI studies (Rabins et al. 1991) used a qualitative approach classifying MRI temporal lobe atrophy as absent, mild, moderate or severe. These researchers studied 21 patients 60 years or older with severe major depression and compared them with 16 Alzheimer patients and 14 age-matched normal subjects. Depressed patients had greater temporal sulcal atrophy than normal controls and they were not statistically different from the Alzheimer patients. Sulcal atrophy was more pronounced in those patients with later onset of depression. A more recent qualitative study (Greenwald et al. 1997) classified atrophy on a 4-point-scale and found the left medial temporal lobes of patients with late-onset depression to be smaller than the right as compared with age-matched early-onset patients. These studies emphasize the greater likelihood of focal abnormalities in late-onset depression and suggest a causal link between the two.

Quantitative studies. Since different structures lie in the temporal lobe (limbic and association cortex, hippocampus and amygdala), the attempt has been made to study these structures separately.

In an early study, Hauser et al. (1989) assessed the area of the hippocampus/amygdala complex, measuring a single coronal slice through the temporal lobe, in 17 patients with bipolar and unipolar depression either euthymic or severely depressed at the time of assessment. They were compared with a significantly younger (mean age 33.8 years ; depressed patients' mean age 40.5 years) control group with more years of education. The depressed patients had a smaller temporal lobe to cerebrum ratio, but hippocampal complex to temporal lobe ratios were similar in both groups.

Altshuler et al. (1991) examined the temporal lobes of ten mostly refractory bipolar patients (five women and five men) of an approximate mean age of 40 years and compared them with ten age and gender-matched controls with no known psychiatric or neurologic history. The temporal lobe volume was estimated by measuring it on five to six coronal slices. The volumes of both temporal lobes, particularly the left one, were significantly smaller in depressed patients. Illness duration correlated negatively with the right temporal volume, but only in men. However, another quantitative MRI study (Hauser et al. 2000) of young bipolar I and bipolar II patients found bipolar II patients to have identical measures as normal controls. On the other hand, bipolar I patients had larger ventricular and left-ventricle-cerebrum ratio measured on a single slice. Volumetric measures of the hippocampus and the temporal lobe as a whole were again similar to those of the normal controls. In a later study, Altshuler et al. (2000) compared 28 bipolar and 20 schizophrenic patients and 18 normal controls (mean age about 50 years) on measures of hippocampal, amygdala and temporal lobe volumes using a volumetric method but without controlling for whole brain volumes. The main findings were significantly reduced hippocampal volumes in the schizophrenic patients and enlarged amydgalae in the bipolar patients compared to normal controls.

Sheline et al. (1999) assessed hippocampal and amygdalar volumes in 24 women between 23 and 86 years (mean age 52.8) with recurrent major depression and compared them with 24 normal age, gender, education and height-matched controls. Absence of medical co-morbidity was a prerequisite for inclusion into the study. The depressed patients were euthymic at the time of assessment. A stereologically based method using grid points that allowed to calculate hippocampal volume estimates based on the number of selected grid points was employed. The patients had smaller hippocampal volumes than controls and hippocampal volume correlated with performance on verbal memory tests. Hippocampal volume did not correlate with age in the depressed patients or the normal controls, but it correlated inversely with the cumulative lifetime duration of depression. The authors argue that repeated stress and cortisol excitotoxicity during recurrent depression may result in cumulative hippocampal injury as reflected in volume loss. This study confirmed the group's earlier findings of reduction in volumes of the core nuclei of the amygdala. Amygdala core nuclei were defined as comprising the basal nucleus, accessory basal nucleus, and the lateral nucleus. The volume of the non-core amygdala nuclei were not different in the two groups. Sheline et al. (1999) also reported a strong correlation between the volumes of the hippocampus and the core nuclei of the amygdala. The authors argue that the glutamatergic pyramidal cells in the core nuclei of the amygdala are predominant and reciprocally connected with the hippocampus ; this interconnection may explain how damage in one part of this circuit leads to neuronal cell loss in the other areas. Non-core amygdala nuclei, however, contain primarily non-glutamatergic cells and may therefore be less vulnerable to excitotoxicity. Steffens et al. (2000), using volumetric MRI, showed reduced hippocampal volumes in 66 elderly patients with incident or recurrent major depression as compared with 18 normal controls. Hippocampal volumes were smaller in those with older age of onset and there was a trend for those with earlier-onset depression to have smaller hippocampi than the normal subjects. According to the authors, this finding favours the hypothesis that late-onset

depression is a risk-factor for dementia rather than hippocampal atrophy being caused by glucocorticosteroid toxicity since there is only a trend towards smaller hippocampi in patients with early-onset depression. Vakili at al. (2000) found no statistical differences in the hippocampal volume of 38 young patients (mean age 38 years) with primary major depression as compared with 20 normal controls. However, there was a negative correlation between left hippocampal volume and the baseline scores of the Hamilton Depression Rating Scale. Female responders to fluoxetine had a higher mean right hippocampal volume than non-responders. These two studies are difficult to compare since the age groups are very different and illness duration and number of depressive episodes in these patients are not clearly stated in the latter study.

Other studies failed to find reduction of the temporal volume in depressed patients. Pantel et al. (1997) found no significant volume decrease neither of the temporal lobe nor the amygdala-hippocampus complex when comparing 19 patients with late-onset depression (mean age 72.4 ± 8.8 years) with 13 age-matched normal controls. Coffey et al. (1993) examined the volumes of both the temporal lobe and the amygdala-hippocampus complex in 48 severely depressed patients (44 with unipolar and 4 with bipolar depression) and 76 age-matched controls. The temporal lobes were measured on 11 to 13 coronal slices, the caudal border being arbitrarily chosen by drawing a line joining the lateral ventricle to the Sylvian fissure. The amygdala and the hippocampus were jointly measured on a slice including the interpeduncular cistern and on an anterior extension of three additional slices. No differences were found in the hippocampus-amygdala complex between the two groups.

Structural brain differences between depression and Alzheimer's disease

Hippocampal atrophy is an outstanding pathological feature of Alzheimer's disease. Since some studies have shown that depressed patients may also

have hippocampal atrophy, O'Brien et al. (1994) rated temporal atrophy in 32 elderly subjects (mean age 70.2 years) with DSM-III-R major depression and in 43 patients with Alzheimer's disease. Anterior hippocampal atrophy distinguished well the two groups. In a second study (O'Brien et al. 1997), measurements were performed in 61 patients with major depression (mean age 71.2 ± 7.8 years), 77 patients with Alzheimer's disease and 44 patients with other cognitive disorders including vascular dementia, Huntington's disease, schizophrenia, alcohol related cognitive impairment and a group of 'memory complainers'. Atrophy was scored independently by two neuroradiologists on a 4-point scale from normal to severe. The anterior hippocampus was the most sensitive region for detecting Alzheimer's disease patients and separating them from those with depression and other cognitive disorders. These results differ from those of Rabins et al. (1991) who studied 21 patients 60 years or older (mean age not stated) with severe major depression and found that depressed patients were not statistically different from patients with Alzheimer's disease with respect to temporal sulcal atrophy rated from mild, moderate to severe.

Loss of normal brain asymmetry

In the normal brain, the left occipital lobe is usually larger than the right, the right frontal region is often larger than the left, and the planum temporale on the left side is larger compared to the right (Woodruff & Lewis 1996). The loss of the pattern of normal asymmetry might indicate, as it is likely to be the case in schizophrenia, that developmental abnormalities may be relevant in depression.

The possibility that abnormal brain asymmetries may be present in patients with affective disorders has been explored in a number of studies, but so far there is little evidence to support this possibility. As an example, the 48 severely depressed patients (mean age about 62 years) in Coffey et al.'s study (1993) showed identical asymmetries in cerebral hemisphere volumes when compared with normal control subjects. Greenwald et al. (1997) found no differences in normal asymmetry between a group of 30 depressed

patients, although those with late-onset depression had more left medial temporal and left caudate atrophy than early-onset counterparts of similar age. Johnstone et al. (1989) compared 21 schizophrenics, 20 bipolars and 21 normal controls, all ranging between 25 and 53 years of age. The left temporal lobes of the normal controls and the manic-depressive patients were larger than the right ones whereas the reverse was true for the schizophrenic patients.

Changes of the basal ganglia

Changes of the basal ganglia have also been observed. Krishnan et al. (1992) used serial axial images to estimate the volumes of the caudate nuclei in 50 patients with major depression (mean age 48 years) and 50 age- and gender-matched normal controls. They used 5mm thick axial slices with a 2.5 mm interslice gap and a grid and point counting method. They reported bilateral reduction of the size of the caudate nucleus in the depressed patients.

In Greenwald et al.'s study (1997) of elderly patients, those with late-onset depression also had atrophy of the caudate nucleus, but only on the left side. Husain et al. (1991) found a reduction of the size of the putamen in a group of 41 subjects with major depression (mean age 56 years) when compared with age-matched healthy volunteers. They used a method similar to Krishnan et al.'s (1992) study.

There are several reasons why the basal ganglia are likely to be relevant in depression. The basal ganglia are connected with limbic structures such as the amygdala and the orbito-frontal cortex and patients with degenerative or vascular damage to the basal ganglia are often depressed. The co-occurrence of late-onset depression and white matter hyperintensities (cf p 71) points to the possibility that depression may result from the disruption of fronto-striatal circuits. It is unclear whether basal ganglia atrophy precedes or follows depression and whether it occurs in parallel with atrophy in other brain regions.

On the other hand, Aylward et al. (1994) using a volumetric MRI technique examined 30 patients with bipolar disorder, most of them euthymic at the time of assessment and with a mean age of 39.3 years. Males but not female patients had larger caudate volumes than controls whereas no statistical differences emerged as to the volumes of the putamen and the globus pallidus. The authors offer no definite answer as to why bipolar patients might have larger caudate volumes, but they point out that this difference could represent one of the various features distinguishing major depression and bipolar disorder. Increased size of basal ganglia structures could also be a medication effect. Thus, Bogerts et al. (1990) have found that in schizophrenia increase of basal ganglia size correlated with exposure to typical neuroleptics. A similar effect may be seen in bipolar depression since many patients with this disorder also receive neuroleptics although this is unlikely to explain the gender differences in Aylward et al.'s (1994) study. However, since the female comparison group in Aylward et al.'s study (1994) had clearly larger caudate volumes than the normal male group, the male comparison subjects may for some reason have had unusually small caudate nuclei.

The specificity of structural brain changes in depression

Structural brain abnormalities are also common in schizophrenia and those described here in affective disorders do not appear to be pathognomonic. A few studies have directly compared the two conditions. Swayze et al. (1990) studied 48 patients with bipolar disease, 54 with schizophrenia and 47 normal controls. The total ventricular volume was significantly greater in the schizophrenic group (12.70 ± 5.70 cm3), in particular in the male subjects, than in bipolar patients (10.82 ± 5.21 cm^3) and healthy controls (9.71 ± 4.20 cm^3). Although these patients were young with a mean age of around 35 years, white matter hyperintensities were present in 19% of the bipolar subjects which is a significantly higher figure than their prevalence in the schizophrenic subjects (9.3%) and the normal controls (4.3%).

Another similar study (Altshuler et al. 2000) compares 28 bipolar and 20 schizophrenic patients as well as 18 normal controls (mean age about 50 years) as to hippocampal, amygdala and temporal lobe volumes using a volumetric method but without controlling for whole brain volumes. The main findings were significantly reduced hippocampal volumes in the schizophrenics and enlarged amydgalae in bipolar patients. The reasons for increased amygdalae is unclear. As discussed by the authors, exposure to neuroleptic treatment has been suggested to cause enlargement of the striatum. Amygdalar enlargement due to neuroleptic exposure seems, however, an unlikely explanation since the schizophrenic control group, more likely to have received neuroleptics, showed no increase in amygdalar size. The association between the size of the amygdala and the number of manic episodes in the patients of this study suggests the possibility that the prolonged or repeated stimulation or kindling of the amygdala results in hypertrophy.

The absence of differences in hippocampal volume between bipolar patients and normal controls is corroborated by the results of Hauser et al.'s (1989) study.

A recent study (Rabins et al. 2000) measured cerebral atrophy in patients with late-onset schizophrenia and late-life bipolar and unipolar depression and normal controls. Late-life depression included both early and late-onset patients. Atrophy was judged using a 4-point rating scale. Schizophrenic subjects were found to have more temporal atrophy and third lateral ventricle enlargement than patients with depression, whereas the depressed group as a whole displayed more superficial cortical sulci enlargement than the schizophrenic patients. This effect was unlikely to be due to medication effects, and the authors felt that the pathogenesis of late-onset schizophrenia and late-life depression was different.

Elkis et al. (1995) performed a meta-analysis to compare the frequency and severity of ventricular enlargement (11 studies included) and sulcal prominence (4 studies included) in patients with mood disorders and schizophrenia. Patients with mood disorders had significantly increased

ventricular volume and sulcal prominence compared with normal controls, but the most significant result was the greater ventricular enlargement in schizophrenic patients compared to those with mood disorders. However, the available studies were too few to support a full quantitative analysis and no conclusion could be reached as to the difference between the depressed and the schizophrenics on cortical sulcal prominence. On the whole, patients with mood disorders were more similar to schizophrenic patients than to normal controls.

Correlation between structural abnormalities and clinical features

Subtypes of depressive illnesses

Whether there are neuroradiological differences with regard to subtypes of depressive illnesses remains inconclusive. According to Videbech's meta-analysis (1997), there seems to be little difference in volume reductions of the frontal and temporal lobes when bipolar and unipolar patients are compared. However, reduction in the volume of the basal ganglia was found in unipolar and not in bipolar patients, but no attempt was made to explain this difference. Rabins et al. (1991) found no differences between depressed patients with and without delusions on any structural MRI measures. Another study (Baumann et al. 1997) compared patients with neurotic and endogenous depression ; the former showed smaller Sylvian, temporal and basal frontal fissures, particularly in the right hemisphere, unrelated to age and duration of illness. Thus, there may be a chronic « over-activation » of these brain regions with subsequent hypertrophy as argued by the authors. Similarly, Alexopoulos et al. (1992) described differences between structural and functional neuroimaging parameters in late-onset and early-onset depression. A combined PET and MRI study (Ebmeier et al.1997) did not find MRI differences between the two groups as to white matter changes and temporal lobe width, although left temporo-parietal cortex perfusion was decreased in late-onset depression.

Age effects

Cortical atrophy (Alexopoulos et al. 1992, Rabins et al. 1991) and ventricular enlargement (Alexopoulos et al. 1992) may be more pronounced in depressed elderly patients, although age effects have not been found in all studies (Baumann et al. 1997). Furthermore, structural abnormalities have also been described in younger depressed patients (Pearlson et al. 1989). This held even true for a small group of treatment-resistant bipolar children and adolescents (Geller et al. 1996).

Severity of the depressive illness

Rabins et al. (1991) suggested that atrophic changes may be related to the severity of the depressive illness rather than to its type. This was based on their finding of more pronounced temporal horn atrophy and greater subcortical abnormalities in patients, as compared with normal subjects, who had undergone ECT and who presumably had a severe form of depression.

Treatment response

Whether or not there is an association between structural changes and treatment response to antidepressants remains unclear. Alexopoulos' study group (1992) observed a correlation between ventricular dilatation and non-response to tricyclic antidepressant treatment, maybe as the result of a loss of serotonin-containing neurons in the periventricular areas.

Predictive value of neuroradiological changes

The predictive value of neuroradiological changes also remains uncertain. In an early CT study, Jacoby et al. (1981) found that depressed patients with ventricular enlargement had higher mortality rates than those without. They

suggest that ventricular enlargement is a manifestation of ageing and of adverse prognostic value in depression in late life.

White matter hyperintensities (WMHIs)

White matter hyperintensities (WMHIs) detected using MRI are thought to represent underlying vascular pathology due to atherosclerosis of the long perforating arteries leading to myelin and axonal damage. However, histological findings visualized as WMHIs may also correspond to perivascular spaces, arteriosclerosis, gliosis, lacunar infarcts, and congenital diverticula (Barber et al. 1999). Deep WMHIs and periventricular WMHIs may have different aetiologies. Thus, deep WMHIs probably arise from perivascular abnormalities or microcystic infarcts and smooth periventricular WMHI may result from loss of ependymal lining of the ventricles and local increase in tissue fluid (Moore et al. 2001).

The clinical significance of WMHIs is not altogether clear and they can be found in patients with hypertension, diabetes, multiple infarct dementia, Alzheimer's disease and cocaine abuse. Furthermore, subcortical hyperintensities have been found to increase with age at a rate of 6.3% per year in the deep white matter and of 8.1% per year in the pons, but this does not appear to be the case for hyperintensities in the periventricular white matter or in the basal ganglia (Coffey et al. 1992). An uncontrolled case study (Fein et al. 1990) found above-average cognitive functioning in three individuals with extensive deep and periventricular WMHIs and follow-up over three years showed unchanged cognitive functioning while WMHIs were at least as extensive as on the initial MRI scan. Similarly, Coffey et al. (1996) found WMHIs to be present in normal people over the age of 50 years. However, when the total WMHIs volume exceeded 10 ml or 0.5% of the total intracranial volume a correlation emerged with cognitive abnormalities. Kramer-Ginsberg et al. (1999) found that WMHIs were associated with cognitive impairment only in those who were depressed, but

not in normal elderly controls suggesting that factors other than WMHIs may be necessary for cognitive impairment to become apparent.

The presence of WMHIs has also been associated with depression. A number of studies looked at the presence of WMHIs in elderly patients with major depression. Coffey et al. (1993) investigated 43 patients with severe depression referred for ECT (mean age 62.4 years) and 60 normal control subjects (mean age 61.6 years) and rated the frequency of WMHIs in the periventricular white matter, deep white matter, basal ganglia, thalamus, and pons. Although WMHIs were more prevalent in all five regions in depressed patients, only those in the periventricular white matter reached statistical significance after adjusting for age. The authors speculate that brain hypoperfusion due to hypoxia or hypotension, secondary to cardiovascular or cerebrovascular disease, or the use of drugs with a hypotensive or cerebrovascular effect such as psychotropic agents, may be the cause of WMHIs. Malnutrition and weight loss, persistent hypercortisolism, drug or alcohol abuse may also play a role. In an earlier study by the same group (Coffey et al. 1989) of elderly patients with severe late-life depression, 80% of whom had late-onset major depression, age alone could not account for the presence of WMHIs. All 51 patients had periventricular WMHIs, 86% had deep WMHIs and 51% had changes in the subcortical grey matter nuclei consisting of punctate or multipunctate/diffuse areas of high signal intensity. Risk factors for vascular disease were present in 58% of patients and were significantly more common in those with deep and subcortical WMHIs. Another study (Rabins et al. 1991) found basal ganglia and white matter lesions to be significantly more frequent in elderly depressed patients than in healthy controls whereas the prevalence of periventricular changes did not reach statistical significance. The effect of age of onset appears to play a minor role in the bipolar patients who develop WMHIs (Videbech 1997), possibly because genetic factors are more important in bipolar disorder.

A few studies have looked at WMHIs in younger bipolar populations. Dupont et al. (1995) compared 36 bipolar with 30 unipolar patients and 26

control subjects. The patients' maximum age was 55 and patients with vascular risk factors and in particular hypertension were excluded. Patients with bipolar disorder demonstrated a higher volume of WMHIs than either control subjects or the unipolar group. Bipolars with high volumes of WMHIs had later age of onset and had cognitive impairment suggestive of subcortical dysfunction compared with those with less WMHIs. Bipolar patients had a preferential frontal distribution of WMHIs. Swayze et al. (1990) compared young (mean age 34 years) bipolar patients in a manic state with schizophrenic subjects and found WMHIs in particular on the lateral border of the ventricles both in the right and left hemisphere in the manic patients (9/39) more often than in the schizophrenic (5/49) and the normal controls (2/45).

The clinical correlates of WMHIs in depression

Some clinical features of depression may be specifically associated with the presence of WMHIs.

The relationship between age of onset of depression and the presence of both periventricular and deep WMHIs was examined by Salloway et al. (1996) in 15 patients with early-onset (mean age of onset 35.8 years ; mean age at time of study 73.3 years) and in 15 patients with late-onset (mean age of onset 72.4 years ; mean age at time of study 77.5 years) depression. The late-onset group had significantly more periventricular WMHIs and showed greater cognitive impairment. Similarly, Coffey et al. (1989) found that WMHIs in 51 patients 60 years or older were commoner in those with late-onset depression.

These observations have led to the formulation of the vascular depression hypothesis (Alexopoulos et al. 1997, Krishnan & McDonald 1995). This hypothesis postulates that cerebrovascular disease may predispose, precipitate, or perpetuate depressive syndromes in old age. It further suggests that some clinical features including outcome may be related to vascular pathology.

Dupont et al. (1995) found an association between increased volumes of WMHIs and higher rates of psychiatric illness among relatives of bipolar and unipolar patients and bipolar patients in this group had a later age of onset.

The presence of WMHIs may be relevant to outcome as suggested by the study of Moore et al. (2001) of bipolar patients aged 20-65 years. 15 patients with poor-outcome as defined by being unwell for 2 years or more despite adequate therapy and periods of remission lasting 8 weeks or less still accompanied by significant functional impairment, were compared to 14 patients with good-outcome as defined by being clinically euthymic for at least 8 weeks at the time of the study and a period of full recovery and normal functioning after each episode of illness. Patients were matched for age and gender. The presence and severity of deep subcortical and periventricular WMHIs was graded on a four-point scale (0-3). Deep WMHIs were seen most frequently in bipolar patients with poor outcome as compared with those who had good outcome and normal controls. However, these abnormalities were found in only 47% of the patients with poor outcome. This suggests that the aetiology of poor outcome is multifactorial. Periventricular WMHIs did not differ significantly between these groups.

It has also been suggested that subcortical vascular disease may underlie treatment resistance in depression. Simpson et al. (1997) studied 14 patients (age between 58 and 84 years) resistent to antidepressant medication as defined by at least one trial for three months or longer with no clinical benefit. Five of them had either CT or MRI suggestive of subcortical vascular pathology. Ten had minor neurological impairment such as slow and restricted eye movements, focal upper motor neuron deficits or frontal lobe release phenomena. In a subsequent study of 75 elderly patients with resistant depression, Simpson et al. (1998) suggested that confluent deep WMHIs and multiple lesions in the basal ganglia and the pontine reticular formation predicted resistance to anti-depressive monotherapy at 12 weeks

of treatment. Lavretsky et al. (1999) followed up 16 patients with late-life depression of whom eight developed a chronic course of unremitting major depression. At baseline, ten patients, six of them in the chronic unremitting group, had WHMIs. At follow-up two years later, the volume of WMHIs had increased by $2cm^2$ or more in four patients with a chronic unremitting course. This was the case in none of those responding to treatment. Chronic depression was also associated with the severity of cerebrovascular risk factors. Thus, the cerebrovascular risk and the rate of increase of WMHIs, but not their volume at baseline, might be a predictor of chronicity of depression in the elderly. O'Brien et al. (1998) followed up 60 patients over 55 years of age with major depressive disorder over a 21/2-year period and found those with severe deep WMHIs to be less likely to recover fully from depression or not to relapse or to decline cognitively than those with less severe lesions. In Coffey et al.'s (1989) study of severely depressed elderly patients, the response to ECT was not associated with frequency or severity of WMHIs as measured on a 0-4-point scale ranging from absence of WMHIs to confluent/extending areas of WMHIs.

Structural and functional changes and cognitive impairment

Structural brain imaging studies

Some studies have addressed whether or not there is a relationship between structural brain changes and cognitive impairment. One of the first such studies (Pearlson et al. 1989) using CT reported larger ventricles in 17 patients with cognitive impairment and long histories of depression as compared with 11 cognitively unimpaired depressed patients and healthy controls. These patients were over the age of 60 years and cognitive impairment was defined as an MMSE score below 24. Medial temporal lobe atrophy is sometimes found in depression and in one study (Launer et al. 1995), it was associated with dementia and cognitive impairment, but not with depressive symptoms, age, education, sex, and evidence of

cardiovascular disease. However, longitudinal studies such as the one performed by Fox et al. (1996) in pre-symptomatic relatives at risk of familial AD who eventually developed dementia would be necessary to determine whether structural brain changes are progressive in depression.
Swayze et al. (1990) studied young bipolar patients in a manic state and found no correlation between the presence of WMHIs and cognitive impairment. However, in Coffey et al.'s (1989) study, the group of patients with severe verbal and/or visual memory impairment had more severe WMHIs than those with less severe memory impairment.

Functional brain imaging studies

Functional brain imaging studies have reported links between cognitive impairment in depression and functional abnormalities in specific brain regions. In a PET study (Dolan et al. 1992), ten cognitively impaired depressed patients (as defined by a MMSE score of 25 or less and a CAMCOG score equal or below 85), were compared with ten cognitively unimpaired subjects with similar moderate to severe depression. rCBF in the cognitively impaired group was decreased in the left antero-medial prefrontal region and increased in the cerebellar vermis. Similar results were obtained by Bench et al. (1992). In a later study by the same group (Dolan et al. 1994) of depressed patients with no cognitive impairment, the left dorso-lateral prefrontal cortex and the left anterior cingulate gyrus showed decreased rCBF. Thus, decreased rCBF in the left anterio-medial prefrontal region and increased rCBF in the cerebellar vermis may be related to the cognitive impairment. In a SPET study (Austin et al. 1992b) of patients with major depression, impairment in memory function was found to correlate with higher uptake of 99m-exametazime in posterior cingulate areas.
Functional neuroimaging studies may have a certain potential to distinguish dementia from depression. Kumar et al. (1993) demonstrated significant decrease of glucose metabolism in depressed patients as compared with normal controls in all major neocortical and paralimbic regions of the brain

as well as in the caudate and in the lenticular nucleus. However, this finding was similar to that seen in Alzheimer patients in whom the distribution pattern was, however, more heterogeneous.

A neuroanatomical model of depression

Mayberg (1997) has attempted to define a neuroanatomical model of depression which consists of a dorsal, predominantly cognitive sub-system that is hypoactive during depression and a ventral, predominantly emotional subsystem which is hyperactive in the depressive state as shown by PET-studies. These cognitive subsystems are linked together via a series of pathways of which the rostral cingulate might play a crucial role since patients with high pretreatment metabolism in this region showed a good response as opposed to those with low pretreatment metabolism. This model not only has the advantage to link functions to brain regions but to distinguish cognitive and affective aspects of depression and to state their interaction.

Conclusions

A series of methodological issues have slowed down the progress in our understanding of the link between structural brain changes and affective disorders. Many of the studies carried out so far have used small samples and yielded contradictory results that are in need of confirmation. Study samples have also been heterogeneous using variable clinical inclusion criteria (i.e. type of depression, euthymia versus current depression, and severity of depression). Age of onset is another important factor that has not always been taken into account. Brain imaging studies have used different criteria to measure brain structures and this makes them difficult to compare. More importantly, longitudinal studies similar to those performed in Alzheimer's disease to determine the progression of structural brain abnormalities over time are not yet available.

Despite these methodological pitfalls, there is emerging evidence that structural brain changes occur in subgroups of depressed patients. These changes include non-specific ventricular dilation and sulcal widening as well as more focal changes such as loss of hippocampal/amygdalar volume and white matter pathology. Structural brain abnormalities appear to correlate with some specific clinical features of depression. Of these late age of onset appears to be more clearly linked to structural brain abnormalities and WMHIs in particular, although these structural brain changes have also been described in younger patients.

THE STUDY

RATIONALE FOR THE STUDY

Over 20% of the general population complain of memory difficulties, increasing to more than 40% in those over the age of 65. Objective memory impairment is about half those rates, but the gap narrows with increasing age (Ogura et al. 1998). Subjective memory problems are also common in depression (O'Connor et al. 1990). The mechanisms underlying these complaints and their relationship to the reported abnormalities in medial temporal structures still remain to be determined.

Objective cognitive abnormalities have been well documented in depression. These abnormalities may cut across a range of cognitive domains, but memory is usually affected (Brown et al. 1994, Burt et al. 1995). There is also increasing evidence that cognitive abnormalities may persist during euthymic phases (Marcos et al. 1994, Paradiso et al. 1997). The neural networks responsible for the cognitive abnormalities of depression are not well understood, but reductions in amygdalar and hippocampal volume (Shah et al. 1998, Sheline et al. 1996, Sheline et al. 1998) have been reported.

This study set out to explore the possibility that different neural structures may be responsible for affective symptoms, subjective memory difficulties and objective cognitive impairment in patients with depression. A group of depressed patients with subjective memory problems, but in whom dementia had been carefully excluded, were recruited for the study. The central hypothesis tested in the study was that affective symptoms and/or subjective memory difficulties would be related to reduction in the volume

of the amygdala, while objective cognitive deficits, if present, would be related to reduction in hippocampal volume. Quantitative MRI techniques and psychometric tests were used in the study.

Chapter 7

METHOD

Subjects

14 non-demented patients (six males, 8 females) who fulfilled ICD-10 criteria for depressive illness (any type) and who persistently complained of "memory" difficulties were recruited from current attenders to the Neuropsychiatric and the Cognitive Disorder Clinics at the National Hospital for Neurology and Neurosurgery (NHNN) in London.

The nature of the memory complaints varied from patient to patient, but in all cases they fell into one of the following categories : difficulty in learning new things, general complaints of forgetfulness, forgetting occasional words and lack of concentration. These complaints were prominent when the patients first attended the NHNN and were consistently mentioned in subsequent consultations. Although they varied over time in some patients, the complaints were a most consistent clinical feature and were still present in all patients at the time of study.

Patients were included in the study if they were not demented according to the NINCDS-ADRDA criteria for dementia (McKhann et al. 1984) and also scored 27 or more in the MMSE (Folstein et al. 1975). Other exclusion criteria were a history of neurological disease, head injury leading to loss of consciousness and a history of alcohol or drug abuse.

Seven patients were taking selective serotonin reuptake inhibitors (SSRIs), two tricyclic antidepressants, one benzodiazepines and one a combination of these drugs.

All patients had been fully assessed neurologically and psychiatrically and had undergone neuropsychological testing when they first attended the NHNN .

Five other patients with persistent memory complaints were excluded from the study because they did not fulfil diagnostic criteria for depression (1), had probable Alzheimer's disease (2), or scored less than 27 on the MMSE (2) .

14 control subjects (six males, eight females) from a bank of healthy volunteers participating in other imaging studies were used as controls for MRI data. They were individually matched to the patients by gender and within 3 years for age. Controls were excluded from the study if they had a history of neurological or psychiatric illness. None of the controls had subjective memory difficulties.

Psychiatric assessment

A detailed psychiatric interview was performed to reach an ICD-10 diagnosis. The Hamilton Anxiety and Depression (HAD) scale (Zigmond & Snaith 1983) was used to measure depression and/or anxiety at the time of the interview. This is a short self-assessment scale with a maximum score of 42. It consists of seven questions targeting depression and seven questions targeting anxiety ; thus, depression and anxiety sub-scores ranging between zero and 21 could be determined.

A score of nine or more was used to determine "caseness" for both depression and anxiety.

Neuropsychological assessment

All patients except one had been previously assessed when first seen at the NHNN. For this study a further neuropsychological assessment was performed in 1998 on the same day as the psychiatric assessment. The mean interval between the two neuropsychological assessments was 3.5 years (SD 1.9 years).

The neuropsychological assessment comprised measures of current intelligence, verbal and visual memory and naming. The tests administered were as follows:

1) NART

The National Adult Reading Test (NART) (Nelson & Willison 1991) was administered to obtain an estimate of premorbid level of intellectual functioning. It consists of the administration of a series of words to be read aloud. These words are mostly spelled in a irregular manner. The level of word reading ability achieved in this test by an adult has been shown to correlate highly with intelligence and proved to be relatively resistant to influences which impair other aspects of cognitive function. After administering the NART, regression equations are used to obtain an estimate of 'minimum premorbid intelligence', and discrepancies between this and current WAIS IQ can then be observed. The test has obvious limitations for whose who were always poor readers or those with acquired reading difficulties.

2) WAIS-R.

A short version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used. This is a standardised instrument for the measurement of

intelligence, providing separate scores for verbal and performance abilities. The full assessment comprises six verbal subtests and five performance subtests.

The verbal subtests include : a) Information : 29 questions covering a wide variety of information and arranged in order of difficulty ; b) Comprehension : 16 items in which the subject must explain what should be done in certain circumstances, the meaning of proverbs, etc ; this aims at measuring practical judgement and common sense ; c) Arithmetic : 14 mental arithmetic problems set in the context of everyday activities ; d) Similarities : 14 items in which the subject must say in what way things are alike ; e) Digit span : lists of 3-9 digits to be reproduced forwards and 2-8 digits to be reproduced backwards ; f) Vocabulary : 35 words graded in difficulty for which the subject must give the meaning.

The performance subtests include : a) Digit symbol : the subject must follow a simple code in matching symbols to digits, as quickly as possible ; b) Picture completion : the subject is shown 20 pictures of human features, familiar objects or scenes, and must say what important part is missing from each ; c) Block design : the subject must reproduce designs with red and white blocks ; d) Picture arrangement : ten sets of cartoon pictures must be arranged in sequence so as to tell a sensible story ; e) Object assembly : four jigsaw-like puzzles of familiar objects must be assembled from their parts.

The short version of the WAIS-R used in this study consisted of four verbal subtests (Verbal IQ as assessed from Arithmetic, Similarities, Digit Span, and Vocabulary) and three performance subtests (Performance IQ as assessed from Picture Completion, Block Design, and Picture Arrangement) that also allowed to calculate the full IQ (Wechsler 1981).

3) Memory tests.

The recognition memory tasks for words and faces were chosen. They allow identical procedures to assess verbal and visual memory and direct comparison of verbal and visual memory. Recognition memory is also less vulnerable to depression and anxiety than free recall.

a) The Recognition Memory Test for words (Warrington 1984) consists of 50 high frequency words, each printed on a card. The words are presented at 3-second intervals, and the subject is asked to say 'yes' or 'no' according to whether he judges the word to be pleasant or not in order to ensure attention to the words. Recognition is tested immediately after the presentation is complete by showing pairs of words, one of which is new whereas the other has already been shown and by forcing the subject to chose one word of each pair.

b) The Recognition Memory Test for faces (Warrington 1984) consists of 50 photographs of faces. The procedure adopted is identical to the one for the above described verbal memory task.

4) Graded naming test

The Graded Naming Test (McKenna & Warrington 1983) was included as some patients complained of forgetting words occasionally. In this test, the subject is shown 30 line drawings of items that they are asked to name. These items vary with regard to lexical frequency and thus naming difficulty.

5) From these tests three derived scores were calculated :

a) The intellectual functioning score was calculated as the difference between the NART and the Full-Scale IQ. This difference should be

zero unless the subject has experienced intellectual decline, in which case the score becomes progressively higher. A difference greater than ten was taken as evidence of intellectual decline.

b) The memory scores were derived by converting the standardised test performances on the memory tests into percentile scores. A percentile score at or below the 5th percentile was taken to indicate a memory impairment.

c) The naming score was derived by converting the standardised test performances on the naming test into percentile scores. A percentile score at or below the 5th percentile was taken to indicate a naming impairment.

The control subjects had received selective cognitive tests before being scanned which included : the MMSE, the NART, the Recognition Memory Test for words and faces, the Paired-Associates Learning test, and the Raven's Progressive Matrices (Raven 1938).
Scoring within the age-scaled norms for these tests was an inclusion criterion for the pool of normal MRI data. Neuropsychological data from the normal controls was not used for other purposes of this study.

Subjective memory assessment

All patients were given the Gilewsky et al.'s (1990) Memory Functioning Questionnaire (MFQ) [cf. appendix]. This questionnaire is a self-assessment tool composed of questions to which the subject has to give an answer on a one-to-seven scale that indicates less subjective difficulty with increasing scores ; thus, a low score stands for severe subjective difficulties.

The MFQ questions are grouped into the following seven categories :

1) How often do specific situations present a problem
2) How frequent are difficulties in remembering when reading a novel
3) How frequent are difficulties in remembering when reading a newspaper or magazine article
4) How well do they remember things that occurred in the past
5) How serious is their memory failure in specific situations
6) How does memory performance now compare with the way it was in the past
7) How often are mnemonic techniques used.

Each category leads to a sub-score that can be summed up to achieve a total score ranging from 63 to 441.

In order to compare subjective memory complaints with the observed performance on daily memory tasks, a modified version of the questionnaire to be completed by an informant who had known the patient for many years and who was still in daily contact was prepared. The questions and the way sub-scores were obtained were identical to the subjective memory complaint questionnaire filled in by the patients. However, the questions related to reading novels and magazines were dropped since it was judged that the relatives were unlikely to answer these questions accurately.
10 out of 14 informants returned the questionnaire.

Magnetic Resonance Imaging

All scans were performed on a 1.5 Tesla Signa system (GE Medical Systems, Milwaukee, USA). The scans included routine sagittal T1-weighted and axial (5mm thick) proton density and T2-weighted sequences. In addition, volumetric imaging was performed using a spoiled gradient echo technique with 24 cm field of view, yielding 124 contiguous 1.5 mm thick coronal slices through the head on a 256*128 matrix. The acquisition parameters were 35/5/1/35 - TR/TE/NEX/FLIP.

Volumetric measurements

All measurements were performed blind to subject identity or group membership. In addition images were randomly left-right flipped so that measurements were also performed blinded to side. Digitised images were analysed using MIDAS software (Freeborough et al. 1997).

The following measurements were obtained :

1) *Intracranial volume.* The inner border of the skull was outlined on the T2-weighted scans using a semi-automated thresholding method (approximately 10 axial slices). Intra-cranial volume below the cerebellum was excluded.
The intra-rater reliability was calculated after re-measuring blindly 5 randomly selected subjects (mean ratio = 0.99 ± 0.007 ; Spearman's rho = 1.0 and $p<0.0001$).

2) *Hippocampal volume.* The hippocampal formation was defined using a neuro-anatomical atlas (Duvernoy 1988) as including the dentate gyrus, the hippocampus proper, the subiculum and the alveus. The region was first manually outlined in the sagittal view and then edited and checked in the coronal view to ensure the accurate determination of anatomical boundaries. The following boundaries were used: the superior and anterior borders were

delineated by the outer limits of the alveus and the fimbria. The anterior separation of the hippocampus from the amygdala was performed on the sagittal view. The inferior border was formed by the white matter of the subiculum. The wall of the lateral ventricle was taken as the lateral boundary and the medial border corresponded to the cerebro-spinal fluid (CSF) of the adjacent cistern. The posterior limit was arbitrarily defined as the coronal slice where the fornix was seen in its longest unbroken extent. On the whole, each hippocampus was processed on approximately 20 sagittal and 25 coronal slices following the algorithm shown in appendix 1.

After a 2-3-week interval, the selected hippocampal regions were rechecked for accuracy and minor adjustments made if necessary again in a blind and randomised manner.

Twelve hippocampi were measured a second time to determine the intra-rater reliability (mean ratio = 0.969 ± 0.027 ; Spearman's rho = 0.916 and $p<0.0001$).

3) Amygdalar volume. The amygdala was measured using a similar procedure. The following boundaries were considered: the superior limit corresponded to a line connecting the most inferior point of the lateral fissure with the most lateral part of the paramedian cisternae and, more posteriorly, the superior and lateral border of the optic tract. The inferior, medial and lateral borders were determined by the boundary between amygdala and adjacent white matter. The most rostral coronal slice was taken as the one where the temporal and frontal lobes were no longer separate. The posterior boundary was formed by the disarticulation from the hippocampus as described above. On average, approximately 20 sagittal and 15 coronal slices were processed for each amygdala. The detailed procedure used to delineate and measure the volume of the amygdala is included in appendix 2.

Fourteen amygdalae were measured twice to determine the intra-rater reliability (mean ratio = 0.947 ± 0.036 ; Spearman's rho = 0.917 and $p<0.0001$).

4) In order to control for brain size hippocampus/intracranial and amygdala/intracranial ratios were calculated.

White matter hyperintensities (WMHIs)

An experienced neuroradiologist blind to age and clinical features of the subjects assessed the presence, number, and location of WMHIs in the patient group.

Data Analysis

Two-tailed non-parametric statistics (Mann-Whitney-U test) were used to compare volumetric data and to compare age, NART IQ and MMSE between groups. Correlations between volumetric, clinical and neuropsychological data were explored using Spearman's correlation. Non-parametric paired sample statistics were used to compare subjective memory complaints with the cognitive performance as judged by the informants using the modified MFQ.

Chapter 8

RESULTS

Subjects' characteristics

The patients and controls were well matched for age and gender (6 males and 8 females in each group). There was a trend for the controls to have higher estimated pre-morbid IQ than the patients, but this fell short of significance.

Demographic details are summarised in table 1 :

	Patients (n=14) Mean ± standard deviation and (range)	Controls (n=14) Mean ± standard deviation and (range)	Mann-Whitney U	p-value
Mean age (range)	57.6 ± 9.4 (37-69)	58.1 ± 10.3 (36-72)	96.0	0.927
Gender f/m	8/6	8/6	-	-
NART FIQ	105.5 ± 12.7 (n=11)	114.9 ± 9.1 (n=12)	36.0	0.064

Table 1. Subjects' characteristics
NART FIQ= Estimated pre-morbid IQ using the National Adult Reading Test

Diagnosis

The diagnostic categories are shown in table 2. Two patients fulfilled ICD-10 criteria for recurrent depressive disorder, nine for depressive episode, one for bipolar affective disorder, one for dysthymia and one for unspecified mood disorder.

At which point did they satisfy criteria?
At initial assess or at 2nd assess?

No	Gender	Age	Duration in years of depression	loss of memory	HAD	Drugs	Diagnosis (ICD-10)
1	F	69	8	11	18	—	Recurrent depressive disorder, moderate (F33.1)
2	F	36	4	1	10	T + SSRI	Mild depressive episode (F32.0)
3	M	59	3	3	6	SSRI	Moderate depressive episode (F32.1)
4	M	54	17	17	18	SSRI	Moderate depressive episode (F32.1)
5	F	64	10	6	2	—	Recurrent depressive disorder, mild (F33.0)
6	F	69	8	8	4	T	Mild depressive episode (F32.0)
7	M	67	6	6	5	—	Moderate depressive episode (F32.1)
8	F	56	2	2	9	T	Bipolar disorder (F31)
9	F	56	5	5	10	SSRI	Moderate depressive episode (F32.1)
10	F	43	5	5	1	SSRI	Other depressive episodes (F32.8)
11	F	52	4	4	7	SSRI	Severe depressive episode (F32.2)
12	M	63	5	5	9	SSRI	Dysthymia (F34.1)
13	M	59	7	7	14	BZDZ	Other depressive episodes (F32.8)
14	M	59	6	6	10	SSRI	Severe depressive episode (F32.2)

Table 2. Clinical features and diagnoses of all patients

Legend :
BZDZ, benzodiazepines; HAD, Hospital Anxiety Depression Scale total score; SSRI, selective serotonin reuptake inhibitor; T, tricyclic antidepressants

At the time of the study, six patients were euthymic (as defined by a HAD depression score < 9 ; mean score : 4.17) whereas eight patients were slightly to moderately depressed (HAD depression score equal or > 9 ; mean score : 12.5). None was severely depressed according to the HAD depression score.

Initial neuropsychological assessment

The results of the initial assessment are given below in table 3.

The means of the scores obtained by the whole patient group are shown together with standard deviation, range of scores, number of subjects with an intellectual functioning score greater than 10 indicating significant decline and/or scoring at or below the standardised 5th percentile on memory and naming measures.

	Mean ± sd	Range	Number scoring NIF-FIQ > 10 < 5 percentile	Number scoring < 5 percentile
FIQ	99.7 ± 13.4	125 - 80	3	-
RM words	43.0 ± 6.3	50 - 32	-	4
RM faces	39.3 ± 7.4	47 - 25	-	4
GNT	22.4 ± 2.9	27 - 18	-	0

Table 3. Neuropsychological scores at initial assessment (n = 13)

Legend:

SD = Standard deviation
FIQ = Full-Scale IQ
NIF = NART Intellectual Functioning
RM Words = Recognition Memory Test for Words
RM Faces = Recognition Memory Test for Faces
GNT = Graded Naming Test

At the time of the initial assessment, eight patients did not show any evidence of cognitive impairment scoring within normal limits on memory and naming tests and showing no significant difference between estimated and current IQ. Of the remaining five, two showed both intellectual and memory under-functioning. Two showed poor performance on memory tests and one selective intellectual under-functioning. In the four patients in whom memory scores were below the 5th percentile both visual and verbal

memory were impaired. These results are summed up in table 5 (together with those of the neuropsychological assessment at the time of the study).

All patients performed within normal limits on the naming test.

Neuropsychological assessment at the time of the study

The patients were reassessed using the same intelligence, memory and naming tests. Their follow up results are shown below in table 4.

	Mean ± sd	Range	Number scoring NIF-FIQ > 10	Number scoring < 5 percentile
FIQ	104.4 ± 11.7	125 - 87	1	-
RM words	45.5 ± 4.2	50 - 35	-	1
RM faces	42.5 ± 4.8	49 - 36	-	1
GNT	22.5 ± 2.9	26 - 18	-	0

Table 4. Neuropsychological assessment at the time of the study (n = 14)

Legend:
SD = Standard deviation
FIQ = Full-Scale IQ
NIF = NART Intellectual Functioning
RM Words = Recognition Memory Test for Words
RM Faces = Recognition Memory Test for Faces
GNT = Graded Naming Test

At follow-up the performance of the whole patient group had improved both on tests of general intelligence as well as on tests of memory and 13 out of 14 patients obtained scores entirely within normal limits.

Only 1 patient continued to have intellectual underfunctioning and poor performance on memory tests, both verbal and visual. This patient (No 14 in Table 5) had initially been tested using an easy verbal and visual recognition test (Clegg & Warrington 1994) and these scores were available for comparison. When this test was administered at follow-up the scores had improved from 14/25 to 21/25 for word recognition and from 16/25 to 19/25 for face recognition.

The normal results in all cognitive tests in 13 patients and the mild improvement in tests of memory in the 14th patient rule out the presence of

progressive cognitive deterioration and serve as validation for the entry criteria into the study.

These results are shown in table 5.

Despite the complaints of some patients of occasional difficulties in finding words, all of them performed within normal limits on the graded naming test.

No	Gender	Age	HAD total	HAD depr	HAD anxiety	ICD-10	NIQ-FIQ>10	Memory <5%ile	Follow up testing
1	F	69	38	18	20	F33.1	yes	no	normal
2	F	36	22	10	12	F32.0	_	_	normal
3	M	59	13	6	7	F32.1	no	no	normal
4	M	54	35	18	17	F32.1	no	no	normal
5	F	64	4	2	2	F33.0	yes	verbal + visual	normal
6	F	69	16	4	12	F32.0	no	no	normal
7	M	67	15	5	10	F32.1	no	no	normal
8	F	56	23	9	14	F31	no	verbal + visual	normal
9	F	56	26	10	16	F32.1	no	no	normal
10	F	43	9	1	8	F32.8	no	no	normal
11	F	52	17	7	10	F32.2	no	no	normal
12	M	63	13	9	4	F34.1	no	no	normal
13	M	59	32	14	18	F32.8	no	verbal + visual	normal
14	M	59	30	10	20	F32.2	yes	verbal + visual	Memory & IQ deficit

Table 5. Individual cognitive performance before the study and at the time of the study
NIQ-FIQ : NART estimated premorbid IQ minus full IQ = intellectual functioning score

Clinical correlations

Cognitively impaired versus cognitively unimpaired patients at initial testing (table 6)

Thirteen patients had initially been tested neuropsychologically. Five of them were considered to have cognitive impairment as defined by a difference between the NART estimated IQ and the current IQ (WAIS-R) of more than 10 points and/or memory performance below the 5th percentile. There was no significant age difference between the patients with and those without cognitive impairment.

Of the five patients who were cognitively impaired at the initial testing only one had become euthymic at follow-up, while this was the case for five out of the eight cognitively unimpaired. Fischer's exact test showed that recovery from depression was not significantly different ($p = 0.163$) in those cognitively unimpaired before the study when compared with the cognitively impaired group.

Likewise, the four patients who were both cognitively impaired initially and who were depressed at follow-up (HAD score 9 or more) did not differ in their HAD global score and the anxiety and depression sub-scores from the three patients who were cognitively unimpaired initially and who were depressed at follow-up [HAD score : 30.75 ± 6.19 versus 24.67 ± 11.06 ; Mann-Whitney-U 4.0, $p = 0.480$; HAD anxiety score : 18.00 ± 2.83 versus 12.33 ± 7.23 ; Mann-Whitney-U = 2.0, $p = 0.154$; HAD depression score : 12.75 ± 4.11 versus 12.33 ± 4.93 ; Mann-Whitney-U = 5.5, $p = 0.856$].

The frequency of subjective "memory" problems at follow up was similar in the two groups : three out of five in the initially cognitively impaired group

felt their memory was better and the same was the case for four out of eight in the unimpaired group.

	Cognitively impaired (n = 5)	Cognitively unimpaired (n = 8)	Mann-Whitney-U	p-value
Women / men	3 / 2	4 / 4	-	-
Age	61.40 ± 5.13	57.88 ± 8.53	14.0	0.376
Euthymic / depressed at follow-up	1 / 4	5 / 3	-	-
Subjective memory improvement / subjective memory unchanged at follow-up	3 / 2	4 / 4	-	-

Table 6. Clinical correlations in cognitively impaired versus unimpaired patients

Euthymic versus depressed patients at follow-up (table 7)

Six patients were euthymic at the time of the study and eight were depressed as defined by HAD scores of 9 and above.

There were no significant age differences between the six patients (four women and two men) who were euthymic at the time of the study and those eight patients who were depressed.

The depressed patients had, as expected, significantly higher depression scores on the HAD scale. They also were significantly more anxious according to the HAD anxiety score.

	Euthymic (n = 6)	Depressed (n = 8)	Mann-Whitney-U	p-value
Women / men	4 / 2	4 / 4	-	-
Age	59.00 ± 9.94	56.50 ± 9.55	19.5	0.559
HAD depression score	4.17 ± 2.32	12.25 ± 3.88	0.0	0.002*
HAD anxiety score	8.17 ± 3.49	15.13 ± 5.28	5.5	0.017*
Cogn impaired / unimpaired (n=13)	1 / 5	4 / 3	-	-
Subjective memory improvement / subjective memory unchanged	4 / 2	3 / 5	-	-

Table 7. Clinical correlates of euthymic versus depressed patients. *significant at < 0.05 level

Patients with subjective memory improvement versus those with no subjective memory improvement (table 8)

Seven patients felt their "memory" had improved at follow up (two out of six men and five out of eight women) and another seven felt it was unchanged. None felt that their memory had deteriorated.

There was no significant age difference between those who felt their memory had improved over time when compared with those who felt their memory had remained unchanged.

No statistically significant differences were present between the two groups as to the HAD depression and anxiety scores.

	improved (n = 7)	unchanged (n = 7)	Mann-Whitney-U	p-value
Women / men	5 / 2	3 / 4	-	-
Age	55.57 ± 6.65	59.57 ± 11.77	15.0	0.222
HAD depression score	6.43 ± 3.69	11.14 ± 5.73	13.5	0.157
HAD anxiety score	11.00 ± 6.08	13.29 ± 5.50	18.0	0.405

Table 8. Clinical correlations in patients with improvement of subjective cognitive impairment versus those with unchanged subjective cognitive impairment

Subjective memory complaints

Correlation between the patients' and the informants' MFQ scores

All patients filled in the MFQ, but only ten informants returned it. Based on these ten patient-informant pairs, the correlation between the patients' self-assessment of memory and the informants' appraisal was calculated. These findings are illustrated in table 9. As the informants had not scored the questions related to memory while reading books or magazines, the total patient score was modified by subtracting the MFQ reading score from the total score.

The total scores given by patients and relatives were significantly correlated, but no significant correlations emerged for any of the sub-scores. However, the subjective scores reported by the patients were lower for the MFQ total score, MFQ frequency, MFQ past, MFQ seriousness and MFQ use-of-mnemotics scores than those given by the informants. Thus, there was a trend for the patients to report more severe difficulties than those reported by their relatives.

	MFQ patient (n=10)	MFQ relative (n=10)	Spearman rho	p-value
MFQ total score #	173.79 ± 57.06	203.50 ± 73.60	0.648	0.043*
MFQ frequency score	59.64 ± 19.43	67.1 ± 22.44	0.406	0.244
MFQ past score	15.14 ± 5.76	16.80 ± 6.49	0.566	0.088
MFQ change from past score	17.43 ± 8.61	14.50 ± 8.05	0.355	0.314
MFQ seriousness score	58.79 ± 20.14	70.20 ± 32.01	0.565	0.089
MFQ use of mnemotics score	22.79 ± 11.55	34.90 ± 14.33	0.492	0.148

Table 9. Correlation between the patients' and relatives' appraisal of memory impairment

* significant at < 0.05-level

: MFQ total score after subtracting the MFQ reading score

Correlation between subjective MFQ scores and clinical variables

Severity of anxiety.

The subjective memory complaints as measured by the total score on the MFQ scale as well as the different sub-scores did not correlate with the severity of anxiety as self-assessed on the HAD (Hamilton Anxiety and Depression scale). The Spearman correlation coefficients and the corresponding p-values are shown in table 10.

	Anxiety (HAD score) (n=14)		Depression (HAD score) (n=14)	
	Spearman rho	p-value	Spearman rho	p-value
MFQ total score	-0.159	0.588	-0.289	0.331
MFQ frequency score	-0.366	0.198	-0.332	0.246
MFQ reading score	-0.134	0.649	-0.099	0.737
MFQ past score	-0.144	0.698	-0.280	0.331
MFQ change from past score	-0.411	0.145	-0.618	0.018*
MFQ seriousness score	-0.150	0.609	-0.305	0.290
MFQ use of mnemotics score	-0.189	0.518	-0.018	0.952

Table 10. Correlation between the patients' appraisal of memory impairment and the severity of anxiety and depression scores
* significant at < 0.05-level

When patients were subdivided into "anxious" and "non-anxious" groups according to the HAD scores, the anxious patients had lower MFQ scores, but only the MFQ frequency score showed a statistically significant though weak

difference between the groups, indicating that anxious patients reported more frequent memory problems. These results are shown in Table 11.

	Anxiety (HAD score)			
	Anxious (n=10) (HAD 9 and >)	Not anxious (n=4) (HAD < 9)	MW-U	p-value
MFQ total score	188.40 ± 56.80	253.00 ± 90.33	12.0	0.258
MFQ frequency score	53.90 ± 15.55	74.00 ± 22.91	6.0	0.048*
MFQ reading score	28.20 ± 13.16	45.25 ± 24.30	13.0	0.322
MFQ past score	14.50 ± 5.95	16.75 ± 15.00	15.0	0.479
MFQ change from past score	15.10 ± 5.82	23.25 ± 12.50	12.5	0.286
MFQ seriousness score	55.50 ± 18.40	67.00 ± 24.82	16.0	0.571
MFQ use of mnemotics score	21.20 ± 10.92	26.75 ± 13.82	13.0	0.322

Table 11. Comparison on the MFQ of anxious versus non-anxious patients as defined by HAD anxiety scores.
* significant at < 0.05-level
MW-U = Mann-Whitney-U value

Severity of depression.

The subjective memory complaints as measured by the total score on the MFQ scale as well as the different sub-scores did not correlate with the severity of depression as self-assessed on the HAD (Hamilton Anxiety and Depression scale) with the exception of the MFQ change from the past score which showed a negative correlation. This correlation suggests that the more depressed patients perceived a greater memory change from the past and they may therefore be more likely to complain about their memory. These results are shown in table 10.

When patients were subdivided into "depressed" and "non-depressed" groups according to the HAD scores, the depressed patients had lower MFQ scores, but only the MFQ change from past score showed a statistically significant

difference between the two groups, indicating that depressed patients reported a more severe decline in memory over time. These results are shown in Table 12.

As in the more anxious patients, these results suggest that those who are more depressed also have more complaints.

	Depression (HAD score)			
	Depressed (n=8) (HAD 9 and >)	Euthymic (n=6) (HAD < 9)	MW-U	p-value
MFQ total score	178.00 ± 46.46	245.33 ± 83.40	14.0	0.197
MFQ frequency score	52.50 ± 13.41	69.17 ± 23.22	15.0	0.245
MFQ reading score	27.50 ± 12.64	40.50 ± 22.19	16.5	0.332
MFQ past score	13.25 ± 5.55	17.67 ± 5.47	12.5	0.137
MFQ change from past score	12.88 ± 4.91	23.50 ± 9.03	5.5	0.016*
MFQ seriousness score	50.50 ± 17.78	69.83 ± 18.87	12.0	0.121
MFQ use of mnemotics score	21.38 ± 6.52	24.67 ± 16.73	23.0	0.897

Table 12. Comparison on the MFQ of depressed versus euthymic patients as defined by HAD depression scores.
* significant at < 0.05-level
MW-U = Mann-Whitney-U value

Age.

Age was not correlated with the total score nor with any of the MFQ sub-scores. The Spearman correlation coefficients and the corresponding p-values are shown in table 13.

	Age (n=14)		Education (n=14)	
	Spearman rho	p-value	Spearman rho	p-value
MFQ total score	0.033	0.910	0.461	0.097
MFQ frequency score	-0.042	0.887	0.420	0.126
MFQ reading score	0.218	0.454	0.224	0.441
MFQ past score	0.198	0.496	0.341	0.232
MFQ change from past score	0.097	0.742	0.166	0.571
MFQ seriousness score	0.081	0.784	0.316	0.271
MFQ use of mnemotics score	-0.128	0.662	0.347	0.224

Table 13. Correlation between the patients' appraisal of memory impairment and age and level of education.

Level of education.

Level of education was not correlated with the total score nor with any of the sub-scores of the MFQ. The Spearman correlation coefficient and the corresponding p-values are shown in table 13.

Gender.

The MFQ scores of the eight female patients were compared to those of the six males. All the scores were lower in the female group, but only the perceived change from the past reached statistical significance. This indicates that women may be more likely than men to consider that their memory has suffered deterioration over time. These results are shown in table 14.

	Gender			
	Females (n=8)	Males (n=6)	MW-U	p-value
MFQ total score	233.13 ± 73.59	171.83 ± 54.14	11.0	0.093
MFQ frequency score	66.38 ± 20.27	50.67 ± 15.38	16.0	0.302
MFQ reading score	33.75 ± 18.85	32.17 ± 18.24	21.5	0.747
MFQ past score	17.38 ± 4.57	12.17 ± 6.21	11.5	0.106
MFQ change from past score	21.75 ± 9.13	11.67 ± 2.50	7.0	0.027*
MFQ seriousness score	66.13 ± 18.12	49.00 ± 19.85	14.5	0.220
MFQ use of mnemotics score	27.75 ± 12.78	16.17 ± 5.12	11.5	0.093

Table 14. Comparison of female and male patients as to their subjective memory complaints.

* significant at < 0.05-level

MW-U = Mann-Whitney-U value

Subjective memory improvement.

The seven patients who felt their memory had improved at follow up consistently had higher MFQ scores - which translates fewer memory complaints – than those who felt their memory had not improved. The MFQ total score, the MFQ frequency of forgetting sub-score and the MFQ past sub-score reached statistical significance. Thus, the subjects' global impression of cognitive change parallels the more detailed subjective MFQ evaluation of cognition. The results are shown in table 15.

	improved (n = 7)	unchanged (n = 7)	Mann-Whitney-U	p-value
MFQ total score	248.43 ± 68.00	165.29 ± 47.44	5.0	0.013*
MFQ frequency score	69.86 ± 19.54	49.43 ± 13.87	8.0	0.035*
MFQ reading score	42.00 ± 17.36	24.14 ± 14.35	10.0	0.064
MFQ past score	18.57 ± 3.16	11.71 ± 5.88	8.0	0.035*
MFQ change from past score	21.54 ± 10.18	13.29 ± 4.11	12.5	0.123
MFQ seriousness score	67.86 ± 19.51	49.71 ± 17.50	11.5	0.096
MFQ use of mnemotics score	28.57 ± 12.92	17.00 ± 6.33	9.5	0.055

Table 15. Comparison of patients with improved and those with unchanged subjective memory impairment on the MFQ.
* significant at < 0.05-level

Imaging findings

Volumetric measurements

Volumetric measurements of the patient and control groups are shown in table 16.

	Patients [mean ± sd]	**Controls** [mean ± sd]	MW-U	p-value
intracranial volume [in mm^3]	1325147 ± 113849	1414827 ± 176145	67.0	0.244
right hippocampal volume [in mm^3]	2597.9 ± 244	2699.5 ± 321.7	82.0	0.462
right hippocampal/intracranial volume ratio	0.001966 ± 0.000178	0.001915 ± 0.000262	72.0	0.357
left hippocampal volume [in mm^3]	2498.6 ± 294.8	2644.4 ± 409.9	78.0	0.358
left hippocampal/intracranial volume ratio	0.001888 ± 0.00019	0.00187 ± 0.000307	74.0	0.409
right amygdala [in mm^3]	1688.5 ± 289.1	1919.5 ± 258.5	53.0	0.039*
right amygdala/intracranial volume ratio	0.001272 ± 0.000163	0.001371 ± 0.000125	57.0	0.099
left amygdala volume [in mm^3]	1559.4 ± 254	1839.6 ± 233.3	37.0	0.005*
left amygdala/intracranial volume ratio	0.00118 ± 0.000186	0.001305 ± 0.000095	48.0	0.037*

Table 16. Intracranial, hippocampal and amygdala volumes in patients and controls

* significant at < 0.05-level

MW-U = Mann-Whitney-U value

Intracranial and hippocampal volumes were not significantly different between patients and controls.

The volumes of the right and left amygdala were significantly smaller in the patient group, and the difference was greater for the left amygdala. When intracranial volume was corrected for, only the left amygdala/intracranial ratio remained significantly different between the two groups. The volume of the left amygdala was considerably smaller in one patient (1030 mm^3) compared to the mean for the group (1560 mm^3). To exclude the effect of this outlayer on the final result, the analysis was repeated excluding this patient. After doing so, the volume of the left amygdala remained significantly smaller in the patient group, but the difference between the left amygdala/intracranial ratios was no longer significant between the two groups (left amygdala $p = 0.009$; left amygdala/intracranial ratio $p = 0.061$).

Clinical correlations with volumetric measurements

Age.

There was no significant correlation between the volumes of the hippocampus and the amygdala and the ratios between the different volumes and the intracranial volume and age in either group with the exception of a significant correlation between age and the right amygdala/intracranial volume ratio in the control group. These results are shown in table 17.

	Correlation with age			
	Patients (n=14)		Controls (n=14)	
	Spearman rho	p-value	Spearman rho	p value
intracranial volume	0.002	0.994	0.138	0.653
right hippocampal volume	-0.071	0.810	0.201	0.491
right hippocampal/intracranial volume ratio	-0.044	0.881	-0.182	0.551
left hippocampal volume	0.024	0.934	0.060	0.839
left hippocampal/intracranial volume ratio	0.024	0.934	0.099	0.747
right amygdala volume	0.114	0.698	-0.360	0.206
right amygdala/intracranial volume ratio	0.250	0.389	-0.575	0.040*
left amygdala volume	0.113	0.651	0.002	0.994
left amygdala/intracranial volume ratio	0.246	0.397	-0.061	0.884

Table 17. Spearman's correlation coefficient between age and the different volumes in the patients and the controls

* significant at < 0.05-level

Depressive caseness.

The volumes of the hippocampi and amygdalae and the hippocampus /intracranial volume and amygdala/intracranial volume ratios were compared between the six euthymic and the eight depressed patients at follow-up. There was a trend for the left and right hippocampi to intracranial volume ratio to be larger in patients who were euthymic at the time of the study, although this difference fell short of statistical significance. These results are shown in table 18.

	Euthymic (n = 6)	Depressed (n = 8)	Mann-Whitney U	p-value
right hippocampal volume [in mm^3]	2514 ± 214.38	2709.83 ± 253.22	11.0	0.093
right hippocampal/intracranial volume ratio	0.00206 ± 0.00097937	0.00189 ± 0.00019362	9.0	0.053
left hippocampal volume [in mm^3]	2401.25 ± 230.06	2628.33 ± 341.36	17.0	0.366
left hippocampal/intracranial volume ratio	0.002 ± 0.00019206	0.0018 ± 0.00014601	9.0	0.053
right amygdala volume [in mm^3]	1677.88 ± 306.89	1702.67 ± 291.53	21.0	0.698
right amygdala/intracranial volume ratio	0.00129 ± 0.00016122	0.00126 ± 0.00017264	21.0	0.699
left amygdala volume [in mm^3]	1500.75 ± 267.55	1637.5 ± 233.96	21.0	0.698
left amygdala/intracranial volume ratio	0.00124 ± 0.00010441	0.00113 ± 0.00022434	17.0	0.366

Table 18. Hippocampus and amygdala volumes and their ratios to intracranial volumes in euthymic and depressed patients at follow-up

Cognitive status.

There were no differences in intracranial or amygdalar volume between the five patients who had cognitive impairment initially as determined by intellectual decline and/or memory impairment and the rest of the group. In those with cognitive impairment at initial testing, the left hippocampal/intracranial ratio was smaller compared with the rest of the group, but the difference fell short of statistical significance. These results are shown in table 19.

	Cognitively impaired (n = 5)	Cognitively unimpaired (n = 8)	Mann-Whitney U	p-value
right hippocampal volume [in mm^3]	2437.60 ± 201.63	2692.75 ± 241.68	7.0	0.057
right hippocampal/intracranial volume ratio	0.00191 ± 0.00017901	0.002 ± 0.00019221	13.0	0.306
left hippocampal volume [in mm^3]	2253.60 ± 184.19	2650.38 ± 269.84	7.0	0.057
left hippocampal/intracranial volume ratio	0.00176 ± 0.000125	0.00196 ± 0.00019	7.0	0.057
right amygdala volume [in mm^3]	1651.20 ± 240.05	1727.25 ± 342.60	18.0	0.769
right amygdala/intracranial volume ratio	0.00129 ± 0.00018479	0.00127 ± 0.0001686	19.0	0.884
left amygdala volume [in mm^3]	1481.80 ± 268.98	1617.50 ± 263.60	14.5	0.420
left amygdala/intracranial volume ratio	0.00116 ± 0.00020446	0.0012 ± 0.00019852	17.0	0.661

Table 19. Hippocampus and amygdala volumes in cognitively impaired and unimpaired patients
[patient 2 = NA since no initial neuropsychological assessment]

Subjective cognitive improvement.

The volumetric measurements of the seven patients whose memory had subjectively improved were compared with those in whom memory difficulties had remained unchanged. There was no significant difference between the two groups. These results are shown in table 20.

	Better (n = 7)	Unchanged (n = 7)	Mann-Whitney-U	p-value
right hippocampal volume [in mm^3]	2580.86 ± 316.47	2615.00 ± 167.73	24.0	0.949
right hippocampal/intracranial volume ratio	0.00200 ± 0.00019889	0.00193 ± 0.00016161	17.0	0.338
left hippocampal volume [in mm^3]	2391.00 ± 313.93	2606.14 ± 250.54	11.0	0.085
left hippocampal/intracranial volume ratio	0.00185 ± 0.00016471	0.00192 ± 0.00021857	23.0	0.848
right amygdala volume [in mm^3]	1631.14 ± 279.19	1745.86 ± 308.92	19.5	0.522
right amygdala/intracranial volume ratio	0.00126 ± 0.00014627	0.00128 ± 0.00018865	21.0	0.655
left amygdala volume [in mm^3]	1552.29 ± 313.55	1566.43 ± 203.43	21.0	0.654
left amygdala/intracranial volume ratio	0.00120 ± 0.00020510	0.00116 ± 0.00017888	20.0	0.565

Table 20. Hippocampus and amygdala volumes in those with global subjective cognitive improvement versus those with unchanged global subjective cognitive impairment

Subjective memory complaints and volumetric measurements

The volume of the left hippocampus was significantly correlated with the total MFQ score and with the frequency of forgetting and use of mnemonics sub-scores. However, this correlation was negative meaning that low MFQ scores or severe subjective memory impairment correlated with larger hippocampal volumes. A positive correlation was present for the right hippocampus/intracranial volume ratio and memory change from the past sub-score. However, when the level of significance was set at 1%, to avoid chance correlations from multiple comparisons, only the negative correlation between the left hippocampal volume and the use of mnemonic strategies remained significant.

There was a trend for the volume of the left amygdala to correlate negatively with the use of mnemonic strategies, but this did not reach the 1% level of significance.
The results are shown in table 21.

	Right hippocampal volume		Ratio right hippocampal/ intracranial volume		Left hippocampal volume		Ratio left hippocampal/ Intracranial volume	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value
MFQ total score	-0.121	0.681	0.257	0.375	-0.569	0.034*	-0.090	0.759
MFQ frequency score	0.152	0.605	0.138	0.637	-0.609	0.021*	-0.253	0.383
MFQ reading score	0.077	0.794	0.444	0.111	-0.409	0.146	0.013	0.964
MFQ past score	-0.189	0.517	0.187	0.522	-0.493	0.073	0.044	0.881
MFQ change from past score	0.332	0.246	0.644	0.013*	-0.071	0.810	0.398	0.158
MFQ seriousness score	-0.185	0.527	0.145	0.620	-0.392	0.166	0.002	0.994
MFQ use of mnemotics score	-0.240	0.409	0.068	0.817	-0.766	0.001**	-0.491	0.075

Table 21a. Correlation between the patients' appraisal of memory impairment and volumetric measures of the hippocampi. *significant at <0.05 level, **significant at <0.001 level. Rho = Spearman rho

	Right amydgala volume		Ratio right amygdala/ intracranial volume		Left amygdala volume		Ratio left amygdala/ intracranial volume	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value
MFQ total score	-0.015	0.958	0.143	0.626	-0.229	0.431	0.147	0.615
MFQ frequency score	0.022	0.940	0.051	0.864	-0.387	0.171	-0.095	0.748
MFQ reading score	0.254	0.380	0.493	0.073	0.127	0.666	0.504	0.066
MFQ past score	-0.117	0.691	0.081	0.782	-0.181	0.536	0.273	0.345
MFQ change from past score	-0.044	0.880	0.088	0.764	-0.140	0.634	0.102	0.729
MFQ seriousness score	-0.033	0.911	0.073	0.805	-0.188	0.519	0.207	0.478
MFQ use of mnemotics score	-0.183	0.532	-0.062	0.834	-0.525	0.054	-0.332	0.246

Table 21b. Correlation between the patients' appraisal of memory impairment and volumetric measures of the amygdalae.

White matter hyperintensities (WMHIs)

The MRI scans of the patient group were inspected by a neuroradiologist blind to the clinical features of the patients. Single white matter hyperintensities were observed in all but three patients who had multiple WMHIs. Of the three patients with more pronounced white matter abnormalities only one showed cognitive impairment when first tested.

Chapter 9

DISCUSSION

Main findings of the study

The study examined subjective memory difficulties in a group of 14 subjects who fulfilled diagnostic criteria for depressive disorder and who were not demented. The subjects had neuropsychological testing when first seen. When this study was performed, a mean of three and a half years after first attendance, neuropsychological testing was repeated and MRI performed. The change of subjective and objective cognitive performance was examined and the correlations with mood changes and structural brain abnormalities examined.

The main findings of the study are :

1) Neuropsychological performance at follow-up had returned to normal in 13 out of 14 patients and improved in the remaining one.
2) Subjective memory problems were still present in all, but seven patients felt their memory had improved. None of the 14 patients felt that their memory had deteriorated further.
3) At follow-up, the volume of the left amygdala, the left amygdala/intracranial volume ratio and the right amygdala were significantly smaller in the patient group when compared to the control group.
4) At follow-up, the volume of the left hippocampus tended to be smaller in those who showed cognitive impairment (intellectual decline and/or memory impairment) when initially tested.

5) At follow-up, there was a trend for the right and left amygdala/intracranial volume ratios to be smaller in those who had remained depressed.
6) WMHIs were not prominent or related to cognitive impairment in this group of patients.
7) Subjective memory problems as rated by the MFQ tended to be more severe in those with higher depressive HAD scores and in women. The patients' appraisal of their own memory was poorly related to that of their relatives and patients tended to report more severe difficulties than their relatives.
8) The severity of subjective memory problems (low MFQ scores) was greater in those with large hippocampi.

Main shortcomings of the study

There are several limitations to this study. The small sample size is a major limitation, but gathering a large number of patients with persistent memory complaints meeting the exclusion criteria (i.e. no evidence of dementia) proved difficult. The shortcoming of the small sample size is, however, partly compensated by the detailed and reliable nature of the image analysis.

The significance levels of the different comparisons were not corrected for multiple comparisons. However, this study is a pilot study in character and therefore I decided not to correct the findings for multiple comparison accepting that all significant results would need to be replicated in a larger study.

The lack of a control group of depressed patients without subjective memory difficulties is also a limitation, as some of the structural brain abnormalities could be attributed to depression rather than to cognitive changes, but the time constraints made it very difficult to find a suitable group.

Cognitive changes

The pattern of cognitive impairment

Cognitive abnormalities across a range of skills have been reported in depression (Brown et al. 1994), although memory and executive skills are more severely affected. This study focused on general intelligence and memory as the main aim of the study was to examine subjective memory problems. In addition, a test of language (Graded Naming) was used as for some patients inability to find words was part of their subjective complaints. In the event, all patients performed within normal limits on this task. The selection of tests routinely used at the NHNN was also dictated by the wish to compare the performance of patients when first seen at the hospital with their performance three and a half years later.

The mild cognitive deficits present in some of the patients are in keeping with those described by others (Brown et al. 1994) :
The depressed patients showed no naming difficulties as assessed by the Graded Naming Test suggesting that language problems are absent or play no part in the subjective memory difficulties.
Memory difficulties are well documented in depression. There is, however, some discrepancy as to whether or not the memory impairment in depression is due to executive dysfunction and / or to encoding difficulties linked to medial temporal lobe dysfunction. Although spontaneous recall was not examined in this study, the recognition deficit highlighted by the neuropsychological investigation points to an encoding problem which is in keeping with other studies (Austin et al. 1992a, Burt et al. 1995, Golinkoff & Sweeney 1989).

The hippocampus is thought to play a major role in encoding new information (Joseph 1996, Walsh 2002). The neuropsychological findings of this study and the trend toward a reduction in left hippocampal volume is in keeping

with the possibility that hippocampal function may be abnormal in these patients.

This study focused on subjective and objective memory difficulties and structural medial temporal lobe abnormalities. Therefore, the possibility that executive functions and prefrontal brain regions may also have been abnormal cannot be excluded.

Cognitive impairment and severity of depression

Cognitive deficits have been reported to improve with the resolution of depression (Plotkin et al. 1985), but others have reported persistent memory and frontal / executive type deficits in euthymic unipolar patients as compared with healthy controls (Marcos et al. 1994, Paradiso et al. 1997). In this study severity or persistence of depression do not appear to be strongly related to the presence of cognitive impairment. At the time of the study, cognitive performance had returned to normal in all but one patient, even if eight out of 14 patients still remained depressed.

The presence of objective, even if transient, cognitive impairment might indicate poor recovery from depression. In this study, four out of five patients who were cognitively impaired initially remained depressed at follow-up whereas this was the case for only three out of eight patients who were cognitively unimpaired initially. Although these data show a trend that cognitive impairment actually may indicate poor recovery form depression, the result was not statistically significant.

The patients who were cognitively impaired initially had similar HAD scores to the rest of the group at the time of the study. Likewise, the four patients who were both cognitively impaired initially and who were depressed at follow-up (HAD score 9 or more) had no higher scores on the HAD global score and its sub-scores than the rest. Thus, there was no evidence that cognitive impairment predicts poor recovery from depression. However, this

result must be interpreted with great caution due to the very small number of patients.

The small number of patients in the study and the careful exclusion of dementia make it difficult to compare it with other studies. A further difficulty is the fact that the severity of depression was not sytematically rated when the patients were first seen three and a half years before the study. However, the findings of the study suggest that cognitive functioning can improve despite the persistence of depressed mood.

Subjective memory impairment

Subjective memory impairment and cognitive performance

All patients in this study had subjective memory difficulties, but only a third showed mild objective intellectual or memory under-functioning when first examined three and a half years earlier and only one showed mild cognitive impairment at the time of the study. This discrepancy between subjective and objective impairment is in agreement with the findings of Bassett and Folstein (1993), who found psychiatric morbidity to be an independent predictor of subjective memory impairment. This is also in keeping with the fact that only half of our patients reported memory improvement despite the normalisation of objective cognitive performance.

Subjective memory impairment and psychopathology

The findings of this study confirm that anxiety and depression may contribute to subjective memory complaints as suggested by several reports in the literature. Basset and Folstein (1993) determined the frequency of memory complaints in 373 individuals with a variety of psychiatric diagnoses. Memory complaints decreased in frequency according to the diagnostic group. About 60% of schizophrenics and 50% of patients with cognitive

disorders complained about their memory. They were followed by those with affective disorders (34%) and those with adjustment and anxiety disorders (both 28%). A number of other studies have also reported an association between subjective memory complaints and depression and/or anxiety (Corcoran & Thompson 1993, Hanninen et al. 1994, Smith et al. 1996).

However, other factors are also likely to contribute to subjective memory impairment as those no longer depressed and/or anxious and who performed within the normal range on cognitive testing continue to complain of memory difficulties. In the absence of dementia, the reasons for their persistent complaints are unclear. A possible explanation could be that these complaints are related to personality traits as suggested by Hanninen et al. (1994) who found subjective memory problems to be more commonly expressed by those prone to experience somatic symptoms and negative feelings about themselves.

Furthermore, some people may constantly monitor their memory performance and be alarmed at the slightest perceived failure. Thus, McPherson et al. (1995) found that relatives of early-onset AD patients within the range of at risk age monitored their memory performance more diligently than relatives of patients whose illness began at a later age or those with no AD relatives. An enhanced capacity for detecting small but "real" memory changes and an increased vigilance in monitoring memory may account for these findings.

Subjective memory evaluation by patients and relatives

The absence of correlation between the patients' and relatives' memory evaluation is in keeping with the discrepancy found between the patient's subjective memory appraisal and their objective cognitive performance. However, the absence of any significant correlation could be attributable to a sample size effect that may have masked a correlation between the observations of the patients and their relatives. Another explanation is also possible : in the absence of objective cognitive impairment, subjective memory deficits appear more clearly related to the presence of depressive

symptoms as evidenced by the significant correlation between the increased use of mnemonic strategies and the HAD depression score or between the frequency of forgetting score and the HAD anxiety score. Thus, depressed patients may overreport the extent of their memory problems which, on the other hand, are not noticed or appear much milder to their relatives.

Subjective memory impairment and dementia

Patients were only included in the study if they failed to fulfil diagnostic criteria for dementia. Within this small and carefully selected group, the results of the study support the idea that subjective memory complaints are poor predictors of progressive cognitive decline as has been suggested by others (Bassett & Folstein 1993, Tobiansky et al. 1995).

MRI abnormalities

The MRI measurements used in this study were designed to be unbiased. The high resolution volumetric acquisition allowed to determine structural boundaries accurately, and the high intra-rater reproducibility of the measurements adds confidence to the findings.

Although the image analysis techniques used in this study have a high intra-rater reliability comparable with other methodologically similar and carefully carried out studies (Tebartz van Elst et al. 2002), they only measure loss of volume, and subtle but functionally relevant neuropathological abnormalities may go undetected. In this study, white / grey matter segmentation was not used to allow more specific localization of volumetric changes. This procedure has now been used by others (Shah et al. 1998). In this recent paper, specifically cortical grey matter reductions in the left temporal cortex including the anterior hippocampus were found in patients with treatment-resistant and chronic unipolar depression.

As a group the patients in this study showed reduction in amygdalar volume, especially on the left. Statistical significance of this finding decreased when the absolute volumes were corrected for by the total intracranial volume although left-sided volumes remained significantly smaller in the patient group. Therefore, the findings of this study are in keeping with those of Shah et al. (1998).

MRI measurements and cognitive impairment

Amygdala.

There were no differences in the volumes of the amygdala between those with and without cognitive impairment at initial assessment. Thus, the reduction in amygdalar volume appears to be more closely related to depression than to cognitive impairment, although it may be relevant to both.

Hippocampus.

There was a trend for the left and right hippocampi to be smaller in the depressed patients with cognitive impairment than in those without cognitive impairment at the initial assessment. This difference fell, however, short of statistical significance. This trend corroborates the finding that some patients had memory difficulties suggesting encoding problems as described above.

The capacity of encoding information is usually linked to the hippocampus (Milner 1972, Scoville & Milner 1957). A correlation between poor performance on tests of memory recall and loss of hippocampal volume has recently been described in a large population study of euthymic, non-demented subjects (Golomb et al. 1993) and in one of Sheline et al.'s (1999) quantitative studies. A correlation between decline in verbal and visual memory and loss of hippocampal volume in those at risk for Alzheimer's disease has also been reported by Fox et al. (1996).

The trend for depressed patients with cognitive impairment to have smaller hippocampi is also in keeping with other studies that have demonstrated hippocampal atrophy to be possibly linked to glucocorticosteroid

hyperproduction. Animal studies (Sapolsky 2000) suggest a variety of adverse effects of glucocorticosteroids on hippocampal morphology including atrophy of dendritic processes, inhibition of adult neurogenesis and direct neurotoxic effects. In contrast to Cushing's syndrome, hippocampal atrophy may not be reversible in depression. The mechanisms of brain atrophy operating in Cushing's syndrome (reduction of water content as a result of decreased permeability of the blood brain barrier and suppression of dendritic growth) are unlikely to operate in depression. Loss of glia and/or neurones may, however, be relevant. Whether glucocorticosteroids actually are excitotoxic in depression remains to be determined. Atrophy seems to be demonstrable in many individuals with depression in whom hypercortisolaemia has not been documented although the possibility remains that hypercortisolaemia may have occurred at earlier stages of the illness.

MRI measurements and their link with depression

Amygdala.

There is considerable evidence from animal and human studies (Abrahams et al. 1997, Adolphs et al. 1994, Cahill et al. 1996, Le Doux 1996, Morris et al. 1998) that the amygdala plays a central role in the processing of emotional stimuli and modulation of emotional responses. Sheline et al. (1998) have reported a focal loss of volume in the core nuclei of the amygdala in depressed patients and suggest that exposure to high levels of excitotoxic glucocorticosteroids may lead to these changes, which in turn may influence memory, attention and perception through the connections of the amygdala with the hippocampus and orbito-medial cortex (Sheline et al. 1998, Sheline et al. 1999).

In this study, the differences in the volume of the amygdala, especially on the left, between patients and controls is more likely to be related to the history of depression than to the presence of cognitive impairment. The fact that no differences were detected in amygdalar volume between those considered to

be cognitively impaired at initial examination and the rest of the group favours this explanation.

Hippocampus.

Hippocampal volumes in the depressed patients and in the controls did not differ in this study. This is in agreement with the findings of Vakili et al.'s (2000) study, but not with other studies (Sheline et al. 1999, Steffens et al. 2000). However, different studies are difficult to compare because of differences in methodology and the small sample size of this study only allows tentative conclusions.

In this study, there was a trend for the left and right hippocampi / intracranial ratios to be larger in patients who were euthymic than in those who were depressed at the time of the study, but this finding fell short of statistical significance. However, it is possible that a larger sample may have yielded stronger associations between hippocampal volume loss and depressive state and, thus, it could explain some of the discrepancies found between different studies. If the association between decreased hippocampal volume and depression is confirmed, this finding is open to different interpretations. The fact that in this study hippocampal volume tended to be smaller in those who had remained depressed suggests that hippocampal abnormalities are likely to influence the outcome of depression. An alternative explanation would be that hippocampal atrophy is state related and that recovery from depression may be accompanied by reversibility of atrophy as is the case in other conditions ((e.g. anorexia nervosa (Swayze et al. 1996), Cushings's syndrome (Sapolsky 2000)). However, longitudinal studies to determine whether this is so have not been carried out. The possibility also remains that, even if atrophy could be reversible, this may only be the case early in the illness, but not after a long chronic course.

The trend for smaller hippocampal volumes in patients who were still depressed at the time of the study suggests that structural brain abnormalities may be associated with chronicity. Shah et al.'s (1998) study adds support to

this view since they have found that loss of cortical grey matter in medial temporal structures was associated with chronicity in patients with treatment-resistent unipolar depression.

MRI measurements and their link with subjective cognitive impairment

Amygdala.

Structural changes in the amygdala may alter the subject's perception of memory function. Whether depression is the mediating mechanism is unclear. In this study, there was a trend for greater severitiy of subjective memory impairment (MFQ use of mnemotics score) to be associated with larger amygdala volume. This counterintuitive trend is difficult to explain. It may be a chance correlation in a very small sample. On the other hand, the change in amygdalar volume may not be related to subjective memory impairment, but to depression. Although this contradicts the possible link between the severity of depression and subjective memory loss, this finding challenges the generally accepted view that structural brain abnormalities associated with depression may be similar to those associated with memory complaints.

Hippocampus.

There were negative correlations between the use of mnemonics, the frequency of memory lapses, the total score of the Memory Functioning Questionnaire and the size of the left hippocampus. In other words, those with a larger left hippocampus had more pronounced subjective memory difficulties. This additional counterintuitive finding is also difficult to explain. The fact that all correlations were negative makes a chance correlation less likely though it cannot be totally excluded. A possible explanation is that hippocampal changes may not be related to subjective memory impairment, but to objective memory deficits. This is supported by the fact that in patients with initial cognitive impairment the left hippocampal / intracranial ratio was smaller compared with the rest of the group.

White matter hyperintensities

White matter hyperintensities were also present in the depressed patients of this study, as reported by others (Videbech 1997). In this study, the abnormalities were mild and usually single and were not associated with the presence of cognitive impairment or poor outcome as reported by others (O'Brien et al. 1998). Moreover, most of the patients did not have late-onset depression which is more regularly associated with the presence of WMHIs (Alexopoulos et al. 1997, Krishnan & McDonald 1995).

Appendices

Appendix 1

Did this follow any previously recognized algorithm.

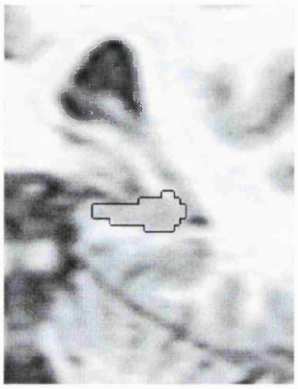
Hippocampal algorithm

The hippocampal formation included the dentate gyrus, the hippocampus proper, the subiculum and the alveus. After determining the most caudal slice, the region was manually outlined in the sagittal view and then edited and checked in the coronal view. The superior and anterior borders were delineated by the outer limits of the alveus and the fimbria. The anterior disarticulation of the hippocampus from the amygdala was performed on the sagittal view. The inferior border was formed by the white matter of the subiculum. The wall of the lateral ventricle was taken as the lateral boundary and the medial border corresponded to adjacent cistern. The posterior limit was arbitrarily defined as the coronal slice where the fornix was seen in its longest unbroken extent. Each region involved approximately 20 sagittal or 25 coronal slices in each hemisphere. After a 2-3-week interval, the selected hippocampal regions were rechecked for accuracy and minor adjustments made if necessary, in a blinded and randomised manner.

The 3-step algorithm is illustrated as follows :

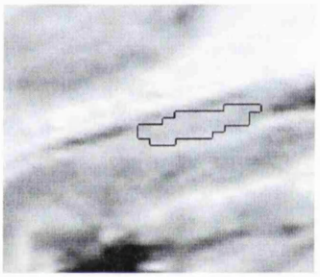
1. Determination of the most caudal slice which corresponds to the one where the fornix is visible at its longest extension.

1st caudal slice :

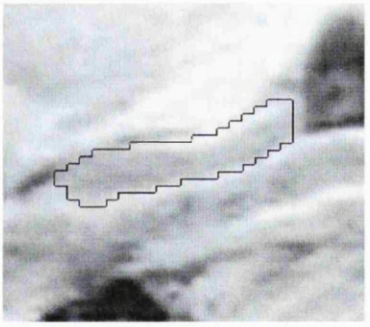


2. The hippocampus is outlined in sagittal view starting from its lateral aspect with progression towards the medial aspect as illustrated by the pictures below. The plexus choroideus and the fimbria hippocampi are excluded whereas the alveus is included.

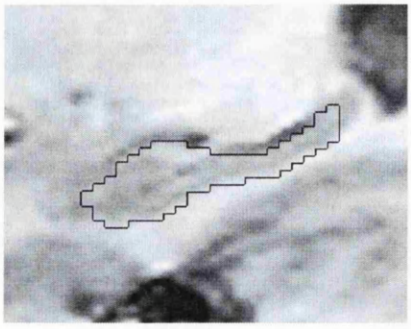
1st most lateral sagittal slice where the hippocampus is first seen as it bulges from the lower ventricular border :



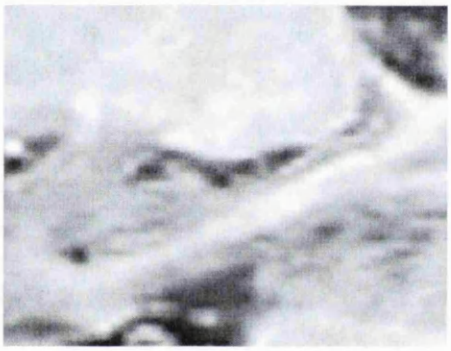
5th sagittal slice :

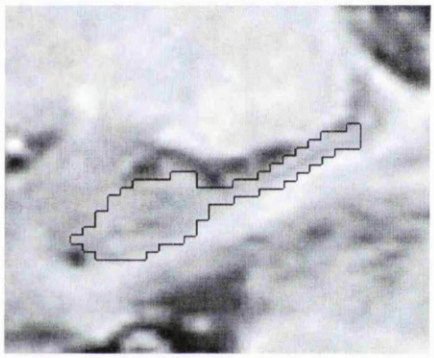


9th sagittal slice :



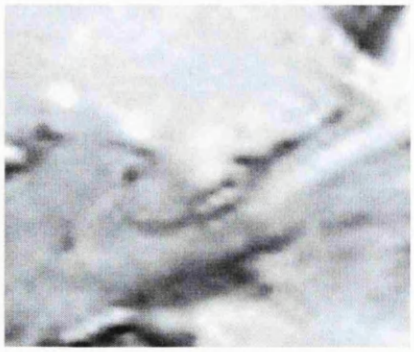
13th sagittal slice :

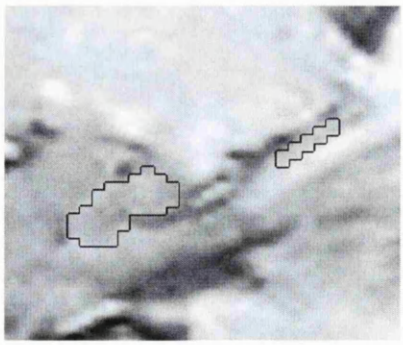




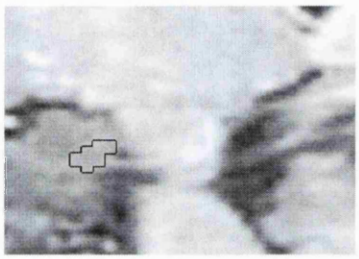
On the following pictures, the caput and cauda hippocampi are apparently separated as a consequence of the reniform shape of the hippocampus :

16th sagittal slice :



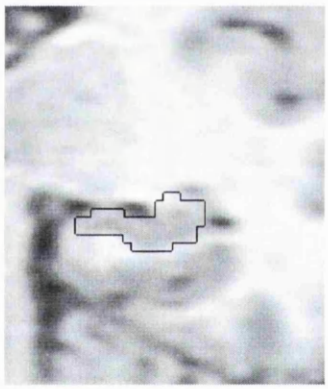


20th and last but one medial slice where the cauda is not distinguishable any more :

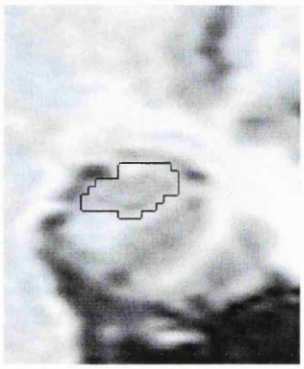


3. On every slice, the border points on sagittal view are compared with the corresponding ones on coronal view to optimize the outlining procedure. Some slices of the coronal sequence are shown below.

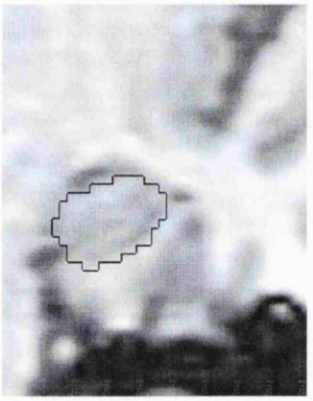
5th coronal slice :



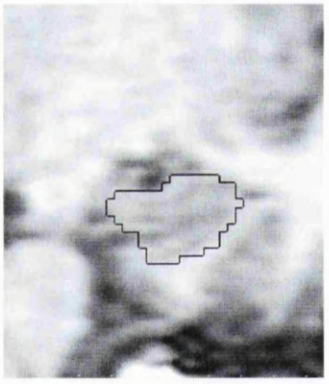
11th coronal slice :



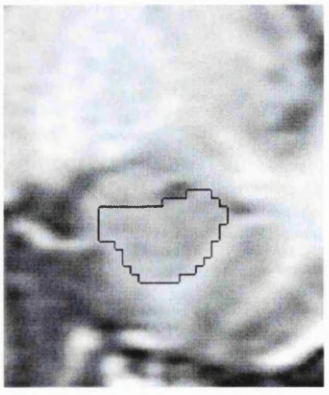
15th coronal slice :



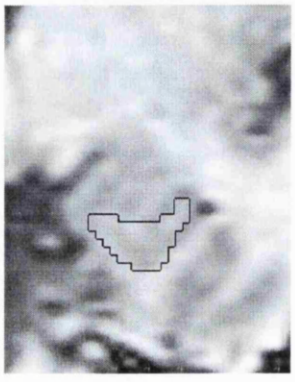
17th coronal slice illustrating that coroid plexus is excluded :



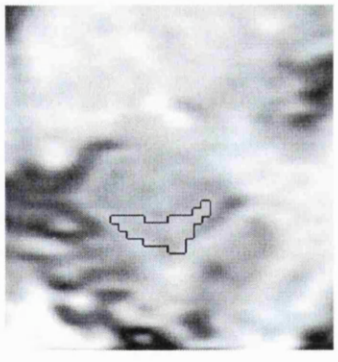
19th coronal slice :



21st coronal slice :



22nd and last but one coronal slice on which the hippocampus has a Aladin's lamp shape which, on the last slice, turns into an approximately 5-voxel bull's eye :



Appendix 2

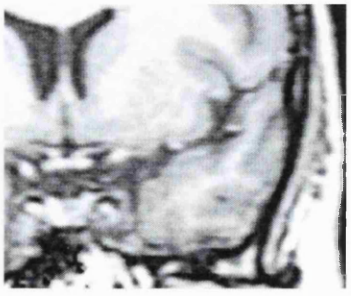
Amygdalar algorithm

The amygdala was measured using a similar procedure. Approximately 20 sagittal and 15 coronal slices were processed. The superior limit corresponded to a line connecting the most inferior point of the lateral fissure with the most lateral part of the paramedian cisternae and, more posteriorly, the superior and lateral border of the optic tract. The inferior, medial and lateral borders were determined by the boundary between amygdala and adjacent white matter. The most rostral coronal slice was taken as the one where the temporal and frontal lobes were no longer separate. The posterior boundary was formed by the disarticulation with the hippocampus as described above.

The 3-step algorithm is illustrated as follows :

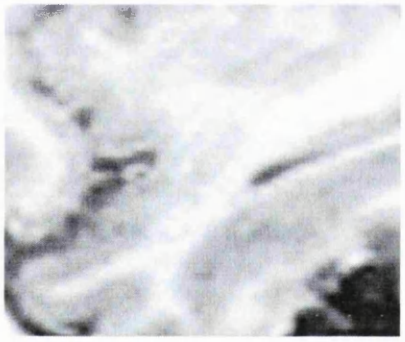
1. Determination of the rostral that corresponds to the one when frontal and temporal lobe start touching one another. This is usually one slice before white fibre tracts [fasciculus uncinatus] start crossing from one lobe to the other.

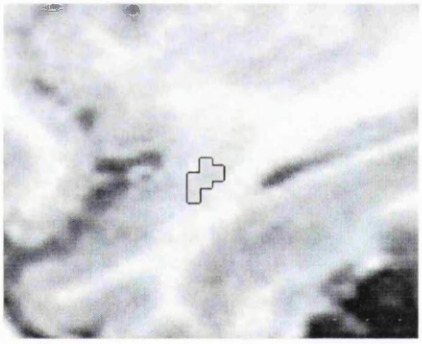
1st rostral slice :



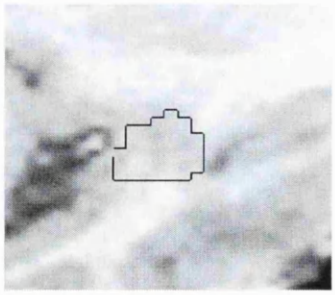
2. The amygdala is then outlined in sagittal view starting from its most lateral part with constant cross-reference to the coronal view for better delineation.

The most lateral slice in sagittal view :

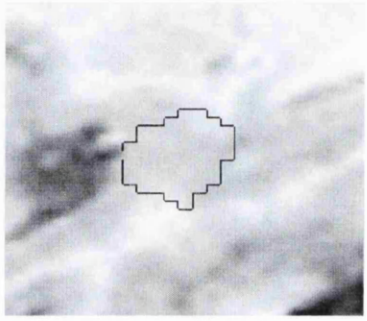




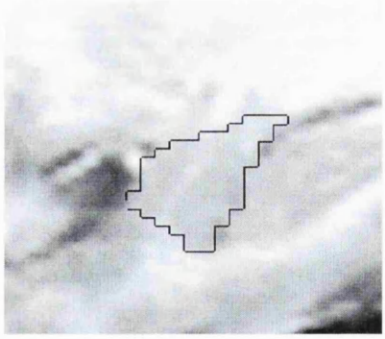
The 3rd sagittal slice :



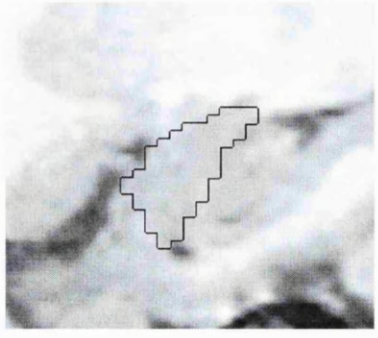
The 5th sagittal slice : This is where the *inferior border* of the amygdala will be determined by white matter running slightly upwards from the most antero-inferior extension of the lateral ventricle in the rostral direction, then upreaching towards the uncal notch where it merges with grey matter pertaining inferiorly to the gyrus ambiens and superiorly to the nucleus corticalis amygdalae. The *posterior border* becomes more clearly delimited by the lateral ventricle and the fimbria/alveus hippocampi which must be excluded :



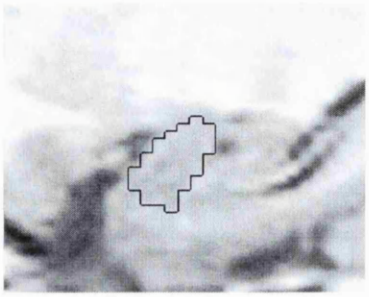
8th sagittal slice :



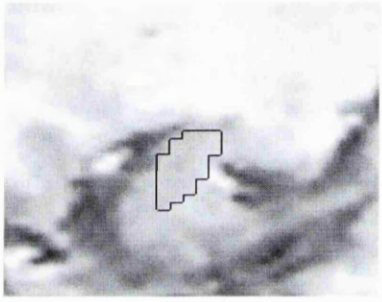
12th sagittal slice :



16th sagittal slice : The claustrum and the nucleus caudatus partially melt with the uppermost posterior parts of the amydgala and should be excluded.

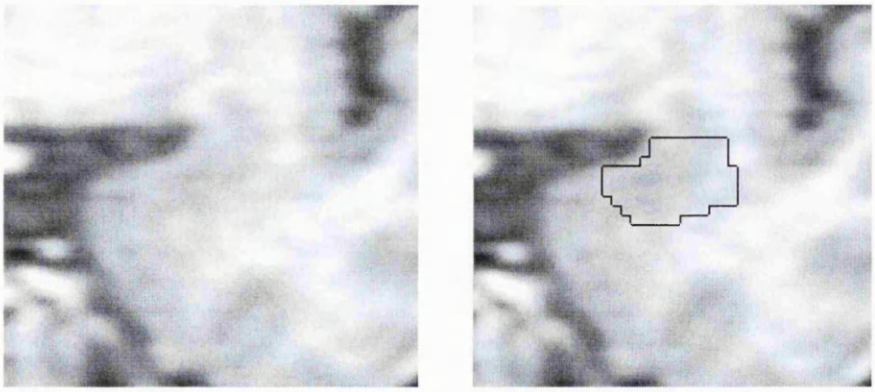


19th and usually last but one sagittal slice :

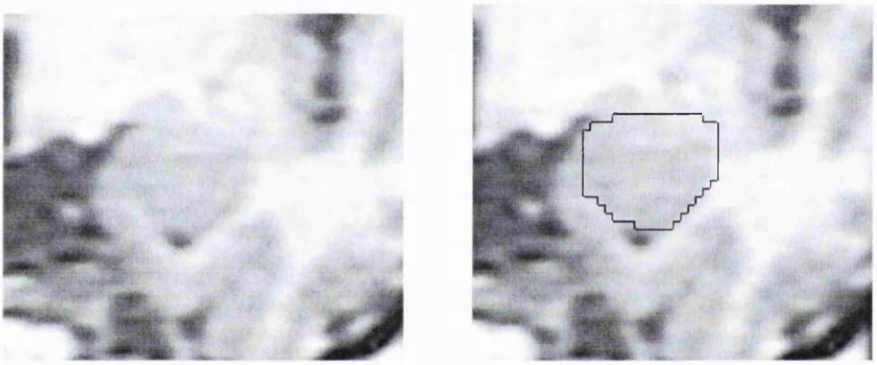


3. Outlining the amygdala in coronal view starting at the most rostral part permanently crosscheck with the sagittal view. The *upper border* corresponds to a line that is artificially determined by a straight line going from the most inferior point of the fissura lateralis to the most lateral part of the median extraventricular liquor system. The medial border is determined by continuing the line from the inferior border consisting of white matter to the uncal notch which allows to exclude the gyrus ambiens and parahippocampalis.

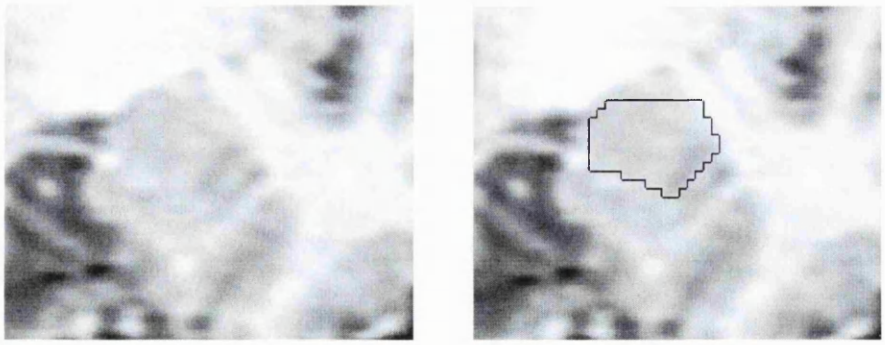
3rd coronal slice :



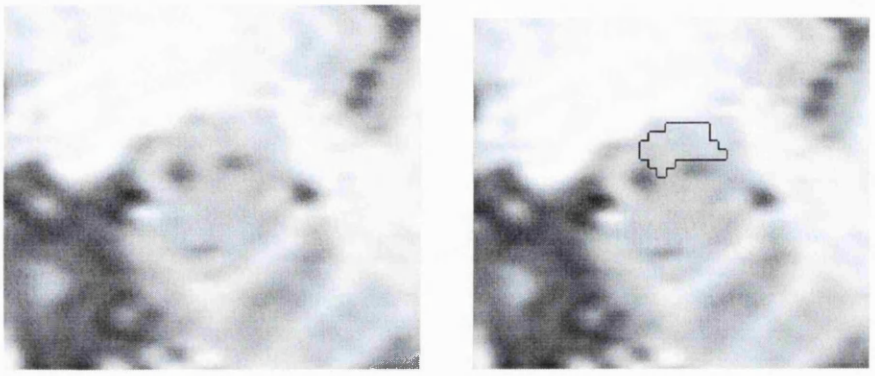
The 6th coronal slice : the lower border is first delineated by a V- or U-shaped white matter band and by the alveus on the following slices :



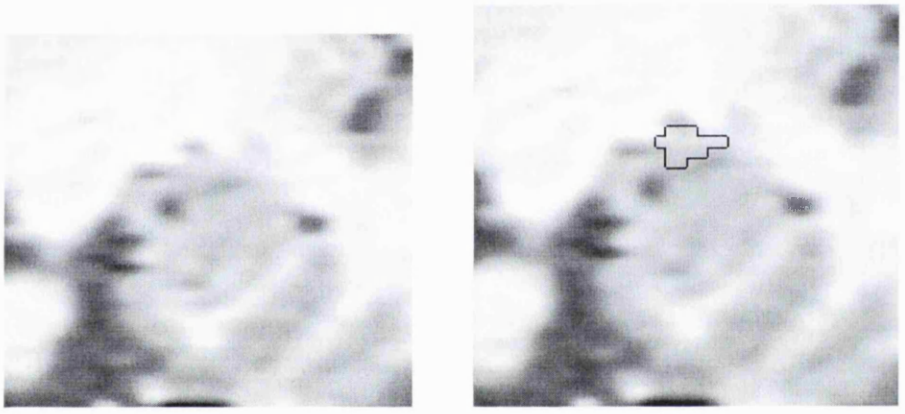
The 8th coronal slice : The line from the upper outer border of the optic tract to the lowest point of the insular subarachnoid space determines the upper border as soon as the optic tract becomes visible.



The 10th coronal slice : The nucleus caudatus fuses with the amygdala in the supero-lateral part and must be excluded.



The 11th and last but one coronal slice :



Appendix 3

The Memory Functioning Questionnaire

(Gilewski M.J. et al. 1990)

General instruction :

How would you rate your memory in terms of the kinds of problems that you have ?

major problems some minor problems no problems

1 2 3 4 5 6 7

How often do these present a problem for you ?

	always			*sometimes*			*never*
names	*1*	*2*	*3*	*4*	*5*	*6*	*7*
faces	*1*	*2*	*3*	*4*	*5*	*6*	*7*
appointments	*1*	*2*	*3*	*4*	*5*	*6*	*7*
where you put things (e.g. keys)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
performing household chores	*1*	*2*	*3*	*4*	*5*	*6*	*7*
directions to places	*1*	*2*	*3*	*4*	*5*	*6*	*7*
phone numbers you've just checked	*1*	*2*	*3*	*4*	*5*	*6*	*7*
phone numbers you use frequently	*1*	*2*	*3*	*4*	*5*	*6*	*7*
things people tell you	*1*	*2*	*3*	*4*	*5*	*6*	*7*
keeping up correspondence	*1*	*2*	*3*	*4*	*5*	*6*	*7*
personal dates (e.g. birthdys)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
words	*1*	*2*	*3*	*4*	*5*	*6*	*7*
going to the store and forgetting what you wanted to buy	*1*	*2*	*3*	*4*	*5*	*6*	*7*
taking a test	*1*	*2*	*3*	*4*	*5*	*6*	*7*
beginning to do something and forgetting what you were doing	*1*	*2*	*3*	*4*	*5*	*6*	*7*
losing the thread of thought in conversation	*1*	*2*	*3*	*4*	*5*	*6*	*7*
losing the thread of thought in public speaking	*1*	*2*	*3*	*4*	*5*	*6*	*7*
knowing whether you've already told someone something	*1*	*2*	*3*	*4*	*5*	*6*	*7*

As you are reading a novel, how often do you have trouble remembering what you have read ....

	always			*sometimes*			*never*
in the opening chapters, once you have finished the book	*1*	*2*	*3*	*4*	*5*	*6*	*7*
three or four chapters before the one your are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the chapter before the one your are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the paragraph just before the one you are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the sentence before the one you are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*

When you are reading a newspaper or magazine article, how often do you have trouble remembering what you have read...

	always			*sometimes*			*never*
in the opening chapters, once you have finished the book	*1*	*2*	*3*	*4*	*5*	*6*	*7*
three or four chapters before the one your are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the chapter before the one your are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the paragraph just before the one you are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*
the sentence before the one you are currently reading	*1*	*2*	*3*	*4*	*5*	*6*	*7*

How well you remember things that occurred ...

	very bad			*fair*			*very good*
last month is	*1*	*2*	*3*	*4*	*5*	*6*	*7*
between 6 months and 1 year ago is	*1*	*2*	*3*	*4*	*5*	*6*	*7*
between 1 and 5 years ago is	*1*	*2*	*3*	*4*	*5*	*6*	*7*
between 6 and 10 years ago is	*1*	*2*	*3*	*4*	*5*	*6*	*7*

When you actually forget in these situations, how serious of a problem do you consider the memory failure to be ?

	very serious					*somewhat serious*	*not serious*
names	*1*	*2*	*3*	*4*	*5*	*6*	*7*
faces	*1*	*2*	*3*	*4*	*5*	*6*	*7*
appointments	*1*	*2*	*3*	*4*	*5*	*6*	*7*
where you put things (e.g. keys)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
performing household chores	*1*	*2*	*3*	*4*	*5*	*6*	*7*
directions to places	*1*	*2*	*3*	*4*	*5*	*6*	*7*
phone numbers you've just checked	*1*	*2*	*3*	*4*	*5*	*6*	*7*
phone numbers you use frequently	*1*	*2*	*3*	*4*	*5*	*6*	*7*
things people tell you	*1*	*2*	*3*	*4*	*5*	*6*	*7*
keeping up correspondence	*1*	*2*	*3*	*4*	*5*	*6*	*7*
personal dates (e.g. birthdays)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
words	*1*	*2*	*3*	*4*	*5*	*6*	*7*
going to the store and forgetting what you wanted to buy	*1*	*2*	*3*	*4*	*5*	*6*	*7*
taking a test	*1*	*2*	*3*	*4*	*5*	*6*	*7*
beginning to do something and forgetting what you were doing	*1*	*2*	*3*	*4*	*5*	*6*	*7*
losing the thread of thought in conversation	*1*	*2*	*3*	*4*	*5*	*6*	*7*
losing the thread of thought in public speaking	*1*	*2*	*3*	*4*	*5*	*6*	*7*
knowing whether you've already told someone something	*1*	*2*	*3*	*4*	*5*	*6*	*7*

How is your memory compared to the way it was ....

	much worse						*much better*
1 year ago ?	*1*	*2*	*3*	*4*	*5*	*6*	*7*
5 years ago ?	*1*	*2*	*3*	*4*	*5*	*6*	*7*
10 years ago ?	*1*	*2*	*3*	*4*	*5*	*6*	*7*
20 years ago ?	*1*	*2*	*3*	*4*	*5*	*6*	*7*
when you were 18 ?	*1*	*2*	*3*	*4*	*5*	*6*	*7*

How often do you use these techniques to remind yourself about things ?

	always			*sometimes*			*never*
keep an appointment book	*1*	*2*	*3*	*4*	*5*	*6*	*7*
write yourself reminder notes	*1*	*2*	*3*	*4*	*5*	*6*	*7*
make lists of things to do	*1*	*2*	*3*	*4*	*5*	*6*	*7*
make grocery lists	*1*	*2*	*3*	*4*	*5*	*6*	*7*
plan your daily schedule in advance	*1*	*2*	*3*	*4*	*5*	*6*	*7*
mental repetition	*1*	*2*	*3*	*4*	*5*	*6*	*7*
associations with other things	*1*	*2*	*3*	*4*	*5*	*6*	*7*
keep things you need to do in a prominent place where you will notice them	*1*	*2*	*3*	*4*	*5*	*6*	*7*

References

Abas M.A., Sahakian B.J., Levy R. 1990. Neuropsychological deficits and CT scan changes in elderly depressives. *Psychol Med* 20:507-520

Abrahams S., Pickering A., Polkey C.E., Morris A.G. 1997. Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. *Neuropsychologia* 35:11-24

Adler G., Bramesfeld A., Jajcevic A. 1999. Leichte kognitive Beeinträchtigung bei älteren depressiven Patienten. *Zeitschrift für Gerontopsychologie und - psychiatrie* 12(2):97-105

Adolphs R., Tranel D., Damasio H., Damasio A. 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* 372:669-672

Alexander G.E., Furey M.E., Grady C.L., Pietrini P., Brady D.R., Mentis M.J., Schapiro M.B. 1997. Association of premorbid intellectual function with cerebral metabolism in Alzheimer`s disease : implications for the cognitive reserve hypothesis. *Am J Psychiatry* 154(2):165-172

Alexopoulos G.S., Meyers B.S., Young R.C., Campbell S., Silbersweig D., Charlson M. 1997. The 'vascular depression' hypothesis. *Arch Gen Psychiatry* 54:915-922

Alexopoulos G.S., Meyers B.S., Young R.C., Mattis S., Kakuma T. 1993. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry* 150(11):1693-1699

Alexopoulos G.S., Young R.C., Shindledecker R.D. 1992. Brain computed tomography findings in geriatric depression and primary degenerative dementia. *Biol Psychiatry* 31:591-599

Altshuler L.L., Bartzokis G., Grieder T., Curran J., Jimenez T., Leight K., Wilkins J., Gerner R.H., Mintz J. 2000. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48:147-162

Altshuler L.L., Conrad A., Hauser P., Li X., Guze B.H., Denikoff K., Tourtellotte W., Post R.M. 1991. Reduction of temporal lobe volume in bipolar disorder : a preliminary report of magnetic resonance imaging. *Arch Gen Psychiatry* 48:482-483

Austin M.P., Ross M., Murray C., O'Carroll R.E., Ebmeier K.P., Goodwin G.M. 1992a. Cognitive function in major depression. *J Affect Disord* 25:21-30

Austin M.P., Dougall N., Ross M., Murray C., O'Carroll R.E., Moffoot A.P.R., Ebmeier K.P., Goodwin G.M. 1992b. Single photon emission tomography with 99m-exametazime in major depression and the pattern of brain activity underlying the psychotic/neurotic continuum. *J Affect Disord* 26:31-44

Austin M.P., Mitchell P. 1995. The anatomy of melancholia: does frontal-subcortical pathophysiology underpin its psychomotor and cognitive manifestations? *Psychol Med* 25:665-672

Aylward E., Roberts-Twillie J.V., Barta P.E., Kumar A., Harris G.J..Geer M., Peyser C.E., Pearlson G.D. 1994. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am J Psychiatry* 151(5):687-693

Barber R., Scheltens P., Gholkar A., Ballard C., McKeith I., Ince P., Perry R., O'Brien J. 1999. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 67:66-72

Bassett S.S., Folstein M.F. 1993. Memory complaint, memory performance, and psychiatric diagnosis: a community study. *J Geriatr Psychiatry Neurol* 6:2-11

Bassuk S.S., Berkman L.F., Wypij D. 1998. Depressive symptomatology and incident cognitive decline in an elderly community sample. *Arch Gen Psychiatry* 55:1073-1081

Baumann B., Bornschlegel C., Krell D., Bogerts B. 1997. Changes in CSF spaces differ in endogenous and neurotic depression : a planimetric CT scan study. *J Affect Disord* 45:179-188

Bazin N., Perruchet P., De Bonis M., Feline A. 1994. The dissociation of explicit and implicit memory in depressed patients. *Psychol Med* 24:239-245

Beats B.C., Sahakian B.J., Levy R. 1996. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* 26:591-603

Bench C.J., Friston K.J., Brown R.G., Scott L.C., Frackowiak R.S.J., Dolan R.J. 1992. The anatomy of melancholia – focal abnormalities of cerebral blood flow in major depression. *Psychol Med* 22: 607-615

Blackburn I.M., Jones S., Lewin R.J.P. 1986. Cognitive style in depression. *Br J Clin Psychology* 25:241-251

Blazer D. 1989. Depression in the elderly. *New Engl J Med* 320:164-166

Bogerts B., Falkai P., Haupts M., Greve B., Ernst S, Tapernon F.U., Heinzmann U. 1990. Postmortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics : initial results from a new bain collection. *Schizophr Res* 3:295-301

Bolla K.I., Lindgren K.N., Bonaccorsy C., Bleecker M.L. 1991. Memory complaints in older adults. Fact or fiction? *Arch Neurol* 48:1-4

Brand A.N., Jolles J., Gispen-de Wied C. 1992. Recall and recognition memory deficits in depression. *J Affect Disord* 25:77-86

Brauer Boone K., Lesser I., Miller B., Wohl M., Berman N., Lee A., Palmer B. 1994. Cognitive functioning in a mildly to moderately depressed geriatric sample: relationship to chronological age. *J Neuropsychiatry Clin Neurosci* 6:267-272

Brayne C., Calloway P. 1988. Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type : a continuum. *Lancet* June 4:1265-1266

Brittlebank A.D., Scott J., Williams M.G., Ferrier I.N. 1993. Autobiographical memory in depression : state or trait marker? *Brit J Psychiatry* 162:118-121

Brown R.G., Scott L.C., Bench C.J., Dolan R.J. 1994. Cognitive function in depression : its relationship to the presence and severity of intellectual decline. *Psychol Med* 24:829-847

Burt D.B., Zembar J.M., Niederehe G. 1995. Depression and memory impairment : a meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 117(2):285-305

Cahill L., Haier R.J., Fallon J., Alkire M.T., Tang C., Keator D., Wu J., McGaugh J.L. 1996. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci USA* 93:8016-8021

Channon S., Baker J., Robertson M.M. 1993. Working memory in clinical depression: an experimental study. *Psychol Med* 23:87-91

Chaves M.L., Bianchin M., Peccin S., Rotta F., Jardim C., Gianlupi A., Eidt L. 1993. Chronic use of benzodiazepines and cognitive deficit complaints: a risk factor study. *Ital J Neurol Sci* 14:26-35

Clegg F., Warrington E.K. 1994. Four easy memory tests for older adults. *Memory* 2:167-182

Coffey C.D., Figiel G.S., Djang W.T., Saunders W.B., Weiner R.D. 1989. White matter hyperintensity on magnetic resonance imaging : clinical and neuroanatomic correlates in the depressed elderly. *J Neuropsychiatry Clin Neurosci* 1(2):135-144

Coffey C.E., Wilkinson W.E., Parashos I.A., Soady S.A.R., Sullivan R.J., Patterson L.J., Figiel G.S., Webb M.C., Spritzer C.E., Djang W.T. 1992. Quantitative cerebral anatomy of the aging human brain : a cross-sectional study using magnetic resonance imaging. *Neurology* 42:527-536

Coffey C.E., Wilkinson W.E., Weiner R.D., Parashos I.A., Djang W.T., Webb M.C., Figiel G.S., Spritzer C.E. 1993. Quantitative cerebral anatomy in depression : a controlled magnetic resonance imaging study. *Arch Gen Psychiatry* 50:7-16

Coffey C.D. 1996. Anatomic imaging of the aging human brain : computed tomography and magnetic resonance imaging. In : Cummings J.L., Coffey

C.E (eds). *American Textbook of Geriatric Neuropsychiatry*, American Psychiatric Association, Washington DC

Cohen R.M., Weingartner H., Smallberg S.A., Pickar D., Murphy D.I. 1982. Effort and cognition in depression. *Arch Gen Psychiatry* 39:593-597

Commissaris C.J., Jolles J., Verhey F.R., Ponds R.W., Damoiseaux V., Kok G.J. 1993. Forgetful or demented? Who worries and why? *Tijdschr Gerontol Geriatr* 24:4-9 (Abstract)

Corcoran R., Thompson P. 1993. Epilepsy and poor memory: who complains and what do they mean? *Br J Clin Psychol* 32:199-208

Crook T., Bartus R.T., Ferris S.H. 1986. Age-associated memory impairment : proposed diagnostic criteria and measures of clinical change - Report of a National Institute of Mental Health work group. *Develop Neuropsychol* 2:261-276

Cummings J.L., Benson D.F. 1992. *Dementia : a clinical approach.* Butterworth-Heinemann, Boston

Danion J., Williard-Schroeder D., Zimmermann M., Grange D., Schlienger J., Singer L. 1991. Explicit memory ad repetition priming in depression : preliminary findings. *Arch Gen Psychiatry* 48:707-711

Derouesne C., Alperovitch A., Arvay N., Migeon P., Moulin F., Vollant M., Rapin J.R., Le Poncin M. 1989. Memory complaints in the elderly: a study of 367 community-dwelling individuals from 50 to 80 years old. *Arch Gerontol Geriatr* 1:151-163

Derouesné C., Thibault S. 1995. Les frontières de la démence : intérêt et limites des critères de diagnostic. In Eustache F., Agniel A. (eds). *Neuropsychologie*

clinique des démences : évaluations et prises en charge. Solal, Marseille, pp 35-48

Dolan R.J., Bench C.J., Brown R.G., Scott L.C., Friston K.J., Frackowiak R.S. 1992. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. *J Neurol Neurosurg Psychiatry* 55:768-773

Dolan R.J., Bench C.J., Brown R.G., Scott L.C., Frackowiak R.S. 1994. Neuropsychological dysfunction in depression: the relationship to regional cerebral blood flow. *Psychol Med* 24:849-857

Dolan R.J., Goodwin G.M. 1996. Brain imaging in affective disorders. In Lewis S., Higgins N (eds). *Brain imaging in psychiatry.* Blackwell Science Ltd, Oxford, pp. 227-245

Dufouil C., Fuhrer R., Dartigues J.F., Alperovitch A. 1996. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. *Am J Epidemiol* 144:634-641

Dunbar G.C., Lishman W.A. 1984. Depression, recognition-memory and hedonic tone : a signal detection analysis. *Brit J Psychiatry* (144):376-382

Dupont R., Jernigan T.L., Heindel W., Butters N., Shafer K., Wilson T., Hesselink J, Gillin J.C. 1995. Magnetic resonance imaging and mood disorders : localization of white matter and other subcortical abnormalities. *Arch Gen Psychiatry* 52:747-755

Ebly E.M., Hogan D.B., Parhad I.M. 1995. Cognitive impairment in the nondemented elderly : results form the Canadian study of health and aging. *Arch Neurol* 52:612-619

Ebmeier K.P., Prentice N., Ryman A., Halloran E., Rimmington J.E., Best J.K.K., Goodwin G.M. 1997. Temporal lobe abnormalities in dementia and depression : a study using high resolution single photon emission tomography and magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 63:597-604

Elkis H., Friedman L., Wise A., Meltzer H.Y. 1995. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. *Arch Gen Psychiatry* 52:715-723

Elliott R., Sahakian B.J., McKay A.P., Herrod J.J., Robbins T.W., Paykel E.S. 1996. Neuropsychological impairments in unipolar depression : the influence of perceived failure on subsequent performance. *Psychol Med* 26:975-989

Elliott R., Sahakian B.J., Herrod J.J., Robbins T.W., Paykel E.S. 1997. Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *J Neurol Neurosurg Psychiatry* 63:74-82

Emery V.O., Oxman T.E. 1992. Update on the dementia spectrum of depression. *Am J Psychiatry* 149(3):305-317

Fein G., Van Dyke C., Davenport L., Turetsky B.I., Brant-Zawadzki M., Zatz L., Dillon W., Valk P. 1990. Preservation of normal cognitive functioning in elderly subjects with extensive white-matter lesions of long duration. *Arch Gen Psychiatry* 47:220-223

Flicker C., Ferris S.H., Reisberg B. 1993. A longitudinal study of cognitive function in elderly persons with subjective memory complaints. *J Am Geriatr Soc* 41:10-32

Folstein M.F., Folstein S.E., McHugh P.R. 1975. Mini-mental state: a practical method for grading the cognitive state of patients for clinicians. *J Psychiat Res* 12:189-198

Fox N., Freeborough P., Rossor M. 1996. Visualisation and quantification of rates of atrophy in Alzheimer's disease. *Lancet* 348(9020):94-97

Freeborough P., Fox N., Kitney R.I. 1997. Interactive algorithms for the segmentation and quantification of 3/D MRI brain scans. *Comput Methods Programs Biomed* 53:15-25

Geerlings M.I., Schoevers R.A., Beekman A.T.F., Jonker C., Deeg D.J.H., Schmand B., Ader H.J., Bouter L.M., Van Tilburg W. 2000. Depression and risk of cognitive decline and Alzheimer's disease : results of the two prospective community-based studies in The Netherlands. *Br J Psychiatry* 176:568-575

Geller B., Todd R.D., Luby J., Botteron K.N. 1996. Treatment-resistant depression in children and adolescents. *Psychiatr Clin North Am* 19:260-267

Gilboa E., Gotlib I.H. 1997. Cognitive biases and affect persistence in previously dysphoric and never-dysphoric individuals. *Cognition and Emotion* 11:517-538

Gilewski M.J., Zelinski E.M., Schaie K.W. 1990. The memory functioning questionnaire for assessment of memory complaints in adulthood and old age. *Psychol Aging* 5(4):482-490

Goldberg T.E., Gold J.M., Greenberg R., Griffin S., Schulz C., Pickar D., Kleinman J.E., Weinberger D.R. 1993. Contrasts between patients with affective disoders and patients with schizophrenia on a neuropsychological test battery. *Am J Psychiatry* 150(9):1355-1362

Golinkoff M., Sweeney J.A. 1989. Cognitive impairments in depression. *J Affect Disord* 17:105-112

Golomb J., de Leon M.J., Kluger A., George A.E., Tarshish C.Y., Ferris S.H. 1993. Hippocampal atrophy in normal aging : an association with recent memory impairment. *Arch Neurol* 50:967-973

Greenwald B.S., Kramer-Ginsberg E., Bogerts B., Ashtari M., Aupperle P., Wu H., Allen L., Zeman D., Patel M. 1997. Qualitative magnetic resonance imaging findings in geriatric depression. Possible link between later-onset depression and Alzheimer's disease. *Psychol Med* 27:421-431

Grut M., Jorm A.F., Fratiglioni L., Forsell Y., Viitanen M., Winblad B. 1993. Memory complaints of elderly people in a population survey : variation according to dementia stage and depression. *J Am Geriatr Soc* 41:1295-1300

Gruzelier J., Seymour K., Wilson L., Jolley A., Hirsch S. 1988. Impairments on neuropsychologic tests of temporhippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. *Arch Gen Psychiatry* 45:623-629

Habib M, Donnet A., Ceccaldi M., Poncet M. 1991. Démences sous-corticales. In : Habib M, Joanette Y., Puel M (eds). *Démences et syndromes démentiels: approche neuropsychologique*. Masson, Paris, pp. 29-43

Hanninen T., Reinikainen K.J., Helkala E.L., Koivisto K., Mykkanen L., Laakso M., Pyorala K., Riekkinen P.J. 1994. Subjective memory complaints and personality traits in normal elderly subjects. *J Am Geriatr Soc* 42:1-4

Hauser P., Altshuler L.L., Berrettini W., Dauphinais I.D., Gelernter J., Post R.M. 1989. Temporal lobe measurement in primary affective disorder by magnetic resonance imaging. *J Neuropsychiatry Clin Neurosci* 1:128-134

Hauser P., Matochik J., Altshuler L.L., Denicoff K.D., Conrad A., Li X., Post R.M. 2000. MRI-based measurements of temporal lobe and ventricular

structures in patients with bipolar I and bipolar II disorders. *J Affect Disord* 60:25-32

Henderson A.S., Jorm A.F. 1997. Some contributions to the epidemiology of dementia and depression. *Int J Geriatric Psychiatry* 12:145-154

Henderson A.S., Korten A.E., Jacomb P.A., MacKinnon A.J., Jorm A.F., Christensen H., Rodgers B. 1997. The course of depression in the elderly : a longitudinal community-based study in Australia. *Psychol Med* 27:119-129

Hentschel F., Forstl H. 1997. Neuroradiologische Diagnostik. In : Förstl H (ed). *Lehrbuch der Gerontopsychiatrie.* Ferdinand Enke Verlag, Stuttgart, pp. 95-107

Husain M.M., McDonald W.M., Doraiswamy P.M., Figiel G.S., Na C., Escalona R., Boyko O.B., Nemeroff C.B., Krishnan K.R.R. 1991. A magnetic resonance study of putamen nuclei in major depression. *Psychiatry Res* 40:95-99

Ilsley J.E., Moffoot A.P., O'Carroll R.E. 1995. An analysis of memory dysfunction in major depression. *J Affect Disord* 35:1-9

Jacoby R.J., Levy R. 1980. Computed tomography in the elderly. 3. Affective disorder. *Br J Psychiatry* 139:288-292

Jacoby R.J., Levy R., Bird J.M. 1981. Computed tomography and outcome of affective disorder : a follow-up study of elderly patients. *Brit J Psychiatry* 139:288-292

Jenkins R., Fox N., Rossor A.M., Harvey R.J., Rossor M. 2000. Intracranial volume and Alzheimer disease : evidence against the cerebral reserve hypothesis. *Arch Neurol* 57:220-224

Johnstone E.C., Owens D.G., Crow T.J., Frith C.D., Alexandropolis K., Bydder G., Colter N. 1989. Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. *J Neurol Neurosurg Psychiatry* 52:736-741

Jonker C., Launer L.J., Hooijer C., Lindeboom J. 1996. Memory complaints and memory impairment in older individuals. *J Am Geriatrics Soc* 44:44-49

Joseph R. 1996. *Neuropsychology, neuropsychiatry, and clinical neuroscience.* Williams and Wilkinson, Baltimore, pp. 178-199

Krabbendam L., Honig A., Wiersma J., Vuurman E.F., Hofman P.A., Derix M.M.A., Nolen W.A., Jolles J. 2000. Cognitive dysfunctions and white matter lesions in patients with bipolar disorder in remission. *Acta Psychiatr Scand* 101:274-280

Kramer-Ginsberg E., Greenwald B.S., Krishnan K.R.R., Christiansen B., Hu J., Ashtari M., Patel M., Pollack S. 1999. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *Am J Psychiatry* 156(3):438-444

Krishnan K.R.R., McDonald W.M., Escalona R., Doraiswamy P.M., Na C., Husain M.M., Figiel G.S., Boyko O.B., Ellinwood E.H., Nemeroff C.B. 1992. Magnetic resonance imaging of the caudate nuclei in depression. *Arch Gen Psychiatry* 49:553-557

Krishnan K.R.R., McDonald W.M. 1995. Arteriosclerotic depression. *Med Hypotheses* 44:111-115

Kumar A., Newberg A., Abass A., Berlin J., Smith R., Reivich M. 1993. Regional cerebral glucose metabolism in late-life depression and Alzheimer

disease: a preliminary positron emission tomography study. *Proc Natl Acad Sci USA* 90:7019-7023

Kumar A., Schweizer E., Zhisong J., Miller D., Bilker W., Swan L.L., Gottlieb G. 1997. Neuroanatomical substrates of late-life minor depression : a quantitative magnetic resonance imaging study. *Arch Neurol* 54:613-617

Launer L.J., Scheltens P., Lindeboom J., Barkhor F., Weinstein H.C., Jonker C. 1995. Medial temporal lobe atrophy in an open population of very old persons : cognitive, brain atrophy, and sociomedical correlates. *Neurology* 45:747-752

Lavretsky H., Lesser I., Wohl M., Miller B., Mehringer C.M. 1999. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry* 7(4):309-316

Le Doux J. 1996. *The emotional brain*. Simon and Schuster, New York

Marcos T, Salamero M, Gutierrez F, Catalan R, Gasto C, Lazaro L. 1994. Cognitive dysfunctions in recovered melancholic patients. *J Affect Disord* 32:133-137

Massman PJ, Delis DC, Butters N, Dupont RM, Gillin JC. 1992. The subcortical dysfunction hypothesis of memory deficits in depression: neuropsychological validation in a subgroup of patients. *J Clin Exp Neuropsychol* 14:687-706

Mayberg H.S. 1997. Limbic-cortical dysregulation : a proposed model of depression. In : Salloway S., Malloy P., Cummings J.L. (eds). *The neuropsychiatry of limbic and subcortical disorders*. American Psychiatric Press, Washington, pp. 167-177

McGlone J., Gupta S., Humphrey D., Oppenheimer S., Mirsen T., Evans D.R. 1990. Screening for early dementia using memory complaints from patients and relatives. *Arch Neurol* 47:1189-1193

McKay A.P., Tarbuck A.F., Shapleske J., McKenna P.J. 1995. Neuropsychological function in manic-depressive psychosis: evidence for persistent deficits in patients with chronic, severe illness. *Br J Psychiatry* 167:51-57

McKenna P.J. 1997. *Schizophrenia and related syndromes*. Psychology Press, Hove

McKenna P.J., Warrington E.K. 1983. *The Graded Naming Test*. NFER-Nelson Publishing Co. Ltd., Windsor, Berks

McKhann G., Drachman D., Folstein M., Katzman R., Price D., Stadlan E.M. 1984. Clinical diagnosis of Alzheimer's disease : report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 34:939-944

McPherson S., La Rue A., Fitz A., Matsuyama S., Jarvik L.F. 1995. Self-reports of memory problems in relatives of patients with probable Alzheimer's disease. *Int Psychogeriatr* 7:367-376

Milner B. 1972. Disorders of learning and memory after temporal lobe lesions in man. *Clin Neurosurg* 19:421-446

Miranda J., Gross J.J. 1997. Cognitive vulnerability, depression, and the mood-state dependen hypothesis: is out of sight out of mind? *Cognition and Emotion* 11:585-605

Mitrushina M., Abara J., Blumenfeld A. 1996. A comparison of cognitive profiles in schizophrenia and other psychiatric disorders. *J Clin Psychology* 52:177-190

Moffoot A.P., O'Carroll R.E., Bennie J., Carroll S., Dick H., Ebmeier K.P., Goodwin G.M. 1994. Diurnal variation of mood and neuropsychological function in major depression with melancholia. *J Affect Disord* 32:257-269

Moore P.B., Shepherd D.J., Eccleston D., MacMillan I.C., Goswami U., McAllister V.L., Ferrier I.N. 2001. Cerebral white matter lesions in bipolar affective disorder : relationship to outcome. *Br J Psychiatry* 178:172-176

Moore R.G., Watts F.N., Williams J.M.G. 1988. The specificity of personal memories in depression. *Br J Clin Psychol* 27:275-276

Morris J.S., Ohman A., Dolan R.J. 1998. Conscious and unconscious emotional learning in the human amygdala. *Nature* 393:467-470

Nathaniel-James D.A. 1996. The contribution of executive dysfunction to memory impairment and confabulation in schizophrenia. PhD thesis. University of London, pp. 25-60

Nelson H.E., Willison J.R. 1991. *The National Adult Reading Test.* NFER-Nelson Publishing Co. Ltd., Windsor, Berks

O'Brien J.T., Ames D., Schweitzer I., Tuckwell V., Tress B. 1994. The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. *Psychol Med* 24:633-640

O'Brien J.T., Desmond P., Ames D., Schweitzer I., Chiu E., Tress B. 1997. Temporal lobe magnetic resonance imaging can differentiate Alzheimer's

disease from normal ageing, depression, vascular dementia and other causes of cognitive impairment. *Psychol Med* 27:1267-1275

O'Brien J.T., Ames D., Chiu E., Schweitzer I., Desmond P., Tress B. 1998. Severe deep white matter lesions and outcome on elderly patients with major depressive disorder: follow-up study. *Br Med J* 317:982-984

O'Connor D.W., Pollitt P.A., Roth M., Brook P.B., Reiss B.B. 1990. Memory complaints and impairment in normal, depressed, and demented elderly persons identified in a community survey. *Arch Gen Psychiatry* 47:224-227

Ogura A., Morinobu S., Kawakatsu S., Totsuka S., Komatani A. 1998. Changes in regional brain activity in major depression after successful treatment with antidepressant drugs. *Acta Psychiatr Scand* 98:54-59

Palsson S., Johannsson B., Berg S., Skoog I. 2000. A population study on the influence of depression on neuropsychological functioning in 85-year-olds. *Acta Psychiatr Scand* 101:185-193

Palsson S., Larsson L., Tengelin E., Waern M., Samuelsson S., Hällström T., Skoog I. 2001. The prevalence of depression in relation to cerebral atrophy and cognitive performance in 70- and 74-year-old women in Gothenburg. The Women's Health Study. *Psychol Med* 31:39-49

Pantel J., Schroder J., Essig M., Popp D., Dech H., Knopp M.V., Schad L.R., Eysenbach K., Backenstrass M., Friedlinger M. 1997. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Dis* 42:69-83

Paradiso S., Lamberty G.J., Garvey M.J., Robinson R.G. 1997. Cognitive impairment in the euthymic phase of chronic unipolar depression. *J Nerv Ment Dis* 185:748-754

Pearlson G.D., Rabins P.V., Kim W.S., Speedie L.J., Moberg P.J., Burns A., Bascom M.J. 1989. Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia ('pseudodementia'). *Psychol Med* 19:573-584

Pearlson G.D. 1996. Structural brain imaging in neuropsychiatry. In : Lewis S., Higgins N (eds). *Brain imaging in psychiatry*. Blackwell, Oxford, pp. 246-265

Plotkin D.A., Mintz J., Jarvik L.F. 1985. Subjective memory complaints in geriatric depression. *Am J Psychiatry* 142:1103-1105

Purcell R., Maruff P, Kyrios M, Pantelis. 1997. Neuropsychological function in young patients with unipolar major depression. *Psychol Med* 27:1277-1285

Rabins P.V., Aylward E., Holroyd S., Pearlson G.D. 2000. MRI findings differentiate between late-onset schizophrenia and late-life mood disorder. *Int J Geriat Psychiatry* 15:954-960

Rabins P.V., Pearlson G.D., Aylward E., KumarA., Dowell K. 1991. Cortical Magnetic resonance imaging changes in elderly inpatients with major depression. *Am J Psychiatry* 148(5):617-620

Raven J.C. 1938. *Standard Progressive Matrices*. H.K. Lewis, London

Reding M., Haycox J., Blass J. 1985. Depression in patients referred to a dementia clinic : a three-year prospective study. *Arch Neurol* 42:894-896

Reischies F.M. 1988. Neuropsychologische Befunde bei der Depression im Involutionsalter und Senium und ihre Beziehung zur regionalen Hirndurchblutung. In : Oepen G (ed). *Psychiatrie des rechten und linken Gehirns*. Deutscher Aerzteverlag GmbH, Koeln, pp.187-197

Reischies F.M. 1997. Normales Altern und leichte Demenz : Auswirkungen normalen Alterns auf kognitive Leistungen und die Differenzierung von der leichten Demenz. In : Förstl H (ed). *Lehrbuch der Gerontopsychiatrie*. Enke Verlag, Stuttgart, pp. 366-377

Richards M. 1995. The epidemiology of Alzheimer`s disease. *Alzheimer`s Review* 5:113-117

Robertson G., Taylor P.J. 1985. Some cognitive correlates of affective disorders. *Psychol Med* 15:297-309

Rund B.R., Landro N.I. 1990. Information processing: a new model for understanding cogntivie disturbances in psychiatric patients. *Acta Psychiatr Scand* 81:305-316

Saccuzzo D.P., Braff D.L. 1981. Early information processing deficit in schizophrenia: new findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry* 38:175-179

Salloway S., Malloy P., Kohn R., Gillard E., Duffy J., Rogg J., Tung G., Richardson E.Thomas C., Westlake R. 1996. MRI and neuropsychological differences in early- and late-life-onset geriatric depression. *Neurology* 46:1567-1574

Sapolsky R.M. 2000. Glucocorticosteroids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 57:925-935

Savard R.J., Rey A.C., Post R.M. 1980. Halstead-Reitan category test in bipolar and unipolar affective disorders: relationship to age and phase of illness. *J Nerv Ment Dis* 168:297-304

Schmand B., Jonker C., Geerling M.I., Lindeboom J. 1997a. Subjective memory complaints in the elderly : depressive symptoms and future dementia. *Brit J Psychiatry* 171:373-376

Schmand B., Smit J.H., Geerlings M.I., Lindeboom J. 1997b. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychol Med* 27:1337-44

Scoville W.B., Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11-21

Shah P.J., Ebmeier K.P., Glabus M., Goodwin G.M. 1998. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. *Br J Psychiatry* 172:527-532

Sheline Y.I., Wang P.W., Gado M.H., Csernansky J.G., Vannier M.W. 1996. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 93:3908-3913

Sheline Y.I., Gado M.H., Price J.L. 1998. Amygdala core nuclei volumes are decreased in recurrent major depression. *Neuroreport* 9:2023-2028

Sheline Y.I., Sanghavi M., Mintun M.A., Gado M.H. 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19(12):5034-5043

Silberman E.K., Weingartner H., Post R.M. 1983. Thinking disorder in depression : logic and strategy in an abstract reasoning task. *Arch Gen Psychiatry* 40:775-780

Simpson S., Talbot P.R., Snowdon J.S., Neary D. 1997. Subcortical vascular disease in elderly patients with treatment resistant depression. *J Neurol Neurosurg Psychiatry* 62:196-197

Simpson S., Baldwin R.C., Jackson A., Burns A. 1998. Is subcortical disease associated with a poor response to antidepressants ? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychol Med* 28:1015-1026

Small G.W., Okonek A., Mandelkern M.A., La Rue A., Chang L., Khonsary A., Ropchan R, Blahd W.H. 1994. Age-associated memory loss : initial neuropsychological and cerebral metabolic findings of a longitudinal study. *Int Psychogeriatr* 6:23-44

Smith G.E., Petersen R.C., Ivnik R.J., Malec J.F., Tangalos E.G. 1996. Subjective memory complaints, psychological distress, and longitudinal change in objective memory performance. *Psychol Aging* 11:272-279

Smith M.J., Brebion G., Banquet J.P., Allilaire J.F. 1994. Experimental evidence for two dimensions of cognitive disorders in depressives. *J Psychiat Res* 28:401-411

Snowdon D.A., Kemper S.J., Mortimer J.A., Greiner L.H., Wekstein D.R., Markesbery W.R. 1996. Linguistic ability in early life and cognitive function and Alzheimer`s disease in late life. *JAMA* 275:528-532

Steffens D.C., Byrum C.E., McQuoid D.R., Greenberg D.L., Payne M.E., Blitchington T.F., MacFall, Krishnan K.R.R. 2000. Hippocampal volume in geriatric depression. *Biol Psychiatry* 48:301-309

Stern Y., Marder K., Tang M.X., Mayeux R. 1993. Antecedent clinical features associated with dementia in Parkinsosn`s disease. *Neurology* 43:1690-1692

Sternberg D.E., Jarvik M.E. 1976. Memory functions in depression. *Arch Gen Psychiatry* 33:219-224

Storandt M., Hill R.D. 1989. Very mild dementia of the Alzheimer type. *Arch Neurol* 46:383-386

Stoudmire A., Hill C.D., Morris R., Martino-Saltzman D., Markwalter H., Lewison B.J. 1991. Cognitive outcome following tricyclic and electroconvulsive treatment of major depression in the elderly. *Am J Psychiatry* 148:1336-1340

Strauss M.E., Bohannon W.E., Stephens J.H., Pauker N.E. 1984. Perceptual span in schizophrenia and affective disorders. *J Nerv Ment Dis* 172:431-435

Swayze V.W., Andreasen N.C., Alliger R.J., Ehrhardt J.C., Yuh W.T.C. 1990. Structural brain abnormalities in bipolar affective disorder : ventricular enlargement and focal signal hyperintensities. *Arch Gen Psychiatry* 47:1054-1059

Swayze V.W., Andersen A., Arndt S., Rajarethinam R., Fleming F., Sato Y., Andreasen N.C. 1996. Reversibility of brain tissue loss in anorexia nervosa assessed with a computerized Talairach 3-D proportional grid. *Psychol Med* 26:381-390

Tarbuck A.F., Paykel E.S. 1995. Effects of major depression on the cognitive function of younger and older subjects. *Psychol Med* 25:285-296

Teasdale J.D., Dent J. 1987. Cognitive vulnerability to depression : an investigation of two hypotheses. *Br J Clin Psychol* 26:113-126

Tebartz van Elst L., Baeumer D., Lemieux L., Woermann F.G., Koepp M., Krishnamoorthy S., Thompson P.J., Ebert D., Trimble M. 2002. Amygdala

pathology in psychosis of epilepsy : a magnetic resonance imaging study in patients with temporal lobe epilepsy. *Brain* 125:140-149

Thuillard F, Assal G. 1991. Donnees neuropsychologiques chez le sujet âgé normal. In : Habib M, Joanette Y., Puel M (eds). *Demences et syndrome dementiels: approche neuropsychologique*. Masson, Paris

Tobiansky R., Blizard R., Livingston G., Mann A. 1995. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychol Med* 25:779-786

Vakili K., Pillay S.S., Lafer B., Fava M., Renshaw P.F., Bonello-Cintron C.M., Yurgelun-Todd D. 2000. Hippocampal volume in primary unipolar major depression : a magnetic resonance imaging study. *Biol Psychiatry* 47:1087-1090

Valdois S., Joanette Y. 1991. Heterogénéité du declin cognitif associé au vieillissement normal. In : Habib M, Joanette Y., Puel M (eds). *Démences et syndromes dementiels: approche neuropsychologique*. Masson, Paris

van der Linden M. 1994. Neuropsychologie de la mémoire. In : Seron X., Jeannerod M (eds). *Neuropsychologie humaine*. Mardaga, Liège, pp. 282-316

van Gorp W.G., Altshuler L.L., Theberge D.C., Wilkins J., Dixon W. 1998. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. *Arch Gen Psychiatry* 55:41-46

Verdoux H., Liraud F. 2000. Neuropsychological function in subjects with psychotic and affective disorders. Relationship to diagnostic category and duration of illness. *Eur Psychiatry* 15:236-243

Videbech P. 1997. MRI findings in patients with affective disorder: a meta-analysis. *Acta Psychiatr Scand* 96:157-168

Walsh K. 2002. The temporal lobes. In: Walsh K (ed). *Neuropsychology : a clinical approach.* Churchill Livingston, Edinburgh, pp. 197-240

Warrington E.K. 1984. *Recognition Memory Test.* NFER-Nelson Publishing Co. Ltd., Windsor, Berks

Watts F.N., Dalgleish T., Bourke P., Healy D. 1990. Memory deficit in clinical depression: processing resources and the structure of materials. *Psychol Med* 20:345-349

Wechsler D.A. 1981. *WAIS-R Manual: The Wechsler Adult Intelligence Scale-Revisited.* Harcourt Brace Jovanovich, New York

Weingartner H., Cohen R.M., Murphy D.L., Martello J., Gerdt C. 1981. Cognitive processes in depression. *Arch Gen Psychiatry* 38:42-47

White J., Davison G.C., Haaga D.A., White K. 1992. Cognitive bias in the articulated thoughts of depressed and nondepressed psychiatric patients. *J Nerv Ment Dis* 180:77-81

Wolfe J., Granholm E., Butters N., Saunders E., Janowsky D. 1987. Verbal memory deficits associated with major affective disorders : a comparison of unipolar and bipolar patients. *J Affect Disord* 13:83-92

Woodruff P.W.R., Lewis S.W. 1996. Structural brain imaging in schizophrenia. In ; Lewis S., Higgins N (eds). *Brain imaging in psychiatry.* Blackwell Science, Oxford, pp.188-214

Zigmond A.S., Snaith R.P. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 67:361-370

Zubenko G.S., Sullivan P., Nelson J.P., Belle S.H., Huff J., Wolf G.L. 1990. Brain imaging abnormalities in mental disorders of late life. *Arch Neurol* 47:1107-1111