Maastricht University

Neuropsychological abnormalities in depression

Citation for published version (APA):

Derix, M. M. A., & Jolles, J. (1997). Neuropsychological abnormalities in depression: relation between brain and behaviour. In *Depression: Neurobiological, Psychopathological and Therapeutic Advances* (pp. 109-126). Wiley.

Document status and date:
Published: 01/01/1997

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

7 Neuropsychological Abnormalities in Depression: Relation Between Brain and Behaviour

M.M.A. DERIX and J. JOLLES
University of Maastricht, The Netherlands

INTRODUCTION

Neuropsychology is a scientific discipline, directed at the study of brain–behaviour relationships. Behaviour denotes a general concept and includes cognitive functions, affect, emotional functioning and observable behaviour. Language, attention, memory, visuoperception, visuospatial ability, problem solving, reasoning and planning all belong to the domain of cognitive functioning.

Animal experiments, imaging studies of dysthymic and of depressive subjects, studies into depressive symptomatology in individuals with brain lesions, and studies of specific cognitive functions of subjects with induced depression have produced evidence associating emotional behaviour and depression with particular brain structures. For instance, there is ample evidence from animal experiments that regions in the frontal lobe are essential for various aspects of social behaviour which are usually compromised in depressive subjects. Animals with lesions in the orbitofrontal cortex are socially less responsive and have altered social preferences, reduced facial expression and body gestures, and reduced vocalizations (Kolb and Whishaw, 1990). Investigations into the neuropsychology of human emotional behaviour also point to the involvement of frontal structures, regions in the right hemisphere being particularly important (Etcoff, 1989).

With respect to brain structures which are involved in emotional behaviour, close connections exist between the orbito-prefrontal cortex and the amygdala. An integrated anatomical system exists, extending from the hypothalamus and amygdala to cortical areas lying on the medial wall of the cerebral hemispheres. In addition, limbic zones organize information from the outside world. There also appears to be a distinction between subcortical and cortical structures in the medial wall and the lateral convexity of the cortical mantle (Gianotti, 1989).

Various brain structures have been implicated in depression as a disorder of emotional behaviour. The focus of this chapter will be on the neuropsychologi-

cal aspects and the cerebral substrates of affective behaviour and depression. These include studies which relate depression to the left and the right hemisphere, and to the frontal lobes.

The remainder of this chapter is divided into five topics: (1) neuropsychological assessment in depression; (2) neuropsychological deficits in depression; (3) dementia and depression; (4) emotion and depression in unilateral brain damage; and (5) depression and the frontal lobes.

NEUROPSYCHOLOGICAL ASSESSMENT IN DEPRESSION

Clinical neuropsychology is an applied science concerned with the behavioural expression of brain dysfunction. Any of four different purposes may prompt a neuropsychological examination: (1) diagnosis; (2) patient care, including questions about management and planning; (3) treatment – for developing treatment programmes and for evaluating their efficacy; and (4) research. With respect to research both applied and fundamental aspects are relevant. For instance, by investigating cognitive functioning as a behavioural manifestation of depression the relationships between brain and behaviour can be explored, and this provides the opportunity to develop inferences about the potential neuroanatomical substrate of the illness. In the neuropsychological literature of the last decade at least three major trends have proved productive for investigating the brain basis of depression: (1) test-based localizing approaches; (2) comparative approach; and (3) experimental studies of information processing (King and Caine, 1990).

TEST-BASED LOCALIZING APPROACHES

The classical neuropsychological test-based approach uses neuropsychological tests to yield information about the contribution of the various cortical structures to behaviour. The inferences are based upon analogy reasoning. Several studies have shown that depressive subjects have an inferior performance in tests which are thought to measure right hemisphere functions (Flor-Henry, 1979), such as selective deficits on visuospatial and motor tasks associated with the non-dominant hemisphere (Goldstein et al., 1977; Gray et al., 1987; Kronfol et al., 1978). Interestingly Kronfol and colleagues (1978) found that right hemisphere function improved in those depressive subjects whose mood improved with electroconvulsive therapy. Likewise, treatment with tricyclic antidepressants improved the performance of children in neuropsychological tests for right hemisphere function (Wilson et al., 1984). In a review Silberman and Weingartner (1986) described several other studies suggesting lateralized cerebral deficits in depression. Marcos and colleagues (1994) examined cognitive dysfunction in recovered melancholic patients. The patient group showed dysfunctions with regard to immediate and delayed visual memory, block design, delayed logical memory and paired associate learning. Although the patients' deficits appeared

in both verbal and perceptual–spatial tasks, the perceptual–visual tasks presented more significant and constant differences from controls, according to the authors an indication for specific right hemisphere involvement. The authors stated that the difference in performance on block design could be interpreted as an indication for dysfunction of frontal structures.

King and Caine (1990) remind us that much of this work must be interpreted cautiously due to methodological shortcomings, such as the lack of normal controls or failure to include controls matched for educational level (Goldstein et al., 1977; Kronfol et al., 1978; Gray et al., 1987). Also, some investigators failed to find evidence of non-dominant hemisphere deficits in depressives (Taylor et al., 1979), and others have reported evidence of significant verbal-mediated learning and memory deficits (McAllister, 1981; Watts et al., 1987; Wolfe et al., 1987). There are two other reasons to be cautious in interpreting this kind of study: (1) test-based inferences on cerebral localization; and (2) understanding of the locus of control of discrete cognitive processes (King and Caine, 1990).

One has to keep in mind that many "localizing" neuropsychogical tests and test batteries are based on studies of patients with focal lesions, such as cerebrovascular accidents and lesion wounds. It is still unknown whether the findings from this kind of cerebral localization can also be applied to less focal cerebral dysfunction such as neurochemical system disease as is the case in depression.

COMPARATIVE APPROACHES

The comparative neuropsychological approach in the study of depression uses well-defined neurological diseases as anchor points from which to make inferences on the nature of the relationship between brain and behaviour in psychopathological disorders such as depression. For instance, the performance of depressive patients is compared with that of patients with Huntington's disease or Parkinson's disease. Although this approach can provide relevant findings, one has to keep in mind that it is subject to limitations, as similar patterns of cognitive deficit may result from different types of underlying neuropathology (King and Caine, 1990, 1996). For this reason it is important to combine the neuropsychological test findings with other measures such as brain imaging techniques.

In one study the performance of depressives was compared with that of matched patients with Huntington's disease and normal healthy controls (King and Caine, 1990). The neuropsychological assessment included tests for word fluency, auditory verbal memory, visual memory, visuospatial ability, ideomotor praxis and primary language tasks. They found no significant differences between the depressives and the patients with Huntington's disease. Compared with the controls the depressives were significantly impaired on tests for word fluency, immediate recall and delayed recall on the 10-word list, immediate recall and multiple-choice recognition of a story, and immediate and delayed recall of

geometric shapes. The pattern of deficits observed in this study in the depressed group involved impaired verbal elaboration (word fluency tasks), difficulty assessing learned information, and inefficient use of a normal learning strategy. A similar pattern was evident in patients with Huntington's disease. The authors suggested that cognitive impairment in both these groups was caused by a common disruption of "psychomotor" or "modulatory" functions. This is a pattern of deficits that has often been found in studies of patients with known subcortical pathology. When compared with these patient groups the performance of depressive patients is often quite similar.

EXPERIMENTAL STUDIES OF INFORMATION PROCESSING

Experimental studies of information processing use cognitive psychological methods to assess the relative contributions of especially cognitive and motor components to overall psychomotor slowing in depression. From studies, using this approach, it appears that motor slowing on complex reaction time tasks is as common in most patients with depression as it is in some specific subcortical disorders (King and Cain, 1990, 1996).

Jolles and colleagues (1993) examined 25 middle-aged, dysthymic patients with regard to memory function and automatic and controlled cognitive information processing. The performance of the dysthymic patients was compared with that of 25 healthy controls, matched for age, sex and educational level. The patients were referred to the Maastricht Memory clinic for evaluation of their memory complaints. The following neuropsychological tests were used: digit span forward; auditory verbal learning test (total in five trials, delayed recall, delayed recognition); Stroop Colour Word tests, Trailmaking test – revised, and a memory scanning test (one to four letters). There were significant differences on nearly all measures. One clear exception was the result on digit span forward, on which the performance of the dysthymics was normal. The number of words recalled by patients on immediate and delayed recall on a Dutch version of the Rey auditory verbal learning test was lower, as was the case on delayed recognition. However, the score of the dysthymic patients on delayed recognition was much better than expected regarding the scores on delayed recall. On the Trailmaking test the patients needed much more time to complete the three different parts. The patients also needed much more time for the three cards of the Stroop Colour Word test; in addition they were significantly more susceptible to interference than the control group. The time needed by the patients for the memory scanning task was longer on all four subtests; their memory–search processes were clearly slower than in the controls, especially when the memory load was increased. The results can be taken to indicate that the dysthymic subjects, apart from being slower, had a particular problem with effort-demanding processing. This type of task requires "controlled processing" as opposed to "automatic processing" (Shiffrin and Schneider, 1977). The results suggest that dysthymic subjects make more use of controlled processing strategy, which costs

them more time and energy. This is exactly the complaint that many of these patients have, namely that they are not able to perform simple tasks as automatically as they used to: that everything costs more energy and effort; that they feel unable to perform complex tasks involving several actions parallel to each other and/or in a short time period. A similar profile of cognitive impairment was found by Moffoot and colleagues (1994), who examined the performance of patients with major depression with melancholia, with respect to diurnal variation of mood and neuropsychological functioning. Their patients showed a significant improvement in the evening as compared with their morning performance on neuropsychological tasks. In the morning their performance differed significantly from normal controls, especially on tasks measuring auditory verbal memory and psychomotor speed. These differences nearly completely disappeared in the evening.

NEUROPSYCHOLOGICAL DEFICITS IN DEPRESSION

Cognitive deficits are more common in the elderly depressed group compared with younger depressed individuals (Emery and Oxman, 1992). Depression in patients aged 70 and older may be a more neuropsychologically and pathophysiologically heterogeneous phenomenon than in younger patients (King and Caine, 1990). Somatic diseases and depression are closely related to each other; nearly all chronic diseases may facilitate a depressive syndrome. This poses a problem in the elderly as the prevalence of a serious illness increases with age. In the elderly the depressed mood is often less explicitly gloomy, but rather more weary or resigned; they are also more apathetic or more passive than younger patients. Also somatic complaints are often more prominent and sometimes can even completely hide the depression. In elderly patients depression can manifest itself as forgetfulness or confusion, which will cause difficulties in their daily life (Gerner, 1979). In younger patients, although they may complain about concentration deficits and memory problems, these problems are seldom so severe as to interfere with their daily functioning.

Kennedy and Kennedy (1992) and Cassens and colleagues (1990) have given an overview of the neuropsychological deficits found in psychiatric disorders, including depression. The following functions can be distinguished: attention, memory (short-term recognition and recall; long-term episodic and semantic memory), abstraction and executive functions, visuospatial functions, language and motor skills.

ATTENTION

There are few systematic investigations of attentional abilities, although clinicians frequently suggest that depressed patients are inattentive. A significant deficit with regard to attentional span has not been described. Vigilance and

selective attention are often impaired in depressive patients. Compared with normal controls no specific deficits are found with regard to divided attention.

MEMORY

In general, short-term memory is normal in depressives. Deficits in verbal as well as non-verbal memory for newly acquired information have often been reported, especially reduced immediate and delayed recall. Depressed patients have also been shown in some, but not all, studies to manifest deficits in retrieval of information from semantic memory, for instance as examined with the controlled word association test. Caley and colleagues (1989) reported that the performance of depressed patients on the category bound word fluency was better than on the controlled word association test. The memory deficits in depressed patients are at least partially related to inattention and distractibility, which leads to poor organization and encoding of information to be processed (Lezak, 1995). Learning–memory deficits are less apparent when depressed patients are provided with structure and organization (Weingartner et al., 1981).

ABSTRACTION AND EXECUTIVE FUNCTION

Depressed subjects with minimal or without cognitive disturbance are unimpaired on the Wisconsin Card Sorting Test (WCST), a test often used to assess executive functioning. Depressed patients with global cognitive disturbance are impaired on this measure. A major covariate of performance on the WCST is attention, and thus it is not surprising that cognitively disturbed patients will have difficulties in performing this task, as on many other tasks assessing executive function. Significant decrements on tasks measuring abstraction have been reported.

VISUOSPATIAL FUNCTIONS

Deficits in visuospatial functions have been consistently found in depressive patients. The deficits appear to be made more prominent as tasks are made more complex and make greater demands for effortful processing.

LANGUAGE

Speech latency is often increased in depressed patients, but no consistent findings of formal language impairment have been reported. Depressive patients often experience difficulties on complex language tasks, in which attention, memory and cognitive effort also play an important role.

MOTOR SKILLS

In general depressed patients perform more slowly than controls on tests measuring reaction time and motor speed.

The neuropsychological findings in depressive patients suggest an underlying deficit in the efficiency or modulation of cognitive processing, which will manifest itself on tasks demanding effort, especially cognitive effort. The memory dysfunction in depression has been interpreted as resulting from "weak" or incomplete encoding strategies (Weingartner et al., 1981) reflecting insufficient or poorly sustained effort, although automatic memory processes remain intact. Thus new information can be learned, but not in such a way as to facilitate retrieval; much of what was learned must wait for the stimulus or cueing or a recognition format to help it become manifest.

In research into the neuropathological substrate of depression, age has up until now not been an important factor. However, data suggest that it may be relevant to take age into consideration when evaluating the effect of brain lesions on affective behaviour. Even in neurologically intact younger persons, depression may interfere with the normal expression of their cognitive abilities, although these are usually milder than in older persons.

The cognitive findings from neuropsychological evaluation of depressed patients suggest the importance of alterations in psychotherapeutic techniques. Apparent resistance to psychotherapy may actually represent a pattern of deficits in attention, memory and cognition. During the period of this cognitive disadvantage, patients may require their therapists to be more active, use shorter sentences, avoid abstractions, and make lists rather than to expect the patient to remember the content of the session (Bostwick, 1994).

DEPRESSION AND DEMENTIA

Affective disorders are common in the elderly. Ten to twenty per cent are estimated to have depressive symptoms requiring a psychiatric intervention (Blazer, 1989). Many patients with a chronic physical illness respond to the illness with a depressive reaction. It is estimated that 0.5–2.5% of the elderly suffer from a major depression. But less severe depressive mood disorders, which also cause problems in daily life, occur even more frequent in the elderly. The percentage varies between 10% and 20% (Saunders et al., 1993). The most common problem complicating differential diagnosis of behavioural disturbances in older persons is depression, which can mimic or exacerbate symptoms of progressive dementing conditions.

Depression and dementia have a complex relation and severe depression may present as dementia, a condition which was called "pseudodementia", but today is termed depressive dementia. However, depression and dementia may coexist, in which case depression may be a secondary reaction to the awareness of

impending deterioration or may be consequent to the biochemical changes in the brain (Zubenko *et al.*, 1990). It is also possible that depression precedes dementia (Kral and Emery, 1989) or that dementia, especially subcortical dementia, manifests itself as a depression. Finally depression and dementia may develop independently (Roberts, 1984).

Cognitive changes occur in both depression and dementia, and it is important to distinguish between these possibilities (Cummings, 1989). Cognitive impairments usually accompany the mood changes of depression. This impairment may be mild to severe. Mild impairment accompanying a major depressive disorder poses little diagnostic or therapeutic uncertainty. However, when the impairment is severe, and when cognitive impairment dominates the clinical picture in patients with depressive symptoms, it is often difficult to evaluate whether the dysfunction is related to the depression or to a brain disorder such as Alzheimer's disease or vascular dementia. Especially elderly patients with depressive disorders frequently have cognitive impairment. In major depressive disorder, memory impairment can become severe in elderly patients, and this impairment more closely resembles the memory changes in mild to moderate stages of cortical dementias (such as dementia of the Alzheimer type) than the changes found in ageing. Similarly the pattern of impaired recall with relatively preserved recognition memory, sometimes found in major depression, is indistinguishable from that of subcortical dementias such as in Huntington's disease or Parkinson's disease, or some cerebrovascular diseases (Massman *et al.*, 1992). Such differential diagnosis is all the more complex because patients with dementia often also have depressive symptoms. As part of a thorough history and mental status examination, information on affective symptoms and testing for cognitive impairment are crucial.

Cognitive changes show a continuum from depression to dementia. This is especially the case in older people as their cognitive functioning is already compromised by age. Emery and Oxman (1992) stated that one has to discern between the following five groups:

1. major depression with minimal or subclinical cognitive deficits;
2. major depression with cognitive deficits which reach clinical proportions – the so-called depressive dementia;
3. degenerative dementia without depression;
4. degenerative dementia with different degrees of depression;
5. dementia and depression which occur independently.

A dementia syndrome can occur in major depressions (single episode or recurrent), in depression in the course of a bipolar disorder, or in depression with elements of a character disorder such as "neurotic depression" or dysthymia (Cummings and Benson, 1992). The profile of cognitive deterioration in depression, the "dementia syndrome of depression" has been ranked under the general term "subcortical dementia" (Cummings and Benson, 1992). These changes include cognitive slowing, forgetfulness or deficient retrieval, intellectual "dil-

apidation" and alterations in mood and affect, such as apathy, decreased drive and depression. Signs of aphasia, apraxia and agnosia are absent (Derix, 1994; Derix *et al.*, 1993). Psychomotor retardation, a common behavioural sign in major depression, seems to be one of the most characteristic clinical features of subcortical dementia (Benson, 1983). Usually depressed mood and affect are present in patients with depressive dementia, and often the patient may express guilt, shame and self-deprecatory feelings; direct questions may be responded to with "I don't know" answers, or patients fail to make or complete a response (Cummings and Benson, 1992; Lezak, 1995).

Depressive dementia is an age-related phenomenon, and patients who experience severe depressions with or without psychosis during recurrent depressive episodes in early and midlife are more prone to the development of a dementia syndrome when depression recurs at an advanced age. Depressive dementia can occur in young patients; however, it is uncommon in early or midlife (Cummings and Benson, 1992). Cummings (1989) states that the dementia syndrome of depression can only be verified in retrospect as the patient's intellectual function must recover after successful treatment of the depression. Cummings and Benson (1992) have given an overview of the major characteristics of the dementia syndrome of depression. These characteristics do not all need to be present at the same time. Besides mental status changes, these include neurovegetative signs, motor manifestations, some items in the history of the patient and laboratory findings such as a positive dexamethasone suppression test and enlarged lateral ventricles. Compared with depressed patients without cognitive impairment, patients with depressive dementia have more delusions, increased anxiety, and more marked cerebral atrophy on brain imaging studies (Lezak, 1995).

It is important to distinguish dementia from depression with respect to treatment. Poor performance of a depressed patient on neuropsychological tests may mislead the clinician to diagnose a dementia syndrome, often with the implication that poor test results indicate structural brain damage (Lezak, 1995). Empirical trials of antidepressants in patients with either major depression and severe cognitive impairment or those with dementia and major depression have shown clinical improvement, including improvement of cognitive functioning even if not to the same degree in both groups (La Rue, 1992). For those who cannot or will not take antidepressants or electroconvulsive therapy, psychosocial treatment can alleviate depression, even in patients with dementia. Cassens and colleagues (1990) examined three groups of depressive patients, e.g. patients with the least cognitive impairment (patients with dysthymia and character-disordered patients), depressed patients with focal neuropsychological deficits and depressed patients with global cognitive impairment. Of these three groups the dysthymics and the character-disordered patients were more likely to be responsive to psychotherapy than pharmacotherapy. The second group improved on a combination of both psychotherapy and pharmacotherapy, and the third group was in need of immediate somatic treatment such as pharmacotherapy or electroconvulsive therapy. Thus an increasingly important issue

is to establish the level of depressive symptomatology and cognitive impairment at which a patient should be urged to undergo somatic or psychotherapeutic treatment for possible alleviation of the depression and cognitive impairment.

Several reports suggest that degenerative dementia is more likely to occur in older patients with depression than in other patients. Relatives of patients with Alzheimer's disease have reported, in retrospect, depression and agitation as being the first symptom in about 40% of cases (La Rue *et al.*, 1993). In longitudinal studies, depression with clear-cut cognitive deficits has been found to be a risk factor for subsequent dementia. For instance Brown and colleagues (1986) reported that more than 60% of patients with affective disorders developed primary degenerative dementia or dementia of vascular origin. Kral and Emery (1989) reported similar findings. They found that nearly 80% of subjects with depression and serious cognitive deficits developed primary degenerative dementia with the neuropathological signs of Alzheimer's disease. Neuropathological studies report findings which suggest that subcortical centres may be pathologically changed in Alzheimer patients with depression compared with those without (Zweig *et al.*, 1988). Thus information exists which suggests that depression and dementia may share a common neuropathology and clinical phenomenology. This should be kept in mind when discussing the brain structures implicated in emotional behaviour and depression. Consideration should be given to the continuum between depression and dementia. The cognitive deficits which are commonly seen in depression (Jolles, 1985; Brand and Jolles, 1987, 1992), especially in old age, may be a determining factor with respect to structural or functional changes in the brain as measured by computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission CT (SPECT) or positron emission tomography (PET). Due consideration should be given to these findings in future studies into brain–behaviour relationships in depression.

EMOTION AND DEPRESSION IN UNILATERAL BRAIN DAMAGE

At the end of the nineteenth century H. Jackson observed that the emotional aspects of language, such as putting the right emotional load into utterances in stressful situations, are preserved in aphasic patients. Several decades later, Babinski noted that patients suffering from right hemisphere damage are seemingly unaware of their defect or are indifferent to their paralysis. In the 1950s several authors observed that patients who were treated with sodium amytal in the left or right middle cerebral artery manifested a different emotional behaviour. Inactivation of the left hemisphere by this substance produced a depressive, catastrophic reaction whereas inactivation of the right hemisphere resulted in a more "euphoric" reaction. Subjects with right brain damage appear to be characterized by an abnormal indifference to failure (Hécaen, 1951). Strokes

involving the left frontal lobe and multi-infarct dementia may influence mood and produce depression; also frontal and subcortical lesions are associated with depression; lesions in the right hemisphere may modify the clinical manifestations of depression (Lezak, 1995).

Neurophysiological studies have indicated an involvement of the right hemisphere in depression. In the 1970s several studies reported unusual electroencephalography (EEG) or evoked response potential (ERP) findings in the right hemisphere of depressive subjects (Flor-Henry, 1979). Von Knorring (1983) showed that depressive subjects did not show the normal pattern of increased right hemisphere EEG activation while listening to music. This hemisphere was in some way unresponsive or underaroused. Other findings which implicate the right hemisphere in depression point more specifically to the right frontal lobe (Tucker et al. 1981). Perris and colleagues (1978) showed that left frontal activity was correlated to symptoms of anxiety whereas right frontal activity correlated to the degree of depressive mood. Schaffer and colleagues (1983) studied university students who suffered from depressive symptomatology as rated on the Beck inventory scale. They found that the subjects with depressive symptomatology differed from controls in showing marked alpha desynchrony over the right frontal region.

Gianotti (1989) undertook a systematic investigation of those emotional reactions that seem to be associated with lesions of both the right and the left hemispheres. He confirmed that patients with left hemisphere brain damage were anxious and burst into tears whereas patients with right hemisphere lesions were indifferent. He suggested that the catastrophic reactions of patients with left brain damage should be considered a dramatic but psychologically appropriate reaction to the effect of the lesion in impaired speech and motor abilities. In his studies, he found that only patterns of behaviour which were directly linked to the emotional storm of the catastrophic reaction were significantly more frequent in the left brain-damaged patients. The indifference of patients with right brain damage was more difficult to explain. He suggested that the symptoms observed could be due to a disruption of structures within this hemisphere which are critically involved in the regulation of emotions and affect.

Patients with right hemisphere cortical and subcortical damage experience generally lowered mood, but they seem to have few specific depressive complaints and are characterized by a tendency towards a lack of initiative and inertia (Finset, 1988). Robinson and colleagues (1984) demonstrated that left anterior cortical or subcortical vascular lesions were associated with depression, while right anterior lesions were associated with inappropriate cheerfulness or apathy. Researches from this group (Starkstein et al., 1987) have reported that significant depression can also be associated with purely subcortical lesions. They found that patients with left-sided damage to the basal ganglia had a significantly higher frequency and a more severe depression than patients with either right- or left-sided thalamic lesions. Furthermore these results could not be explained by differences in the degree of physical, cognitive or social impair-

ment. PET studies have also reported a decreased metabolism in the basal ganglia (Buchsbaum *et al.*, 1986); and a significant lower rate of metabolic activity in the caudate nucleus of carefully diagnosed, psychoactive-medication-free, depressed patients has been reported (Baxter *et al.*, 1985).

Gianotti (1989) states that the indifference of patients with right hemisphere damage is confined to acute periods of the event; with time these patients become aware of their disease and, in the chronic stage, may become depressed. Downhill and Robinson (1994) examined the longitudinal course of cognitive impairment related to depression in stroke patients. A difference was found with regard to the occurrence of depression and cognitive impairment. Depression with cognitive impairment appeared to be a phenomenon produced by left hemisphere lesions. Frontal dysfunction seems to be related to the occurrence of cognitive impairment, whereas depression is related to temporal dysfunction.

Investigations into comprehension and expression of emotions have shown that patients with right hemisphere damage are unable to recognize the emotion expressed by the tone of voice of a speaker (Heilman *et al.*, 1975) or to recognize facial expressions (Etcoff, 1989). In addition, patients with right hemisphere damage are relatively unable to express emotions by the tone of voice and facial expression (Pizzamiglio *et al.*, 1989). These findings suggest that the right hemisphere is more important than the left hemisphere with regard to emotion, indicating that emotional language is organized especially at the level of the right hemisphere (Ross, 1981, 1984). According to this view, indifference reactions should be considered as a consequence of an inability to correctly express normally experienced emotional reactions; patients with right hemisphere damage are as depressed as patients with left hemisphere damage but are unable to express their emotions adequately and give the examiner an impression of indifference (Ross and Rush, 1981).

Thus, hemisphere asymmetries exist with respect to the organization of emotional behaviour; depressive symptomatology can result from unilateral lesions in either hemisphere. Studies of patients with focal brain lesions suggest that both cortical and subcortical regions are involved in the production of depressed mood states. Lesions in left anterior cortical and left subcortical regions result in the experience of a dysphoric mood that resembles unipolar depressed states. These patients manifest the full range of syndromically defined depressive symptoms. Damage to right hemisphere structures often results in hypo- or hyperarousal, which is frequently encountered in affective disorders. These patients may also manifest alterations in the expression and perception of emotion, but typically they fail to conform to specific diagnostic criteria. The left and right hemispheres both have a function in emotional behaviour, and especially in depression. The symptomatology differs with the size of the lesions. Right hemisphere damage gives rise to emotional disturbances which are most probably due to a defect in the right hemispheric organization of emotional behaviour. Right hemisphere-damaged patients do not experience emotions any less than other people. Rather their experience of emotional communication,

and their capacity to transmit the nuances and subtleties of their own feeling stated, differ from normal affective processing (Lezak, 1995).

It appears that left hemisphere pathology is primarily implicated in disturbed mood, while the right hemisphere dysfunction is more often associated with disturbed affect – mood being the inner feeling tone and the subjective feelings of the patient, and affect defined as the outward expression of emotion.

DEPRESSION AND THE FRONTAL LOBES

Involvement of the frontal lobe in depression was suggested by psychosurgical interventions in this structure; symptoms of anxiety and depression are substantially reduced by lesions in the ventral or orbital regions (Tucker and Liotti, 1989). In addition, regional cerebral blood flow is reduced after benzodiazepine treatment, especially on the right side (Mathew *et al.*, 1985).

PET with fluorodeoxyglucose (FDG) has consistently shown diminished metabolism of the anterolateral dorsal prefrontal cortex curing the course of depressive episodes (Baxter *et al.*, 1989). Baxter and colleagues (1989) found that, prior to treatment, glucose metabolic rates were reduced for patients with either unipolar or bipolar major depression in both the left and right prefrontal cortex. With treatment, metabolic rates increased in the left, but not the right, prefrontal cortex, suggesting a left prefrontal abnormality. Significant cerebral blood flow reduction has been found with SPECT in older, medication-free depressed patients compared with age-matched control subjects, with regard to the orbitofrontal and anterior temporal regions, especially in the right hemisphere. A study by Lesser and colleagues (1994) showed that cerebral blood flow, measured with SPECT, was lower in older, medication-free, depressed patients than in age-matched controls, and this involved the orbitofrontal and anterior temporal regions. Also the cerebral blood flow reduction was more pronounced in the right hemisphere. Lesions in the dorsomedial frontal cortex may give rise to loss of initiative and in the extreme case akinetic mutism. Goldberg (1985) suggested that this region is important for its limbic contributions to emotionally significant actions. The cingulate cortex, which receives particularly rich noradrenaline connections, may be involved in this respect. Interpretation of the different contributions of the frontal left and right hemisphere has been complicated by the findings of Robinson and colleagues (1984). These authors studied patients suffering from depression after stroke and found that the characteristic emotional effects of unilateral lesions occur primarily with frontal lesions. Depression was greater with more anterior lesions but less when the lesion was more anterior in the right hemisphere. These findings are relevant in terms of the functions of the frontal lobes in the inhibitory control of other brain structures (Goldman-Rakic, 1984) and suggest that the typical effect of unilateral lesions is to inhibit the hemisphere's normal emotional orientation.

There are several theories which try to explain the emotional behaviour of right and left brain-damaged subjects. One theory states that there is a different hemispheric specialization for positive and negative emotions; however, Gianotti (1989) concluded that this theory meets with serious empirical objections. Another theory suggests that both hemispheres are involved in the regulation of each type of emotion but that the right hemisphere is dominant (Gianotti, 1989). There is empirical evidence in favour of this theory. For instance, patients with right hemisphere damage suffer from inappropriate emotional reactions which have a negative implication for recovery (Hurwitz and Adams, 1972). Research performed during the last two decades has shown that patients with right hemisphere damage show a defect of autonomic arousal during emotionally loaded tasks (Heilman et al., 1978). These patients show emotional indifference to stress situations. Zoccolotti and colleagues (1986) found that these subjects show only very weak sympathetic and parasympathetic reactions to emotional stimuli. Thus, the difference displayed by these patients is a reflection of both an inability to express an emotional experience and a diminished capacity to feel affect. Tucker and colleagues (1981) suggested that right frontal lobe activity in depression might represent an inhibitory influence which operates to suppress posterior right hemisphere functioning.

Taken together, both hemispheres, including the frontal lobes, appear to be involved in the manifestation of depression although the right hemisphere is dominant in this function. A variety of studies with divergent methodologies have reported right hemispheric control for the processing of emotional information and for modulating cortical arousal levels (Silberman and Weingartner, 1986). In addition, circumstantial evidence obtained with a variety of methods suggests that the frontal lobes contribute in a specific way to the organization of emotional behaviour and depression. The specific contributions of left versus right lobes are as yet not clear. More research has to be performed into the relation between the involvement of neural and anatomical structures on the one hand (e.g. frontal lobes, the hemispheres) and biochemical measures on the other. Imaging studies in depression may prove relevant in this respect in the future.

CONCLUSION

Animal experiments, imaging studies of dysthymic and of depressed subjects, studies into depressive symptomatology in individuals with brain lesions, and studies of specific cognitive functions of subjects with induced depressive mood have produced evidence associating emotional behaviour and depression with particular brain structures. PET and SPECT studies show changes in glucose metabolism in depressive subjects, which differ from those found in subjects with dementia of the Alzheimer type. Depression and dementia have a complex relation: severe depression may present as dementia ("depressive dementia"); depression and dementia may coexist; depression may precede dementia; de-

mentia – especially subcortical dementia – can manifest itself as a depression; finally depression and dementia may develop independently. Research has shown that there is a continuum between depression and dementia and it is suggested that major depression with profound cognitive deficits may be characterized by more clear-cut brain abnormalities than major depression without cognitive deficits.

Neuropsychological evaluation of depressed patients had revealed deficits in memory, attention, concentration, processing speed, spontaneous elaboration of information and analysis of detail suggesting an underlying deficit in the efficiency or modulation of cognitive processing, which will manifest itself on tasks demanding (cognitive) effort. The findings from neuropsychological evaluation suggest the importance of alterations in psychotherapeutic techniques. Apparent resistance to psychotherapy may actually represent a pattern of deficits in attention, memory and cognition.

Investigation of cognitive functioning as a behavioural manifestation of depressive disorder allows one to explore behaviour-brain relationships and provides the opportunity to develop inferences about the potential neuroanatomical substrates of the illness. Disorders of emotional behaviour are noted in brain-injured subjects, with differences in behaviour, depending on the hemisphere damaged. A catastrophic-like depressive reaction is seen with left hemisphere lesions and indifference with right hemisphere lesions. Evidence suggests that depressive symptomatology may result from a unilateral lesion in either hemisphere, although the right hemisphere appears to be dominant in the organization of emotions. Patients with lesions of the right hemisphere show emotional indifference to stress situations. Frontal mechanisms also play an important role in emotional behaviour in depression, although it is not clear what role the left versus right frontal lobe plays. More research has to be performed into the relation between the neuropsychological findings, the involvement of neural and anatomical structures, and biochemical measures. Imaging studies may prove relevant in this respect in the future.

REFERENCES

Baxter LR, Phelps ME, Mazziotta JC et al. (1985) Cerebral metabolic rates for glucose in mood disorders: studies with positron emission tomography and fluorodeoxyglucose F18. Arch Gen Psychiatr 42: 441–447.

Baxter LR Jr, Schwartz JM, Phelps ME et al. (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatr 46: 243–250.

Benson DF (1983) Subcortical dementia: a clinical approach. In The Dementias, ed. by R Mayeux and WG Rosen. Raven Press, New York, pp. 185–194.

Blazer D (1989) Depression in the elderly. N Engl J Med 320: 164–166.

Bostwick JM (1994) Neuropsychiatry of depression. In The Psychotherapist's Guide to Neuropsychiatry: Diagnostic and Treatment Issues, ed. by JM Ellison, CW Weinstein

and T Hodel-Malinofsky. American Psychiatric Press, Washington, DC, pp. 409–431.

Brand N and Jolles J (1987) Information processing in depression and anxiety. *Psychol Med* 17: 145–154.

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

Brown R, Colter N, Corsellis JN *et al.* (1986) Postmortem evidence of structural brain changes in schizophrenia. *Arch Gen Psychiatry* 43: 36–42.

Buchsbaum MS., De Lisi LE, Holcomb HH *et al.* (1984) Antero-posterior gradients in cerebral glucose: use in schizophrenia and affective disorders. *Arch Gen Psychiatry* 41: 1159–1166.

Buchsbaum MS, Wu J, DeLisi LE *et al.* (1986) Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with (18F)-2-deoxyglucose in affective illness. *J Affect Disord* 10: 137–152.

Calev A, Nigal D and Chazan S *et al.* (1989) Retrieval from semantic memory using meaningful and meaningless constructs by depressed, stable bipolar and manic patients. *Br J Clin Psychol* 28: 670–673.

Cassens G, Wolfe L and Zola M (1990) The neuropsychology of depressions. *J Neuropsychiatry* 2 (2): 202–213.

Cummings JL (1989) Dementia and depression: an enigma evolving. *J Neuropsychiatry* 1 (3): 236–242.

Cummings JL and Benson DF (1992) *Dementia: A Clinical Approach*, 2nd edn. Butterworth–Heinemann, Boston, MA.

Derix MMA (1994) *Neuropsychological Differentiation of Dementia Syndromes.* Lisse, Swets & Zeitlinger, Lisse.

Derix MMA, Gilhuis HJ and Hoogendijk W (1993) Depressive syndrome in Parkinson's disease: clinical pitfalls. In *Mental Dysfunction in Parkinson's Disease*, ed. by ECh Wolters and P Schelten. Vrije Universiteit, Amsterdam, pp. 325–348.

Downhill JE and Robinson RG (1994) Longitudinal assessment of depression and cognitive impairment following stroke. *J Nerv Ment Dis* 182: 425–431.

Emery VO and Oxman TE (1992) Update on the dementia spectrum of depression. *Am J Psychiatry* 149: 305–317.

Etcoff NL (1989) Asymmetries in recognition of emotion. In *Handbook of Neuropsychology*, vol. 3. ed. by L Squire and G Gianotti. Elsevier, Amsterdam, pp. 363–382.

Finset A (1988) Depressed mood and reduced emotionality after right-hemisphere brain disease. In *Cerebral Hemisphere Functions in Depression*, ed. by M Kinsbourn. American Psychiatric Press, Washington, DC. pp. 50–64.

Flor-Henry P (1979) On certain aspects of the localization of cerebral systems regulating and determining emotion. *Biol Psychiatry* 14: 677–698.

Gerner RH (1979) Depression in the elderly. In *Psychopathology of Aging*, ed. by OJ Kaplan. Academic Press, New York.

Gianotti G (1989) Disorders of emotions and affect in patients with unilateral brain damage. In *Handbook of Neuropsychology*, Vol. 3, ed. by L Squire and G Gianotti. Elsevier, Amsterdam, pp. 345–361.

Goldberg G (1985) Supplementary motor area structure and function: review and hypotheses. *Behav Brain Sci* 8: 567–616.

Goldman-Rakic PS (1984) The frontal lobes: uncharted provinces of the brain. *Trends Neurosci* 7: 428–429.

Goldstein SG, Filskov SB, Weaver LA *et al.* (1977) Neuropsychological effects of electroconvulsive therapy. *J Clin Psychol* 33: 798–806.

Gray JW, Dean RS, Raltan G and Kramer KM *et al.* (1987) Neuropsychological aspects of primary affective depression. *Int J Neurosci* 32: 911–918.

Hécaen H, De Ajuiriaguerra J and Massonet J (1951) Les troubles visuoconstructifs par

lésion pariéto-occipitale droite. *Encéphale* **40**: 122–179.

Heilman KM, Scholes R and Watson RT (1975) Auditory affective agnosia: disturbed comprehension of affective speech. *J Neurol Neurosurg Psychiatry* **38**: 69–72.

Heilman KM, Schwartz HD and Watson RT (1978) Hypoarousal in patients with neglect and emotional indifference. *Neurology* **28**: 229–232.

Hurwitz LJ and Adams GF (1972) Rehabilitation of hemiplegia: indices of assessment and prognosis. *Br Med J* i: 94–98.

Jolles J (1985) Early diagnosis of dementia: possible contributions from neuropsychology. In *Senile Dementia of the Alzheimer Type*, ed. by J Traber and WH Gispen. Springer-Verlag, Berlin, pp. 84–100.

Jolles J, Verhey FRJ, Houx PJ and Reyersen van Buuren EJ (1993) Cognitive dysfunctions in middle-aged subjects with late-onset dysthymia attending a memory clinic. In *Dementia, Depression and Forgetfulness*, ed. by FRJ Verhey. Universitaire Pers Maastricht, pp. 83–92.

Kennedy JS and Kennedy JT (1992) Cognitive disorders associated with psychiatric illnesses. In *Cognitive Disorders: Pathophysiology and Treatment*, ed. by LJ Thal, WH Moos and WR Gamzu. Marcel Dekker, New York, pp. 133–158.

King DA and Caine ED (1990) Depression. In *Subcortical Dementia*, ed. by JL Cummings, Oxford University Press, New York, pp. 218–230.

King DA and Caine ED (1996) Cognitive impairment and major depression: beyond the pseudodementia syndrome. In *Neuropsychological Assessment of Neuropsychiatric Disorders*, 2nd edn, ed. by J Grant and KM Adams. Oxford University Press, New York, pp. 200–217.

Kolb DB and Whishaw IQ (1990) *Fundamentals of Human Neuropsychology*. Freeman, New York.

Kral VA and Emery O (1989) Long term follow-up of depressive pseudodementia. *Can J Psychiatry* **34**: 445–447.

Kronfol Z, De Hamsher KS, Digre K and Waziri R (1978) Depression and hemisphere functions: changes associated with unilateral ECT. *Br J Psychiatry* **132**: 560–567.

La Rue A (1992) *Ageing and Neuropsychological Assessment*. Plenum Press, New York.

La Rue A, Watson J and Plotkin DA (1993) First symptoms of dementia: a study of relative's reports. *Int J Geriatr Psychiatry* **8**: 239–245.

Lesser IM, Mena I, Boone KB, Miller BL, Mehringe CM and Wohl M (1994) Reduction of cerebral blood flow in older depressed patients. *Arch Gen Psychiatry* **51**: 677–686.

Lezak MD (1995) *Neuropsychological Assessment*, 3rd edn. Oxford University Press, New York.

Marcos T, Salamero M, Gutiérrez F, Catalán R, Gasto C and Lázaro L (1994) Cognitive dysfunctions in recovered melancholic patients. *J Affect Disord* **32**: 133–137.

Massman PJ, Delis DC, Butters N *et al* (1992) The subcortical dysfunction model of memory deficits in depression: neuropsychological validation in a subgroup of patients. *J Clin Exp Neuropsychol* **14**: 687–706.

Mathew RJ, Wilson WH and Daniel DG (1985) The effect of nonsedating doses of diazepam on regional cerebral blood flow. *Biol Psychiatry* **20**: 1109–1116.

McAllister TW (1981) Cognitive functioning in the affective disorders. *Compr Psychiatry* **22**: 572–586.

Moffoot APR, O'Carroll RE, Carroll BS, Dick H, Ebmeier KP and Goodwin GM (1994) Diurnal variation of mood and neuropsychological function in major depression with melancholia. *J Affect Disord* **32**: 257–269.

Perris C, Monakhov K, Von Knorring L, Boskarev V and Nikirforov A (1978) Systemic structural analysis of the EEG of depressed patients. *Neuropsychobiology* **4**: 207–228.

Pizzamiglio L, Caltagirone C and Zoccolotti P (1989) Facial expression of emotion. In

Handbook of Neuropsychology, Vol. 3, ed. by L Squire and G Gianotti. Elsevier, Amsterdam, pp. 383–401.

Roberts JKA (1984) *Differential Diagnosis in Neuropsychiatry*. Wiley, Chichester.

Robinson RG, Kubos KL, Book Starr L, Rao K and Price TR (1984) Mood disorders in stroke patients: importance of location of lesion. *Brain* **107**: 81–93.

Ross ED (1981) The aprosodias. *Arch Neurol* **38**: 561–569.

Ross ED (1984) Right hemisphere's role in language, affective behaviour and emotion. *Trends Neurosci* **7**: 342–346.

Ross ED and Rush AJ (1981) Diagnosis and neuroanatomical correlates of depression in brain damaged patients. *Arch Gen Psychiatry* **38**: 1344–1354.

Saunders PA, Copeland JRM, Dewey ME *et al.* (1993) The prevalence of dementia, depression and neurosis in later life: the Liverpool MRC–ALPHA study. *Int J Epidemiol* **22**: 838–847.

Schaffer CE, Davidson RJ and Saron C (1983) Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biol Psychiatry* **18**: 753–762.

Shiffrin RM and Schneider W (1977) Controlled and automatic human information processing. II. Perceptual learning, automatic attending and a general theory. *Psychol Rev* **84**: 127–190.

Silberman EK and Weingartner H (1986) Hemispheric lateralization of functions related to emotion. *Brain Cogn* **5**: 322–363.

Starkstein SE, Robinson RG and Price TR (1987) Comparisons of cortical and subcortical lesions in the production of post-mood disorders. *Brain* **110**: 1045–1059.

Taylor MA, Greenspan B and Abrams R (1979) Lateralized neuropsychological dysfunction in affective disorder and schizophrenia. *Am J Psychiatry* **136**: 1031–1034.

Tucker DM and Liotti M (1989) Neuropsychological mechanisms of anxiety and depression. In *Handbook of Neuropsychology*, Vol. 3, ed. by L Squire and G Gianotti, Elsevier, Amsterdam, pp. 443–475.

Tucker DM, Senslie CE and Roth RS (1981) Right frontal lobe activation and right hemisphere performance decrement during a depressed mood. *Arch Gen Psychiatry* **38**: 169–174.

Von Knorring L (1983) Interhemispheric differences in affective disorders. In *Laterality and Psychopathology*, ed. by P Flor-Henry and J Gruzelier. Elsevier, Amsterdam.

Watts FN, Morris L and McLeod AK (1987) Recognition memory in depression. *J Abnorm Psychol* **96**: 273–275.

Weingartner H, Cohen RM, Murphy DL, Martello J and Gerdt C (1981) Cognitive processes in depression. *Arch Gen Psychiatry* **38**: 42–47.

Wilson H and Staton RD (1984) Neuropsychological changes in children associated with tricyclic antidepressant therapy. *Int J Neurosci* **24**: 307–312.

Wolfe J, Granholm R and Butter N (1987) Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. *J Affect Disord* **13**: 175–179.

Zoccolotti P, Caltagirone C, Benedetti N and Gianotti G (1986) Pertubation des résponses végétative aux stimuli émotionelle au cours des lésions hémispherique unilatérales. *Encephale* **12**: 263–268.

Zubenko GS, Moossy J and Kopp U (1990) Neurochemical correlates of major depression in primary dementia. *Arch Neurol* **47**: 109–214.

Zweig RM, Ross CA, Hedreen JC *et al.* (1988) The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol* **24**: 233–242.