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Brain and behavior mechanisms in depression

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ABSTRACT

Evidence that emotional behavior and depression involve particular brain structures comes from animal experiments, from imaging studies in depression and from investigations into depressive symptomatology in brain-lesioned individuals including patients suffering from Parkinson's disease (PD). Studies of depression and depression-related disorders show that there is tissue atrophy or ventricular enlargement in older depressive subjects, although differences appear to exist with respect to early and late onset depression. The most outspoken indications of brain atrophy were found in depressive subjects who had profound cognitive deficits. PET studies show changes in glucose metabolism in depressive subjects. Disorders of emotional behavior are noted in brain-injured subjects, with differences in behavior, 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 emotion. Patients with lesions of the right hemisphere show emotional indifference to stress situations. Frontal mechanisms also play an important role in emotional behavior in depression, although it is not clear what role the left versus right frontal lobe play. Research has shown that there is an 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. Future research should take this finding into consideration.

INTRODUCTION

Evidence associating emotional behavior and depression with particular brain structures has been provided by animal experiments, imaging studies of depressive subjects as well as from studies into depressive symptomatology in individuals with brain lesions, including PD patients. For instance, there is ample evidence from animal experiments that regions in the frontal lobe are essential for various aspects of social behavior which are usually compromised in depressive subjects. Animals with lesions in the orbital-frontal cortex are less socially responsive and have altered social preferences, reduced facial expression and body gestures, and reduced vocalizations

(see ref. 1 for review). Investigations into the neuropsychology of human emotional behavior also point to the involvement of frontal structures, regions in the right hemisphere being particularly important (2).

With respect to the brain structures which are involved in emotional behavior, close connections exist between the orbital-prefrontal cortex and the amygdala. An integrated anatomical system exist, 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 appears to be a distinction between subcortical and cortical structures in the medial wall and the lateral convexity of the cortical mantle (3).

Various brain structures have been implicated in depression, as a disorder of emotional behavior. As a chapter in a book on brain-behaviour mechanisms in PD, the present paper describes studies on the cerebral substrate of depression and affective behavior. These are known to be relevant aspects of the symptomatology in PD patients. Thus, implicitly, the following paragraphs refer to research which is important in understanding the cerebral substrate(s) which are involved in these aspects of PD. The evidence which relates depression to the left and the right hemisphere, and to the frontal lobes will be reviewed. The paper starts with a discussion of the relation between depression and dementia. A more elaborate discussion of several aspects of brain-behavior relations in depression will be found in the excellent reviews by Kolb and Wishaw (1), Etcoff (2), Gainotti (3),Tucker and Liotti (4) and Emery & Oxman (5). Other chapters in this volume give an excellent review with respect to the relation between PD, cognitive dysfunction, dementia and depression.

DEPRESSION AND DEMENTIA

An important problem in clinical research into depression in older subjects is the differential diagnosis between depression and dementia. Depression and dementia have a complex relation, and severe depression may present as dementia, a condition which is called 'pseudodementia' (6). However, depression and dementia may coexist, in which case, depression may be a secondary psychological reaction to the awareness of impending deterioration or may be consequent to biochemical changes in the brain (7). It is also possible that depression precedes dementia (8), or that dementia, especially subcortical dementia, manifests itself as a depression. Finally, depression and dementia may develop independently (see ref. 9).

Cognitive changes occur in both depression and dementia, and it is important to discern between these possibilities. Cognitive impairments usually accompany the mood changes of depression. This impairment may be mild to severe; when severe, it is often difficult to evaluate whether the dysfunction is caused by the depression or by a brain disorder such as

Alzheimer's disease or vascular dementia. According to several authors (see ref. 5) 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. According to Emery and Oxman (5), it is important 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, ('depressive dementia'); 3) degenerative dementia without depression; 4) degenerative dementia with different degrees of depression; and 5) dementia and depression which occur independently.

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 (10). In several longitudinal studies, depression with clear-cut cognitive deficits has been found to be a risk factor for subsequent dementia. For instance, Brown et al. (11) reported that more than 60% of patients with affective disorders developed primary degenerative dementia or vascular pathology. This figure was only 16% in schizophrenic subjects. Kral and Emery (8) 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. Other prospective studies have shown that the prevalence of depressive symptomatology is not increased in subjects who subsequently develop dementia (12). Neuropathological studies, however, report findings which suggest that subcortical centres may be pathologically changed in Alzheimer patients with depression compared to those without (13).

Thus considerable information exists which suggests that depression and dementia may share a common neuropathology and clinical phenomenology. This is important for the remainder of this chapter which discusses brain structures that are implicated in emotional behavior and depression. In research into the neurological substrate of depression, age has up till now not been an important factor. However, data suggest that it may be relevant to take age in consideration when evaluating the effect of brain lesions on affective behavior (see also chapter by Ravid and Swaab).

NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL STUDIES

Classical neuropsychology uses neuropsychological tests to yield information about the contribution of the various cortical structures to behavior. 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 (14). Goldstein et al. (15) found depressive subjects to have an inferior performance in right

hemisphere tests, as did Kronfol et al. (16). Interestingly, these latter authors 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 (17).

Other indications for an involvement of the right hemisphere in depression come from neurophysiological studies. In the 1970s, several studies reported unusual EEG or ERP findings in the right hemisphere of depressive subjects (see ref. 14). Von Knorring (18) 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. Perris et al. (19) showed that left frontal EEG activity was correlated to symptoms of anxiety whereas right frontal activity correlated the degree of depressive mood. Schaffer et al. (20) studied university students who were rated as depressed on the Beck inventory scale. They found that the depressive subjects differed from controls in showing marked alpha-desynchrony over the right frontal region. Patients with depressive dementia show a higher percentage of generalized abnormal EEGs than control subjects. In addition, some changes have been noted in the sleep-EEG of elderly persons with depression without dementia. However, there is an overlap between normal aging and depression with or without dementia (5). Tucker et al. (21) suggested that right frontal lobe activity in depression might represent an inhibitory influence which operates to suppress posterior right hemisphere functioning. Taken together, the results of studies with depressive subjects who have no organic etiology suggest the involvement of the right hemisphere. Thus this hemisphere may have a role in emotional communication and/or in the regulation of arousal and attention.

IMAGING STUDIES

Imaging studies of subjects with depression and depression-related conditions have provided evidence that both tissue density, as measured by CT-scan, and ventricle size increase with age. Substantial differences exist between demented subjects and controls, but, up till now, no CT or MRI finding is pathognomonic for primary degenerative dementia. Ventricular enlargement and tissue atrophy have also been observed on CT-scans of elderly depressive subjects (22,23). Furthermore, differences appear to exist between early and late onset depression; late onset depression appears to be more comparable to primary degenerative dementia (24,25). Pearlson et al. (26) noted that more CT-scans were abnormal in depressive patients older than 59 years than in normal subjects of similar age, and that

abnormalities were most prevalent in depressive subjects with cognitive dysfunctions.

Several authors have investigated depressive subjects with MRI and found hyperintensities which were not demonstrated with CT (27). In PET studies, quite characteristic differences were noted between late life major depression and primary degenerative dementia. Small et al. (28) made the important discovery that there is a specific pattern of glucose hypometabolism in primary degenerative dementia in the posterior parietal cortex and the adjacent temporal and occipital lobes. This pattern was not seen in patients with depression or in age-matched controls. Depressive subjects were characterized by a smaller anteroposterior gradient compared to controls (29). Finally, Baxter et al. (30,31) found metabolic asymmetries in younger patients with unipolar depression, and these asymmetries were most prominent in the posterior-inferior frontal lobe. These studies suggest a left anterolateral prefrontal cortex abnormality in major depression. The data obtained with imaging studies confirm the notion that various brain areas are involved in depression, and especially in depression with profound cognitive deficits. However, as yet it is not known which particular structures are involved.

EMOTION AND DEPRESSION IN UNILATERAL BRAIN DAMAGE

At the end of the 19th century Jackson observed that emotional language is 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 (see ref. 3 for a thorough discussion). In the 1950s, several authors observed that patients who where treated with sodium amytal in the left or right middle cerebral artery manifested a different emotional behavior. 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. Such a catastrophic reaction usually prevails in aphasic left brain-damaged patients, as noted by Goldstein (32). Subjects with right brain damage appear to be characterized by an abnormal indifference to failure (33).

Gainotti (34) 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 different. 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 on impaired speech and motor abilities. In his studies, he found that only patterns of behavior which were directly linked to the emotional storm of

the catastrophic reaction were significantly more frequent in left brain damaged patients. The indifference of patients with right brain damage was more difficult to explain. Gainotti 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.

Interesting results have been reported about the time course of disease in relation to the emotional reaction: Robinson and Price (35) showed that the incidence of depression rose from 35% immediately after stroke to more than 75% 6 months to 2 years after the stroke. Similarly, Gainotti (3) states that the indifference of patients with right hemisphere damage is confined to acute periods after the event; with time these patients become aware of their disease and, in the chronic stage, may become depressed.

On the basis of these findings and suggestions, there has been considerable research into the incidence of depression in left versus right-brain lesioned subjects. Studies which have assessed mood changes by means of standardized depression measures have by and large failed to demonstrate significant relationships between the incidence of depression and the laterality of brain injury. Likewise, the number of pathological responses to the dexamethasone suppression test as a biological marker for depression in stroke patients has failed to show any differences between left and right brain damage (36). Thus, the emotional reaction of patients with left hemisphere brain damage cannot be regarded as a sort of endogenous depression.

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 (37) or to recognize facial expressions (see ref. 2). In addition, patients with right hemisphere damage are relatively unable to express emotions by the tone of voice and facial expression (38). These findings suggest that the right hemisphere is more important than the left hemisphere, indicating that emotional language is organized especially at the level of the right hemisphere (39,40). According to this view, indifference reactions should be considered as consequence of an inability to correctly express normally experienced emotional reaction: patients with right hemisphere damage are thus as depressed as patients with left hemisphere damage but are unable to express their emotions adequately and thus give the examiner a superficial impression of indifference (41).

Thus, hemisphere asymmetries exist with respect to the organization of emotional behaviour: depressive symptomatology can result from unilateral lesions in either hemisphere. The left and right hemispheres both have a function in emotional behavior, 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 behavior.

DEPRESSION AND THE FRONTAL LOBES

Involvement of the frontal lobes 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 (4). In addition, regional cerebral blood flow is reduced after benzodiazepine treatment, especially on the right side (42). Finally, lesions in the dorsomedial frontal cortex may give rise to loss of initiative and in the extreme case akinetic mutism. Goldberg (43) suggested that this region is important for limbic contributions to emotionally significant actions. The cingulate cortex, which receives particularly rich norepinephrine connections, may be involved in this respect.

Interpretation of the different contributions of the left and right hemispheres (see above) has been complicated by the findings of Robinson et al. (44). 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 (45) and suggest that the typical effect of unilateral lesions is to inhibit the hemisphere's normal emotional orientation. However, there is still uncertainty about the possible role of substructures within the frontal lobe such as the orbital region and the dorsolateral regions, and about the different functions of the left and right frontal lobes. Possibly relevant in this respect is the finding that monoaminergic pathways may be asymmetric. For instance, Gottfries et al. (46) found that CSF levels of a serotonin metabolite were correlated to particular variables of event-related potentials in the right hemisphere but not in the left hemisphere. Interestingly, Mandell and Knapp (47) found that asymmetries in left and right hemisphere serotonin levels in mouse brain were enhanced by cocaine and decreased by lithium. Similar findings have been reported for noradrenalin (NA): Pearlson and Robinson (48) found that suction lesions of right but not left frontal lobe resulted in bilaterally reduced NA levels in the cortex and locus coeruleus. In addition, Oke and coworkers (49) found greater amounts of NA in most regions of the right part of the thalamus of the human brain. More research is necessary to understand this interesting relation between monoamines, brain laterality and depression in more detail.

CONCLUSIONS

There are several theories which try to explain the emotional behavior of right and left brain-damaged subjects. One theory states that there is a different hemispheric specialization for positive and negative emotions; however, Gainotti (3) 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 (3). 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 (50). 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 (51). These patients show emotional indifference to stress situations. Zoccolotti et al. (52) found that these subjects show only very weak sympathetic and parasympathetic reactions to emotional stimuli. Thus, the indifference displayed by these patients is a reflection of both an inability to express an emotional experience and a diminished capacity to feel affect.

Taken together, both hemispheres appear to be involved in depression although the right hemisphere is dominant in this function. 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 behavior and depression. The specific contributions of left versus right frontal 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 (eg. frontal lobes, the hemispheres) and biochemical measures on the other. The finding of asymmetry in monoaminergic fibres is not convincing but points to a potentially important area of investigation which relates biochemical psychopharmacology to the neuropsychology of depression. Imaging studies in depression may prove relevant in this respect in the future.

Finally, consideration should be given to the continuum between depression and dementia. The cognitive deficits which are commonly seen in depression (54-56), especially in old age, may be a determining factor with respect to structural or functional changes in the brain as measured by CT, MRI, SPECT or PET. Due consideration should be given to these findings in future studies into brain-behavior relationships in depression. More knowledge of this relation may prove fruitful for an understanding of the cerebral substrate(s) underlying mental dysfunction in PD.