Asymmetries of Activation and Arousal in Psychopathology

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In the recent research on brain function and psychopathology, an important issue has been differential hemispheric function in psychiatric disorders. In her suggestions for the organization of this conference, Dr. Koukkou has suggested that we emphasize the theoretical considerations that direct our current research hypotheses. Although comparing results across research laboratories requires methodological consistency, attempts to clearly formulate hypotheses should facilitate communication across laboratories in both the design of research and interpretation of results.

When it is observed that certain hemispheric asymmetries are characteristic of a certain psychiatric disorder, the question becomes the implication of this asymmetry for the patient’s functioning. Perhaps the initial implication is that the lateralization results from some insidious brain lesion, which produces both the brain asymmetry and the psychopathological symptomology. When the psychiatric symptoms are secondary to known brain dysfunction, this interpretation seems reasonable.

However, with other evidence of hemispheric asymmetries in psychiatric patients, there are no known brain lesions. Perhaps more importantly, at least some of the asymmetries have been observed to appear or remit as a function of the patient’s affective status. In this case, the hemispheric asymmetries seem to result from some intrinsically asymmetric patterns of brain activation associated with the disordered emotional state. In depression, for example, several studies have suggested impaired functioning of the right hemisphere [Goldstein et al., 1977; Kronfol et al., 1978]. When treatment results in clinical improvement, the right hemisphere’s performance capacity may also improve [Kronfol et al., 1978]. Tucker et al. [1981] have observed that normal depression may also inter-
fere with right hemisphere function specifically. Students reporting greater depression also report poor visual imagery. Hypnotic induction of a depressed mood in normals results in impairment of visual imagery but not arithmetic performance. EEG changes during a depressed mood were specific to the right hemisphere [Tucker et al., 1981]. Thus, in clinical and normal populations, depression seems associated with right hemisphere function, but with changes in the arousal status of that hemisphere rather than a neurophysiologic disorder.

In schizophrenia, concepts of brain activation are also important for interpreting the observed hemispheric asymmetries. A left hemisphere dysfunction in schizophrenia [Flor-Henry, 1976] seems to be associated with overactivation of that hemisphere [Flor-Henry 1976; Gur, 1978]. Although changes with affective state did not seem to be as marked in schizophrenics as with depressed patients, an abnormal sensitivity of the right ear to auditory stimuli [Gruzelle and Hammond, 1976] observed during schizophrenics’ first visit to the laboratory did not appear when the patients returned to the laboratory on successive occasions, suggesting that the high left hemisphere activation was specific to the initial encounter with the laboratory procedures. In several studies with university students, we have observed increased left hemisphere activation [Tucker et al., 1978] and evidence of increased left hemisphere contribution to cognition [Tyler and Tucker, 1982] in trait anxious students. Although we can draw only limited parallels between the left hemisphere activation in trait anxiety and that in schizophrenia, the findings with normals suggests that hemispheric asymmetries involving left as well as right hemisphere activity are influenced by normal emotional processes.

To interpret the current data on hemispheric asymmetries in normal and abnormal emotion thus seems to require some theoretical model how emotional processes influence brain asymmetry. Another important line of evidence that requires concepts of brain activation and arousal systems comes from the initial suggestions that primary neurotransmitter systems in the human brain may be asymmetric in their anatomy and function [Tucker, 1981].

Tucker and Williamson, [in preparation] have attempted to formulate a model of regulatory systems in the brain that operate as a function of the patient’s emotional state and that exert specific influences on attentional processes. This formulation begins with a model of attentional control described by Pribram and McGuinness [1975], then elaborates this attentional control model based on evidence of the characteristics of the neurot-
ransmitter-specific pathways that support attentional control. The apparent asymmetry of these systems in the human brain suggests implications for differential hemispheric function in emotional processes.

In their discussion of the control circuits of the brain that determine the brain's activity level, Pribram and McGuiness [1975] differentiate between an activation system controlling motor readiness and an arousal system that is responsive to perceptual input. The activation system involves the dopaminergic and cholinergic systems of the basal ganglia and maintains a tonic level of brain activity to support motor readiness. Whereas motor preparation is the observable function of this circuitry in lower organisms, there seem to be higher order attentional functions served by this system in the human brain. The tonic level of brain activity supported by the activation system is required for the active, internally-directed attention in vigilance. In contrast, a different form of neural control is offered by the arousal system. McGuinness and Pribram [1980] suggest that the noradrenergic and serotonergic pathways are important to the role of arousal in mediating the brain's phasic response to perceptual input. At a primitive level, the operation of the arousal system can be seen as an orienting response; at higher levels the arousal system is involved in the increases in neural activity with the perception of novel or rewarding stimuli.

Drawing from the qualitatively distinct effects of pharmacologically augmenting brain activity via dopaminergic versus noradrenergic pathways in animal experiments. Tucker and Williamson [in preparation] have attempted to characterize the specific changes in the brain's information processing that occur with activation versus arousal. Dopaminergic activation seems to introduce a redundancy bias on the brain's information flow. Animals with pharmacologic augmentation of this system show a restricted range of behavior; with increased activity in this circuitry, behavioral stereotypy eventually appears. This contrasts with an opposite bias on the brain's information flow supported by noradrenergic arousal. The arousal system seems to respond to novel input, as in the orienting response, and to rapidly decrease its response to repetitive stimulation.

These opposite biases on information processing resultant from basic control systems in the brain seem to offer important modes of attentional, and cognitive, control. Perhaps more important to hypotheses of brain function in psychopathology, there also seem to be distinct affective characteristics of each of these neural control systems. Since the initial evidence suggests that these systems may be asymmetric in the human brain, the emotional and motivational characteristics of the neurotransmitter sys-
tems may be important to interpreting lateral asymmetries in psychopathology.

Several features of the activation system suggest that as it operates it may be experienced subjectively as anxiety. A common symptom of anxiety is muscle tension. Increased motoric activity often accompanies high anxiety. In persons who are chronically anxious, such as obsessive-compulsives, anxiety is accompanied with a stereotypy of motoric function that is remarkably similar to that of experimental animals with pharmacologic stimulation of the dopamine system. In humans whose chronic abuse of amphetamines augments dopaminergic systems, motor stereotypes are also observed [Ellinwood, 1967] as well as an anxious, vigilant attentional mode. With continued amphetamine abuse, this hypervigilance may produce symptoms of paranoid schizophrenia [Ellinwood, 1967].

There is some direct evidence that the dopaminergic activation system is left-lateralized. Gottfries et al. [1974] observed in a sample of psychiatric patients that a dopamine metabolite in the cerebral spinal fluid correlated with evoked potentials from the left but not right hemisphere. Since the dopamine pathways are thought to operate in conjunction with cholinergic fibers, it is relevant that an enzyme indexing cholinergic activity has been observed to be higher in the left temporal than right temporal region [Kononeko, 1980]. In both schizophrenics and normals, phenothiazines, thought to achieve their clinical effect through blocking dopaminergic neurotransmission, have been found to target left hemisphere activity specifically. Serafetinides [1973] observed the high activation of the left hemisphere in a sample of schizophrenics to normalize following chlorpromazine treatment. Laurian et al. [this volume] have reported stronger left than right hemisphere EEG changes with phenothiazine administration to normals.

Although the direct neurochemical evidence is still tentative, perhaps more compelling is the indirect evidence of the importance of the activation attentional control system to left hemisphere cognitive operations. Amphetamine abusers have been observed to operate with an excessively focal attentional mode [Matthysse, 1977], and show evidence of compulsively analytic cognitive operations [Ellinwood, 1967] suggestive of a preponderance of left hemisphere cognitive operations. Since the left hemisphere is especially important to the control of complex motor operations [Heilman, 1979], it seems reasonable that the left hemisphere would draw on the motor regulatory system for attentional control. Under the assumption that anxiety is the affective characteristic of dopaminergic activation, a left-lateralization of the system would be consistent with the evidence of left
hemisphere activation in trait anxious normals and obsessive-compulsive personalities.

There may also be important affective characteristics of the noradrenergic arousal system. In the animal literature, the locus ceruleus norepinephrine pathway is thought to mediate reward effects [Mason and Fibiger, 1979]. The catecholamine hypothesis of the affective disorders suggests that mania is associated with high, and depression with low, levels of noradrenergic activity centrally [Shildkraut et al., 1978]. A number of drugs used as euphoriants have been observed to augment noradrenergic neurotransmission, including cocaine and alcohol [Cooper et al., 1974]. The short-term mood elevation following amphetamine administration has been observed to be associated with increases of norepinephrine metabolites in the urine; the depressive phase following the initial euphoriant effects is associated with depleted levels of noradrenergic metabolites [Shildkraut et al., 1978]. It seems reasonable to speculate that the attentional control effects of the arousal system would be augmented in a rewarding context. The organism opens up sensory channels and orients to novel features of the rewarding stimulus array.

The initial indications that norepinephrine may be especially important to the functioning of the right hemisphere [Oke et al., 1978] may be consistent with the evidence of changes in the right hemisphere’s level of arousal and functional capacity associated with the mood changes of the affective disorder [Flor-Henry, 1976; Kronfol et al., 1978]. McGuinness and Pribram [1980] have suggested that norepinephrine operates on a serotonergic matrix to mediate the arousal system. In the Gottfries et al. [1974] study of psychiatric patients, a serotonin metabolite in the cerebrospinal fluid correlated with right but not left hemisphere evoked potentials. In studies of mice, Mandell and Knapp [1979] observed that cocaine increased the asymmetry of serotonin, while lithium decreased this asymmetry. Flor-Henry and Koles [1981] observed that lithium administered to normals produces EEG slowing in the right hemisphere specifically. Hallucinogens, thought to achieve their psychotropic effects through interfering with normal serotonin metabolism, have also been observed to target the right hemisphere [Goldstein et al., 1963].

The complexities of the neurophysiological characteristics of the neurotransmitter pathways have caused difficulty in interpreting the effects of psychopharmacologic intervention in psychiatric patients, and will also pose difficulties for interpretations of the functional significance of asymmetries of neurotransmitter pathways in the human brain. Although it may
be premature to interpret this neurochemical evidence, concepts of the asymmetries of attentional control systems in the brain may prove helpful to attempts to interpret data on hemispheric asymmetry in disordered emotional states.

References


