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Emotional consequences of focal brain lesions: an overview

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Introduction

The brain mediates all cognitive activities and emotional experiences. Cognitive dysfunction following brain injury or associated with brain disease, while still incompletely understood, has been extensively studied. The aphasias, acalculias, and apraxias associated with left hemisphere injury (Levin, Goldstein and Spiers, 1993; Heilman and Gonzalez-Rothi, 1993; Benson and Ardila, 1996), the several types of agnosias associated with unilateral and bilateral brain injury (Bauer, 1993), and the amnestic syndromes associated with hippocampal dysfunction (Bauer, Tobias and Valenstein, 1993) have been the subject of numerous investigations. The emotional consequences of focal brain injury have been much less well researched. The relationships between brain dysfunction and psychosis, depression, mania, anxiety, and paraphelia are in the early phases of pathogenetic study, and more subtle changes in emotional function (such as apathy, irritability, disinhibition, and lability) are also in the initial phases of definition and descriptive linkage to regional brain dysfunction.

Investigation of the emotional correlates of regional brain dysfunction is encumbered by methodological challenges beyond those encountered in studying the relationship between cognitive impairment and brain dysfunction. Emotional disturbances are more influenced by the premorbid personality of the individual, more variable over time, and more difficult to define consistently in research investigations. On the other hand, the emotional consequences of brain dysfunction are a source of enormous distress to the patient and to the patient's family members. They may be more easily impacted through pharmacologic interventions and their importance to patient management cannot be underestimated. The recognition and treatment of these conditions constitute an important dimension of patient care. In addition, a comprehensive understanding of brain–behavior relationships depends on progress in defining the correlations between regional brain dysfunction and human emotion to complement our growing understanding of the relationship of regional brain dysfunction and intellectual disorders. The interaction of emotional and cognitive disorders also warrants study.

Regional brain dysfunction is the focus of interest in this chapter and in this volume. The pitfalls of assessing regional roles in cognition and emotion must be acknowledged. As for cognitive disorders, the occurrence of a deficit or the appearance of new, neuropsychiatric symptoms (e.g., psychosis, depression) in concert with the occurrence of focal brain lesions does not necessarily imply that a particular brain region is uniquely or even primarily involved with that specific cognitive or emotional activity. Nevertheless, there has been an encouraging concordance between models of regional brain function derived from observing patients with focal lesions and the models derived from functional brain imaging (Frith and Dolan, 1997). Extension of the lesion model to understanding human emotional function is an important first step toward establishing a neuroanatomy of emotion that can be challenged, confirmed, and remodelled based on neuroimaging, neurophysiological, neurochemical, neuropharmacological, and neuropathological research.

Focal lesions may produce local effects or may cause symptoms by disrupting functional neuronal networks. Brain regions are linked through white matter tracts into extensive circuits that mediate information processing. Some focal lesions produce signature syndromes with unique clinical symptoms arising from specific brain lesions; other brain lesions have no unique associated syndromes, and several brain lesions may produce similar clinical abnormalities. Extensive processing networks mediate the emotional functions of the nervous system, and focal lesions within the networks tend not to produce discrete localizable syndromes. The limbic system and frontal–subcortical networks are two examples of extensive brain organizational systems that mediate emotional functions (Cummings, 1993a; Mega et al., 1997).

This chapter provides an overview of the regional relationships between emotional function and brain organization. Definitions and distinctions between fundamental and instrumental functions, the integration of executive and emotional functions, relevant anatomy of the limbic system and frontal–subcortical circuitry, regional neurochemical influences based on the distribution of receptors, and clinical–regional behavioral correlations are emphasized.

Definitions of emotion

Many definitions of emotion have been proffered and none has proven completely satisfactory or has achieved consensus endorsement. *The Concise Oxford Dictionary* (Thompson, 1995) defines emotion as strong mental or instinctive feeling, such as love or fear. Rolls (1995) adopted a behavioral psychological approach in defining emotions as 'states produced by instrumental reinforcing stimuli.' Pribram and Melges (1969) recognized that there are two conceptual frames of references for

emotions: (1) the social–behavioral, which includes the subjective or intrapsychic aspects of emotion, such as psychodynamic approaches, and (2) the physical, chemical, and neurological frame of reference emphasizing a physiological and neurobiological approach to emotions. Heilman (1983) adopted an operational approach to the neuropsychological study of emotion, emphasizing subjective feelings that can be expressed and behavioral and physiological changes that can be measured. Feyereisen (1989) explicitly acknowledged that 'the category of emotion may formally be described as fuzzy.' He noted different dimensions of emotion, including behaviors such as laughing, being frightened or crying; physical and mental states, such as sexual desire, doubt, and envy; and mental states such as moods or feelings of pleasure or distress.

Heilman and colleagues (Heilman, Bowers and Valenstein, 1993) also noted that there are several ways in which neurological disorders and emotions may interact: (1) changes in emotional experience and behavior can be caused directly by diseases of the nervous system; (2) patients with neurological diseases may have an emotional response to their illness, such as becoming anxious or depressed; (3) emotional states may enhance neurological symptoms, such as when anxiety aggravates a tremor; and (4) emotional states may induce neurological symptoms, such as when stress induces headaches.

For the purposes of this chapter, emotion will be defined as the experience and expression of feeling states. This definition includes sadness, elation, changes in motivation, reduced empathy or an inability to emphathetically experience another's predicted feeling state, irritability, lability, fear, anxiety, sexual desire (lust), and feelings of persecution or threat of personal harm. There are many dimensions of emotion that influence the final feeling state of the individual. These include the developmental experiences of the individual, the physiological aspects of arousal associated with many emotions, the visceral changes present with many escalated feeling states, the interaction with cognition and memory, as well as the anatomical and biochemical aspects of emotion emphasized here. Many emotions occur on a continuum from mild to extreme (such as from happiness to elation to grandiosity and mania). In the normal condition, the experience and expression of emotion are conjoined in the laughter of happiness or the crying of sadness; in neurological illnesses, experience and expression of emotion may be disassociated, such as occurs in pseudobulbar palsy, the flattened affect of parkinsonism, or the loss of inflection in aprosodia.

Another definition that bears on the terminology of this chapter is *mood*, defined as a pervasive and sustained emotion that colors the perception of the world. *Affect* refers to a pattern of observable behaviors that is typically the expression of a subjectively experienced feeling state. *Anxiety* is the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms

of tension. *Grandiosity* is an inflated appraisal of one's worth, power, knowledge, importance or identity. *Psychosis* may be defined restrictively as delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature (American Psychiatric Association, 1994).

Instrumental and fundamental functions

Albert (1978) described the neuropsychological dichotomy of instrumental functions versus fundamental functions. In this approach, instrumental functions refer to activities of communication, perception, and praxis, and deficits in these functions produce the clinical syndromes of asphasias, agnosias, and apraxias. Fundamental functions include memory, the ability to learn new information, set shifting, and rate of information processing. Fundamental functions were posited to facilitate instrumental functions.

Cummings (1990) expanded the fundamental/instrumental dichotomy to include anatomic, phylogenetic, ontogenetic, and biochemical dimensions. Instrumental functions were expanded to include language, perceptual recognition, praxis, and calculation, whereas fundamental functions included timing, arousal, attention, motor programming, motivation, mood, and emotion. The corresponding neuropsychological deficits associated with instrumental functions include aphasia, agnosia, apraxia, and acalculia. Disorders of fundamental function include slowing, forgetfulness, executive dysfunction, depression, apathy, and emotional disorders. Thus, this dichotomy of instrumental and fundamental functions created an approach to emotion with anatomic and physiologic implications.

Abnormalities of instrumental functions are prominent in cortical dementias, whereas fundamental functions are associated with subcortical, limbic, and frontal disorders. Instrumental functions are mediated by the neocortex, particularly temporal and parietal neocortex, whereas fundamental functions are mediated by prefrontal cortex, frontal–subcortical circuits, and the limbic system. White matter tracts subserving instrumental functions are discrete, well-myelinated, long, intrahemispheric and interhemispheric fibers, whereas those mediating fundamental functions are shorter, less well-myelinated projections that are more diffuse. Organizationally, instrumental functions are serial connections of functional units with well-lateralized and highly specialized functional modules. The organization of fundamental functions depends on parallel structures with overlapping functions that are less modularized. Interruption of the serial organization of instrumental functions produces signature syndromes, such as discrete aphasias, agnosias or apraxias, whereas disruption of the organization of fundamental functions produces circuit-related disorders, such as depression, apathy, and irritability and impaired executive function, that lack unique local significance.

Phylogenetically, instrumental functions are a recent evolutionary acquisition that are most well developed in humans. Fundamental functions are more primitive and present in the triune organization of the reptile brain. The ontogenetic development of instrumental functions is incomplete at birth and continues throughout childhood with maturation of the central nervous system (CNS). The anatomical structures underlying fundamental functions are largely functional at birth or soon thereafter.

The principal transmitters of instrumental functions include acetylcholine, glutamate, and gamma-aminobutyric acid (GABA). Fundamental functions are influenced more heavily by modulatory transfers, such as dopamine, norepinephrine, serotonin, and acetylcholine.

Disorders of instrumental function are largely deficit syndromes with an impairment of premorbid skills, whereas abnormalities of fundamental function may be 'productive,' with the appearance of new symptoms in concert with the CNS dysfunction, including depression, mania, psychosis, and anxiety. The existence of long, white-matter tracts associated with instrumental functions is the basis for the occurrence of disconnection syndromes that underlie some instrumental disturbances (apraxia; alexia without agraphia; conduction aphasia), whereas disconnection syndromes are unusual as the etiology of fundamental disorders.

Mesulam (1985) introduced an alternative complementary terminology suggesting that instrumental functions are 'channel dependent' whereas fundamental functions are 'state dependent.' The anatomy of channel functions is point-to-point connectivity. In state-dependent functions, there are more diffusely organized projections from the intralaminar thalamic nuclei, cholinergic neurons of the basal forebrain, neurons of the lateral and medial hypothalamus, serotonergic neurons, reticular cholinergic neurons, noradrenergic neurons, and dopaminergic neurons. These systems are characterized by a relatively small group of neurons positioned to modulate the information processing of wide regions of the cortex and thalamus. Mesulam (1985) emphasized that these modulatory projections could influence many neural operations and are poised to mediate aspects of mood, motivation, memory, arousal, and vigilance. He noted that pathways mediating state-dependent functions could influence channel-dependent functions without altering the content of the transmitted information.

Instrumental, fundamental, and executive functions

The division of neuropsychological functions into instrumental and fundamental types was a conceptual advance that has had substantial heuristic value. Current advances in understanding the behaviorally relevant organization of the nervous system allow a reformulation and extension of this framework. Progress in research

concerning frontal lobe functions and frontal–subcortical circuits facilitates the reformulation of the neurological basis of emotions (Stuss and Benson, 1986; Cummings, 1993a). The original conception of fundamental functions encompassed activities of both the limbic–reticular system and the frontal–subcortical system. Sufficient information is now available to allow the recognition of three distinct domains of mental function: instrumental, fundamental, and executive/integrative. In this framework, instrumental activities include language, perceptual recognition, and praxis. Fundamental functions include speed of processing, mood, motivation, and emotion. Executive functions include abstraction, sequencing, attentional focusing, and responses to changing contingencies. When the instrumental domain is dysfunctional, the corresponding clinical syndromes associated with instrumental dysfunction are aphasia, agnosia, and aphraxia. Those disorders accompanying fundamental function disturbances include bradyphrenia, amotivational states, reduced arousal, and a variety of emotional disorders. Abnormalities of executive function include concrete thinking, distractibility, and environmental dependency. Lesions can produce signature syndromes indicative of the interruption of specific instrumental functions, whereas lesions of both fundamental and executive systems produce circuit-related symptoms.

Neuropsychiatric disorders associated with instrumental function include anosognosia; those associated with fundamental dysfunction include apathy, irritability, depression, mania, anxiety, and psychosis; and those associated with executive dysfunction may include loss of empathy. Disruption of emotional function associated with abnormal instrumental activities encompasses disorders of emotional comprehension (such as receptive aprosodia and the inability to interpret emotional facial expressions); disturbances of fundamental function produce disorders of emotional experience such as mood abnormalities and the abnormal experience of threat; disorders of emotional function associated with frontal–subcortical disorders include executive aprosodias, flattened affect, and pseudobulbar palsy.

Three dementia syndromes have also been recognized: cortical dementias (especially Alzheimer's disease) associated with disturbances of instrumental function; limbic dementias associated with temporal lobe syndromes and amygdala involvement; and frontal and subcortical syndromes associated with frontotemporal degenerations and basal ganglia diseases. Motor syndromes representative of instrumental dysfunction are the apraxias, whereas extrapyramidal syndromes are characteristic of disorders with fundamental dysfunction, and pyramidal syndromes occur with lesions of the final common pathways associated with the processing of executive function. Disconnection syndromes are typical of the instrumental level of organization and include apraxia and alexia without agraphia. Disconnection syndromes are not typical of fundamental or executive functions. Table 1.1 summarizes the clinical aspects of this tripartite approach to mental functions.

Table 1.1. Clinical features of syndromes associated with instrumental, fundamental, and executive dysfunction

Characteristics	Instrumental	Fundamental	Executive/integration
Neuropsychological functions	Language Perceptual recognition Praxis	Speed of progression Mood Motivation Emotion	Abstractions Sequencing Attentional focusing Response to changing contingencies
Neuropsychological disorders	Aphasia Agnosia Apraxia Signature syndromes	Bradyphenia Avolition Reduced arousal Limbic system syndromes	Concrete Distractable Environmental dependency Frontal–subcortex circuit syndromes
Neuropsychiatric conditions	Anosognosia	Deficit – apathy Productive: irritability depression mania anxiety psychosis obsessive–compulsive disorder	Deficit – loss of empathy
Emotional disorders	Disorders of emotional vocal comprehension Receptive aprosodia Aprosonosia Difficulty understanding emotional facial expressions	Disorders of emotional experience – mood, threat	Disorders of emotional expression (aprosodias) and control (pseudobulbar palsy)
Dementia associated	Cortical dementia (especially Alzheimer's disease)	Limbic system dementia	Frontal and subcortical dementia
Motor syndrome associated	Apraxia	Extrapyramidal disorder	Pyramidal syndromes
Disconnection syndrome	Apraxias Alexia without agraphia	None	Locked-in syndrome (disconnection of descending pyramidal pathways)

Instrumental functions are mediated predominantly by the posterior heteromodal cortical regions. The cortical regions associated with fundamental functions include the cingulate cortex, orbitofrontal cortex, and hippocampus. Cortical regions associated with the executive function include the dorsolateral prefrontal heteromodal areas. Thalamic nuclei associated with each of the three functions include the pulvinar (instrumental function), the anterior thalamic nuclei (fundamental function), and the dorsal medial nuclei (executive function). Basal ganglia have little role in instrumental functions, but the ventral striatum, nucleus accumbens, and pallidum are intimately involved in mediating fundamental functions, and the dorsal striatum and pallidum are involved in mediating executive functions. The white matter tracts underlying instrumental function are long, well-myelinated intrahemispheric and interhemispheric fasciculi. White matter tracts related to fundamental functions include the medial forebrain bundle and other shorter, less well-myelinated tracts. White matter tracts mediating executive functions include the frontal–basal ganglionic connections and thalamofrontal projections.

The anatomical organization associated with instrumental functions is characteristically a serial linking of specialized modules. Hemispheric specialization is most marked at this level of CNS organization. In contrast, parallel circuits are characteristic of both fundamental and executive functions. There is little hemispheric specialization or lateralization of fundamental functions and a limited hemispheric specialization of executive functions.

Phylogenetically, fundamental functions are the most primitive; instrumental functions are relatively recent; and executive functions are nearly unique to humans and the most recent evolutionary acquisitions. Similarly, fundamental functions are functional at birth, whereas instrumental functions are incomplete at birth and develop throughout childhood. The anatomical pathways underlying executive functions are incompletely functional at birth, and development continues through early adulthood.

The principal neurotransmitters mediating instrumental functions are GABA and glutamate, mediating direct, fast-acting interneuronal communication. Fundamental functions depend more heavily on projection neurons of the cholinergic, dopaminergic, serotonergic, and noradrenergic systems. These are modulatory neurons that exert tonic influences. In the executive function system, both fast-acting and tonic transmitters are well represented in the circuitry.

This approach has important implications for treatment. This is limited response to pharmacologic treatment of instrumental syndromes such as aphasia, agnosia or apraxia. Emotional disorders associated with fundamental dysfunction respond well to pharmacotherapy. These disorders include psychosis, depression, mania, and anxiety. At the executive level, abnormalities of abstraction, sequencing, and environmental dependency are treatment resistant. Table 1.2 summarizes the neurobiologic aspects of the tripartite approach to mental functions.

Table 1.2. Neurobiologic characteristics of instrumental, fundamental, and executive functions

Characteristics	Instrumental	Fundamental	Executive/integration
Gray matter structures			
Cortical	Posterior heteromodal cortex (six-layered)	Hippocampus cingulate orbitofronto cortex (three-layered and transitional)	Dorsolateral prefrontal heteromodal cortex (six-layered)
Thalamus	Pulvinar	Dorsomedial anterior	Dorsomedial
Basal ganglion	None	Ventral striatum Pallidum	Dorsal striatum Pallidum
White matter tracts	Long, intrahemispheric and interhemispheric association fibers	Medial forebrain bundle; mostly shorter tracts	Frontal–basal ganglia and thalamo-frontal connections
Organization	Serial linking of modules Hemisphere specialization (lateralization)	Little hemisphere specialization	Limited hemisphere specialization
Phylogeny	Recent evolutionary development	Primitive	Most recent evolutionary acquisition
Ontogeny	Incomplete at birth; development continues through childhood	Functional at birth	Incomplete at birth, development continues through early adulthood
Neurotransmitters			
Type	GABA Glutamate Acetylcholine	GABA Glutamate Acetylcholine Dopamine Serotonin Norepinephrine	GABA Glutamate Acetylcholine Dopamine Serotonin Norepinephrine
Primary function	Direct information transfer	Modulation	Information transfer and modulation
Speed	Fast acting	Tonic	Fast acting and tonic
Organization	Local circuit neurons	Projection neurons (brainstem and basal forebrain nuclei with widespread projections)	Local circuit cortical neurons Patch/matrix arrangement in striatum Regions receive projection neurons
Pharmacological treatment	Limited response	Responsive	Limited response

This organization of mental functions into three domains facilitates a more comprehensible approach to the discussion of the emotional disorders emphasized in this volume. The principal emotional disorders associated with instrumental dysfunction are anosognosia and associated anosognosic phenomena. There are many emotional abnormalities associated with disorders of fundamental function, including deficit syndromes such as apathy and avolition and productive syndromes such as depression, mania, psychosis, and anxiety. Emotional disorders associated with executive dysfunction have been less well studied, but empathy (the ability to imagine the emotional experience of another) is a candidate emotion for the executive system.

The anatomy described here sets up a stimulus–response channel system with thalamocortical projections mediating sensory input; long intrahemispheric projections, as well as interhemispheric projections, connecting the posterior heteromodal to frontal heteromodal cortex; and projections out via the basal ganglia and thalamus to primary motor cortex with eventual projections to bulbar and spinal motor neurons. This sensory association–motor arc is largely based on well-myelinated, long axons with excitatory and inhibitory amino acid transmitters. Information entering the nervous system, however, also spreads to the limbic cortex where emotional valence as well as memory is integrated to give the stimulus meaning and to provide a context of experience for the response. The integration of this historical–emotional information with the primary stimulus occurs in frontal heteromodal cortex and the volitional act is further modified in frontal–subcortical systems prior to exit from the nervous system via the descending pyramidal system. Thus, the frontal cortex in this schema becomes the site for the integration of emotional and cognitive information, as well as the principal region for the initiation of volitional activity.

Anatomy of emotion

The limbic system is the principal anatomical substrate of emotion. Both Thomas Willis in 1664 and Paul Broca in 1887 called attention to the anatomy of the limbic lobe comprising the cortical border that encircled the brainstem (Mega et al., 1997). Neither of these authors, however, attributed emotional function to this brain region. It was Papez (1937) who surmised that the limbic structures served the 'stream of feeling' underlying emotional expression and experience. Papez included the hippocampus, fornix, anterior thalamus, and cingulate gyrus as principal anatomical components of the limbic system.

The concept of the limbic system has been progressively expanded to include multiple brain structures in both subcortical and cortical brain regions. Table 1.3 provides a summary of structures currently included in the expanded concept of