Frontal lobe syndrome reassessed: comparison of patients with lateral or medial frontal brain damage

Sergio Paradiso, Eran Chemerinski, Kazim M Yazici, Armando Tartaro, Robert G Robinson

Abstract

Examination of mood and behaviour changes after frontal damage may contribute to understanding the functional role of distinct prefrontal areas in depression and anxiety. Depression and anxiety disorders, symptoms, and behaviour were compared in eight patients with single lateral and eight patients with single medial frontal lesions matched for age, sex, race, education, socioeconomic status, side, and aetiology of lesion 2 weeks and 3 months after brain injury. DSM IV major depressive and generalised anxiety disorders were more frequent in patients with lateral compared with medial lesions at 2 weeks but not at 3 months. At 3 months, however, patients with lateral damage showed greater severity of depressive symptoms, and greater impairment in both activities of daily living and social functioning. At initial evaluation depressed mood and slowness were more frequent, whereas at 3 months slowness, lack of energy, and social unease were more frequent in the lateral than the medial group. Patients with lateral lesions showed greater reduction of emotion and motivation (apathy) during both examinations. Medial frontal injury may fail to produce emotional dysregulation or may inhibit experience of mood changes, anxiety, or apathy. Lateral prefrontal damage may disrupt mood regulation and drive while leaving intact the ability to experience (negative) emotions.

Keywords: frontal lobe; depression; anxiety; apathy; disinhibition

Prefrontal dysfunction has been found in mood disorders and anxiety. Neuroimaging, however, has failed to consistently identify specific locations and types of functional changes within the prefrontal cortex associated with depression or anxiety.

The prefrontal lobe has been divided into dorsal lateral, medial, and orbital cortices. Patients with lateral prefrontal damage may show apathy, indifference, speech poverty, and poor executive abilities, and with acute left hemispheric injuries, major depression. Damage to the orbital prefrontal cortex may lead to poor impulse control, puerility, euphoria, increased energy, aggression, and violence. The orbital cortex can be divided into medial and lateral subregions. The medial subregion connects with limbic areas whereas the lateral subregion connects with the primary and sensory association cortex. For its limbic connections, the medial prefrontal wall resembles the medial subregion of the orbital cortex. Large lesions of the frontal medial walls (and anterior cingulate) have been associated with apathy but emotional and instinctual disorders as well as sociopathy have been associated with damage to the confluence of the medial and orbital cortex.

Much of our knowledge of the psychiatric consequences of lesions involving the medial prefrontal cortex in humans is based on case report studies. This literature tends to select positive findings. We therefore report on the first systematic examination of depression, anxiety, apathy, disinhibition, and psychosocial functioning at 2–4 weeks and at 3 months after injury in patients with lateral or medial damage to the prefrontal cortex. We hypothesised that medial frontal injury would lead to euphoria and agitation, whereas lateral injuries would lead to depression. No selective association of either medial or lateral lesions with apathy was predicted.

Methods

Data from about 360 CT scans were reviewed by a neurologist, a neuroradiologist (AT), and a psychiatrist with experience in neuroanatomy (KY) blind to the other measures. Scans were from a consecutive series of prospectively evaluated patients admitted to the Shock Trauma Center of the Maryland Institute of Emergency Medical Services System (MIEMSS) for traumatic brain injury, or the University of Maryland Hospital for acute stroke, or the Youngker’s Rehabilitation Hospital in Des Moines, Iowa following acute stroke.

The inclusion criterion was a single lateral or medial (including anterior cingulate gyrus)
Medial and lateral frontal lobe damage

frontal lesion as ascertained by all raters. Scans were performed using GE 9900, AS and E 500, and EMI 1010 scanners (stroke patients from Baltimore), GE 1010 (trauma patients from Baltimore), and Picker international 1200 or Somaton plus 24 B30B (stroke patients from Iowa) without contrast at 0 degrees angle from the canthomeatal line. Assessment of lesion location involved transposing the area of ischaemia as visualised on CT onto standard templates of axial brain slices (figure).14

Exclusion criteria were: history of other neurological disorders or life threatening physical illness, CT evidence of previous brain injury, decreased level of consciousness or medical instability at the time of interview, aphasic disorders (not able to follow a three stage command or complete the first part of the token test), penetrating head injury, associated spinal cord injury, multiple non-CNS involvement, or secondary brain damage due to severe hypotension or hypoxia.

Thirty two patients with lateral and 14 patients with medial lesions met these criteria. Eight of fourteen patients with medial frontal lesions were matched as closely as possible for age (±5 years), sex, education (±2 years), race, socioeconomic status (±1 social class), side, and aetiology of lesion with eight patients with lateral lesions. The two groups constituted the study sample. Six medial patients could not be matched or had incomplete data. A patient (medical group) had a small thalamic lesion.

PSYCHIATRIC EXAMINATION

After giving written informed consent, patients were administered quantitative psychiatric and psychosocial measures including the Hamilton rating scale for depression (Ham-D), the mini mental state examination (MMSE), and the Johns Hopkins functioning inventory (JHFI) measuring physical independence in activities of daily living (ADL, higher scores=greater impairment). Social functioning was assessed using the social ties checklist (STC) and the social functioning examination (SFE). The STC quantifies the number of social connections available to the patient (higher scores=less social support). The SFE assesses patients’ satisfaction with their social functioning (higher scores=less satisfaction). A modified present state examination (PSE),15 was administered by a psychiatrist. A diagnosis of major or minor depression, or generalised anxiety disorder (GAD) was made by using DSM-IV criteria.

Seventeen PSE symptom clusters were calculated using the method described by Wing et al.15 The presence and severity of disinhibition (agitation/irritability/violence, embarrassing behaviour/loss of social restraint, irreligious/histrionic behaviour, hypomanic affect, pressured/non-social speech), and reduction in emotion and motivation (self-neglect, slowness/underactivity, mannerism/posturing, stereotypies/ catatonie movements, blunted affect, slow/restricted quantity of speech/muteness) were assessed using the PSE.

STATISTICAL ANALYSIS

Data were analysed using means (SD), F tests, and likelihood ratio (LR) $\chi^2$ for frequency distributions. Values of p are two tailed unless
Severity of psychiatric symptoms, cognitive impairment, activities of daily living, and social functioning

<table>
<thead>
<tr>
<th></th>
<th>Medial</th>
<th>Lateral</th>
<th>Effect size</th>
<th>Power</th>
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<tr>
<td>Initial evaluation:</td>
<td></td>
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<tr>
<td>Ham D</td>
<td>8.1 (8.1)</td>
<td>14.0 (5.3)*</td>
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<td>PSE</td>
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<td>21.1 (10.0)</td>
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<td>JHIFI</td>
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<td>7.1 (8.1)</td>
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<tr>
<td>SFE</td>
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<td>3 months:</td>
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<tr>
<td>Ham D</td>
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<td>9.6 (3.0)†</td>
<td>1.06</td>
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<td>PSE</td>
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<td>0.24 (0.16)‡</td>
<td>1.07</td>
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</table>

*P<0.05 one tailed; **P<0.01; †P<0.05; ‡P<0.06; ††P<0.001; ‡‡P<0.005; ‡‡‡P<0.0001; other comparisons p>0.10.
†P<0.01; ‡P<0.05; ††P<0.001; ‡‡P<0.0001; other comparisons p>0.10.

Results

Background Characteristics

Each group was composed of three women and five men, right and three left hemispheric lesions, and three head injuries and five strokes. Mean age of the medial group was 39.5 years (SD 17, range 27–74), and that of the lateral group was 44.1 (SD 17, range 20–61). Five white, two African-American, and one Hispanic patient were in the medial, and six white and two African-American patients were in the lateral group. Five patients in the medial and four in the lateral group were of socioeconomic (Hollingshead) class IV and V. Both groups had 11.8 (SD 3) mean years of education. No statistically significant differences were found.

Psychiatric Evaluation

Depression or anxiety

At initial evaluation, depression was more frequent in lateral (six or 75%, three major, and three minor depression) than medial lesion patients (two or 25%, one major, and one minor depression) \( \chi^2=4.2, p<0.05, \text{power}=0.99, \text{ES}=1.1 \). Five (62.5%) patients had GAD in the lateral and one (12.5%) in the medial group. \( \chi^2(1)=4.5, p<0.04, \text{power}=0.98, \text{ES}=1.0 \). Patients with lateral damage showed less satisfaction with their social functioning (table). At 3 months, seven patients (87.5%) in both groups no longer fulfilled criteria for depression and/or GAD. However, patients with lateral damage showed greater severity of depressive symptoms, impairment in ADL, and psychosocial functioning (table). Comparing the symptom clusters from the PSE at initial evaluation, the lateral group showed a greater frequency of simple depression \( \chi^2=4.2, p<0.05, \text{power}=0.99, \text{ES}=1.1 \) and slowness \( \chi^2=4.3, p<0.04, \text{power}=0.98, \text{ES}=1.0 \). At 3 months, patients with lateral damage showed higher frequency of slowness \( \chi^2(1)=6.9, p<0.01, \text{power}=0.97, \text{ES}=0.98 \), and greater lack of energy and social unease \( \chi^2(1)=4.8, p<0.03, \text{power}=0.88, \text{ES}=0.79 \).

Disinhibition or hypomania

During the initial evaluation, four patients in the lateral (three displayed agitation and hostile irritability; one histrionic and hypomanic behaviour) and two in the medial group (one hypomanic affect, another agitation) had symptoms of disinhibition/hypomania. Total number of symptoms was fourfold greater (nine) in the lateral than in the medial group (two). The mean number of symptoms was 1.12 (SD 1.35) in the lateral and 0.25 (SD 0.46) in the medial group \( t(14)=1.27, p=0.10, \text{power}=0.36, \text{ES}=0.86 \). At 3 months, three patients in the lateral group and one patient in the medial group showed disinhibition/hypomania \( \chi^2(1)=9.29, p<0.003, \text{power}=0.99, \text{ES}=1.3 \).

Reduction in emotion and motivation

Five patients (62.5%) in the lateral and one (12.5%) in the medial group showed decreased emotion and motivation \( \chi^2(1)=4.55, p<0.04, \text{power}=0.98, \text{ES}=1.0 \). These patients showed a combination of severe self neglect, slowness, blunted affect, and decreased speech. One patient was almost mute at both evaluations. No patient in either group showed mania, posturing, or stereotypes. At 3 months, five patients in the lateral group showed decreased emotion and motivation compared with none in the medial group \( \chi^2(1)=9.29, p<0.003, \text{power}=0.99, \text{ES}=1.3 \).

Discussion

During the inhospital evaluation, patients with single lesions of the lateral prefrontal cortex showed more frequent depression and anxiety disorders than patients with medial frontal lesions and a greater frequency of symptoms of depression and anxiety at 3 months postinjury. Patients with lateral lesions also showed greater reduction of emotion and motivation/apathy at both evaluations.

Before discussing these findings, the limitations of our methods should be acknowledged. Due to a relatively few patients some important differences may have been missed. Although laterality questions were not examined, our findings were unlikely to be influenced by laterality effects because of the side matched group design. The aetiology of the brain injury may have influenced some of our findings such as duration of depression (trauma has been associated with shorter duration of depression than stroke) or the role of non-brain injury factors in depression. Patients with lateral damage had larger lesions. This may have influenced some of our findings.

A most surprising finding was that medial frontal lesions did not lead to higher euphoria, disinhibition, loss of emotion, or apathy than...
lateral lesions. The same instruments used in this study, however, were sensitive to increased cheerfulness and hypomania associated with right frontal compared with right temporal lesions. Apathy has been associated with extensive damage to the cingulum and mesial frontal areas as well as other structures. Decreased blood flow in the right dorsal lateral frontal and left frontotemporal cortices was found in 40 patients with apathy after stroke to diverse brain areas compared with non-apathetic stroke controls.

The human prefrontal cortex has been shown to be involved in the experience of emotion and appraisal of emotion as well as in primary and secondary mood disorders. No consensus has been achieved, however, regarding the specific location of the prefrontal dysfunction in mood disorders. Cummings found personality but not mood changes after damage to the frontal-cingulate circuit. Medial and ventral medial frontal cortex participates in the response to emotion evoking stimuli and selective attention to subjective emotion. Therefore, medial frontal activity may be necessary to experience emotion including depressed mood, anxiety, or apathy. Medial frontal injury may either not lead to emotional changes or may inhibit the perception of mood changes, anxiety, or apathy. Unilateral damage to the lateral prefrontal cortex may disrupt mood regulation and drive while leaving intact the ability to experience (disturbed) emotions.

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