[Articles]

Neuropsychiatric Effects of Insular Stroke

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Abstract

The neuropsychiatric effects of insular damage in humans have not previously been examined. We therefore examined the neuropsychiatric impairment in seven patients with left insular stroke, six patients with right insular stroke, six patients with left hemisphere noninsular stroke, and six patients with right hemisphere noninsular stroke. Between 4 and 8 weeks after acute stroke, patients were administered a neuropsychiatric battery. Patients with right insular lesions had a greater frequency of subjective anergia and underactivity (Fisher's exact p = .002) as well as tiredness (Fisher's exact p < .002) compared with patients with non-insular lesions or left insular lesions. Subjective feelings of impaired energy or drive after right insular damage may result from disconnection between the insula and the frontal lobe or the anterior cingulate cortex, structures that have been associated with willed action and motor behavior.

The insular cortex consists of four to six gyri encircled by the circular insular sulcus. The central insular sulcus divides the human insula into anterior and posterior portions. The main branch of the middle cerebral artery can be found in the central insular sulcus. Small arterioles of the middle cerebral artery (MCA) penetrate the insular cortex (Agustine, 1985). Proximal branches of the MCA also supply frontal, parietal, and temporal cortex. Based on this vascular anatomy, isolated infarctions of the insula rarely occur.

The insula is a major component of the limbic brain (Yakovlev, 1959). The insular lobe in primates including humans has connections with the frontal lobe, parietal lobe, temporal lobe, basal nuclei, amygdala, limbic areas, parietal lobe, temporal lobe, and dorsal thalamus (Agustine, 1996).

Prior studies have shown that the insula is part of the primary gustatory cortex (Yaxley et al., 1990), somatosensory cortex (Schneider et al., 1993), limbic integration cortex (Markowitsch et al., 1985), autonomic system (Anderson et al., 1994), motor association cortex (Agustine, 1996), vestibular system (Aziz et al., 1995), and participates in language (Agustine, 1996). The insular cortex also has lateralized effects on the nervous system. Right insular stimulation in humans produces increased heart rate and blood pressure, whereas left insular stimulation leads to decreased blood pressure and bradycardia (Oppenheimer, 1993).

Although this wide variety of functions has been associated with the insula, the normal role of the insula in emotions as well as the effect of insular damage on emotions has not been identified. The current study examined the neuropsychiatric consequences of restricted infarcts of insular cortex. Based on findings from previous studies, we hypothesized that the consequences would be relatively subtle and might include depression after left hemisphere damage and apathy (Starkstein et al., 1992) or indifference after right hemisphere damage (Starkstein et al., 1989).

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Methods

Patients were recruited from among 330 patients admitted to Younkers Rehabilitation Hospital in Des Moines, Iowa, for treatment after an acute cerebral infarction. After obtaining informed consent, detailed neuroradiological, neurological, and neuropsychiatric examinations were performed on all patients, excluding only those who had severe comprehension deficits (*i.e.,* as indicated by an inability to complete part 1 of the token test) or markedly decreased level of consciousness.

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Neuroradiological Evaluation

Patients were included if they had a single lesion demonstrated by CT and/or MRI scan that revealed an ischemic infarction restricted to the insula or other cortical areas. Patients with frontal lobe lesions were excluded to eliminate the effect that frontal lobe lesions might have on mood. It has been demonstrated in several studies that, during the acute stroke period, depression is significantly more frequent after left frontal compared with other cortical lesion locations (Robinson, 1998). An MRI was performed 2 weeks after the stroke. All scans were read by a neurologist and neuroanatomist (F.M.) and a psychiatrist with experience in neuroimaging (S.P.) who were blind to results of the neuropsychiatric examination. All lesion locations were determined and transposed onto standardized schematic templates according to the procedure described by Levine and Grek (1984). Although insula lesions extended beyond the insular cortex, more than 80% of the lesion was within the insular cortex as determined by area measurements in the slice showing the largest cross-sectional area of the lesion (Figure 1). All noninsular lesions were purely cortical involving either the parietal, temporal, or occipital lobes (Figure 1).

A total of 25 patients met the selection criteria. Patients were classified into four groups. There were six patients with right insular lesions (right insular group), seven patients with left insular lesions (left insula group), six patients with left restricted cortical lesions, and six patients with right restricted cortical lesions. Templates demonstrating the location of the lesions are shown in Figure 1.

Patients were evaluated between 4 and 8 weeks after acute stroke.

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Neurological Examination

The neurological examinations and diagnoses for all patients were performed using the National Institute of Health stroke scale (Brott et al., 1989). All neurological evaluations were carried out blind to the findings on the neuropsychiatric examination.

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Neuropsychiatric Evaluation

Mini Mental State Exam (MMSE). The MMSE was selected to provide a brief assessment of cognitive function. It is an 11-task examination that has been found to be reliable and valid in assessing cognitive functions in stroke patients (Robinson et al., 1986). Scores may range from 0 to 30, and a score of 23 or below has been found to be indicative of significant cognitive impairment (Folstein et al., 1975).

The Hamilton Depression Scale (HAM-D). The HAM-D is a 28-item interviewer-rated scale, which measures psychological and physiological symptoms of depression (Hamilton, 1960). It was selected to quantify depressive symptoms and to assess our hypothesis that depression would be associated with left insular lesions.

The Zung Self-Rating Depression Scale (ZDS). The ZDS is a 20-item questionnaire, which was read to each patient and their responses were scored using the four Zung categories (Zung, 1965). It was selected to be a self-assessment of mood and was expected to show mood symptoms associated with left insular lesion.

The Hamilton Anxiety Scale (HAM-A). The HAM-A is an 11-item interviewer-rated scale that measures the severity of generalized or persistent anxiety (Hamilton, 1959). It was selected to quantify anxiety symptoms because prior studies have shown anxiety to be comorbid with depression after stroke (Robinson, 1998).

Mania Rating Scale (MRS). The MRS was selected to quantify the severity of manic symptoms such as euphoria, hyperactivity, flight of ideas, hypersexuality, and decreased sleep (Young et al., 1978).

The Modified Present State Exam (PSE). The PSE is a semi-structured mental status examination (Wing et al., 1974). The examination was conducted by a fully trained psychiatrist. Using the symptoms elicited by the PSE, a diagnosis of major or minor depression was made using DSM-IV symptom criteria (American Psychiatric Association, 1994). The PSE was modified to specifically identify the presence or absence of all DSM-IV symptoms of major depression (available upon request). It was selected to provide a standardized examination of mental state and to assess our hypothesis that indifference would be associated with right insular lesions and major or minor depression with left insular lesions (Robinson, 1998). The PSE symptoms have been clustered into syndromes (Wing et al., 1974) and 17 PSE syndromes were assessed in this study.

The Johns Hopkins Functioning Inventory (JHFI). The JHFI contains 10 items and evaluates a patient's degree of independence in activities of daily living such as walking, dressing, and eating (Robinson and Szetela, 1981). Scores range from 0 to 27, and higher scores indicate greater degrees of impairment. It was selected to quantify activities of daily living (ADL) impairment and was not expected to be associated with insular lesions.

Functional Independence Measure (FIM). The FIM assesses self-care, sphincter control, mobility, locomotion, communication, and social cognition (Granger and Hamilton, 1990). Higher scores indicate less impairment in ADL. This scale was

selected because it is a well standardized quantitative assessment of impairment in ADL.

Social Functioning Exam (SFE). The SFE provides quantitative assessments of social functioning (Starr et al., 1983). Scores may range from 0.0 to 1.0 with higher scores indicating greater social impairment. It was selected to determine whether psychopathological findings might be associated with social impairment.

Social Ties Checklist (STC). The STC is a 10-item scale that assesses the quantity and quality of social supports; scores range from 0.0 to 1.0, and higher scores indicate fewer social supports (Starr et al., 1983). It was selected for similar reasons as the SFE.

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Statistical Analysis

Statistical analysis was done using means, standard deviations and Student's *t*-tests. For discrete variables, we used chi-square tests. For the PSE symptoms and syndrome comparisons, we used Fisher's exact test at a conservative [alpha] = .01 significance level. All tests were two-tailed.

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Results
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Background Characteristics

Background characteristics of the sample are shown in Table 1. The groups were not significantly different in their age, education, socioeconomic status, marital status, race, or personal or family history of psychiatric disorders or time since stroke. There were 12 (92.3%) males in the combined vasula group and 5 (41.6%) in the combined hemispheric lesions group (Fisher's exact *p* = .01)

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Neurological Findings

All patients were right handed. Each group showed a similar frequency of visual field and motor deficits. One patient with a left insular lesion had a visual field deficit as did one patient with a right insular lesion. One patient with a left insular lesion had a motor deficit in the right lower limb, and one patient with a right insular lesion had a motor deficit in the left lower limb.

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Neuropsychiatric Findings

The results of the neuropsychiatric examination are shown in Table 2. There were no significant intergroup differences in the severity of depressive, anxiety, or manic symptoms, cognitive impairment (MMSE), functional disability (JHFI), and social functioning (SFE, STC). Similarly, there were no significant intergroup differences in the frequency of depressive disorder. Two patients in the left insula group and two patients in the right insula group developed major depression. One patient developed major depression in the noninsula right hemisphere group, and two patients in the non-insula left hemisphere group developed minor depression. Because there were no differences in total scores on any of the exams that assessed psychopathology, we examined specific symptoms of psychopathology using the PSE. Two symptoms, subjective anergia with underactivity (Fisher's exact *p* < .002), and tiredness (Fisher's exact *p* < .002) were significantly more frequent in patients with right insula lesions (*i.e.*, 5 of 6 anergia, 5 of 6 tiredness) than patients with either right or left noninsula

lesions (*i.e.,* 0 of 12 anergia, 0 of 12 tiredness). Right insula lesion patients were not significantly different from left insula lesion patients (*i.e.,* 3 of 7 anergia, 3 of 7 tiredness) in these two symptoms. However, the combined group of right and left insula lesion patients had a significantly higher frequency of anergia and tiredness than the combined group of right or left noninsula (cortical) lesion patients.

In addition to this individual PSE item analysis, the symptoms of the PSE have been clustered into syndromes (Wing et al., 1974). The frequency of each syndrome was compared across patient groups. The results are shown in Figure 2. The only significant difference in syndrome profiles among the four groups (*i.e.,* 5 of 6 patients) was a higher frequency of loss of energy in the right insula group compared with the lesion control groups (*i.e.,* 0 of 12 patients; Fisher's exact $p < .002$). This finding also held true if the right and left insula groups were combined (*i.e.,* 8 of 13 versus 0 of 12; Fisher's exact $p = .011$).

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Discussion

This study found that patients with right insular infarction had a significantly higher frequency of subjective anergia, underactivity and tiredness than patients with either right or left non-insula lesions. These findings were not related to depression in the right insula lesion group.

Before discussing these findings, some limitations of this study should be acknowledged. First, the number of patients with localized insular lesions was limited, and therefore more subtle differences may have been missed due to a lack of statistical power. However, this is the first empirical study to examine psychopathological symptoms among patients with isolated insula damage. Second, the existence of anergia, underactivity, and tiredness was based on subjective responses to a semi-structured interview administered by a psychiatrist and not on behavioral measures. Third, patients included in this study represented a consecutive series of patients who had been admitted to a rehabilitation hospital (a subset of all acute stroke patients) and who agreed to participate in this study. Therefore, they may not represent consecutive stroke patients with insular lesions. Fourth, all of the patients in the right insula group were male. Thus, the finding of anergia and tiredness associated with right insula lesions may be a phenomenon of male subjects and further study will be needed to determine whether these findings are applicable to female subjects.

Given these limitations, how might these finding be interpreted? Insular efferents have been identified in the anterior cingulate gyrus (Agustine, 1996). Morecraft and VanHoesen (1998) suggested that the cingulate motor cortex forms a strategic cortical entry point for limbic influence on the voluntary motor system. The cingulate motor cortex is connected with prefrontal cortex (Bates and Goldman-Rakic, 1993) and projects topographically to the primary and supplementary motor cortices (Biber et al., 1978). Perhaps, due to its connections with anterior cingulate cortex, right insular damage interrupts structures that govern the expression of voluntary motor behavior and lead to subjective anergia, underactivity, and tiredness.

On the other hand, insular cortex is also reciprocally connected with the frontal lobe (Agustine, 1996). Prefrontal cortex has been associated with willed action. Using positron emission tomography, Frith et al. (Frith et al., 1991) showed brain activation in the prefrontal cortex associated with "willed action." Thus, subjective anergia, underactivity, and tiredness after right insular damage may be the result of a disconnection between insula and frontal lobe. Moreover, it has been suggested

(Berthier et al., 1988; Mesulam and Mufson, 1985) that insula-amygdala interaction is essential to appraise the affective-motivational content of perceptual experience. Thus, if this interaction is disrupted because of damage to the insula, patients may fail to react to experiences in their life with appropriate emotions. The participation of insular cortex in cognitive generation of affect has recently been demonstrated using functional magnetic resonance imaging (Teasdale et al., 1999). Roalso et al. (1997) have recently suggested that apathy and neglect may be aspects of the same phenomenon. In their study, apathy in patients with CVA at 1 week post-stroke was significantly associated with neglect and was more frequent after right compared with left hemisphere damage. We have previously reported that neglect was associated with right insular lesions (Manes et al., 1999), and in the present study, four of six patients with right insular lesions and anergia also had neglect. Thus, our study is consistent with the hypothesis that anergia, apathy, and neglect may all be related and insula dysfunction may play a role in their production. There are, of course, other possible explanations for these findings and further research will be needed to identify the mechanism of this lateralized phenomenon.

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Conclusions

In conclusion, right but not left insular damage was associated with subjective anergia, underactivity, and tiredness. Due to the insula's reciprocal connections with anterior cingulate, amygdala, and prefrontal cortex, insular damage may disconnect circuits related to voluntary motor behavior or willed behavior.

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