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BASIC RELATIONS AMONG LESION LATERALITY, LESION VOLUME AND NEUROPSYCHOLOGICAL PERFORMANCE

ERIC TURKHEIMER,*† RONALD A. YEO‡ and ERIN D. BIGLER§

†University of Virginia; ‡University of New Mexico; and §University of Texas and Austin Neurological Clinic; U.S.A.

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Abstract—Although it is widely accepted that lesion size is an important determinant of severity of deficit, difficulties in the quantification of lesion size and the absence of a theoretical model of how lesion volume combines with lesion locus to produce deficits have inhibited the development of methodological and statistical procedures for studying naturally occurring lesions in humans. We propose such a unified model and apply it to the analysis of neuropsychological performance in a sample of patients with naturally occurring unilateral lesions. The analysis suggests that a statistical interaction between lesion size and laterality may be an important determinant of neuropsychological deficit.

INTRODUCTION

IN ONE of the most common and powerful research designs in human neuropsychology, subjects with traumatic, neoplastic, cerebrovascular or surgical brain lesions are divided into groups on the basis of lesion locus, and means of the groups on neuropsychological measures are compared. Most often the subjects are grouped according to laterality of lesion, although groupings according to cerebal lobes, cortical vs subcortical, or anterior vs posterior, locus are also employed.

Clinical brain lesions vary in volume, and lesion volume may covary with lesion locus. No concensus appears to have emerged about how lesion volume should be included in analyses of lesion effects and as a result, few studies attempt to measure lesion volume. A review of papers published between 1986 and 1989 in three major neuropsychological journals (*Brain and Cognition*, *Cortex*, and *Neuropsychologia*) revealed that 14% (78 of 556) of all papers (including reviews and case studies) utilized the focal lesion method in a group study. Of these, only 15% (12 of 78) attempted some kind of lesion measurement. Quantification efforts ranged from a simple rating as to "small" vs "large" lesions [11] to determination of lesion volume (e.g. [4]). Generally, analysis of lesion size played an important role in interpretation of results in these studies.

Often, lesion volume is measured and the mean volumes of left and right hemisphere lesions are compared; if they do not differ significantly the effects of volume are not considered further [18]. Occasionally, volume is included as a covariate in an analysis of covariance (ANCOVA) of regional differences [9], or correlations between volume and a performance measure are computed separately in the two hemispheres [2].

*Address correspondence to: Eric Turkheimer, Department of Psychology, University of Virginia, Charlottesville, VA 22903, U.S.A. BITNET: ENT3C@VIRGINIA.

One feature shared by these approaches is that they presume independent effects of lesion locus and volume. Lesion volume has proved difficult to integrate with findings concerning hemispheric differences in lesion effects, however, because the magnitude of the relation between volume and performance appears to depend on the site of the lesion.

Relationships among lesion locus, volume and measured deficit are often quite complex. A study of frontal lobe lesions and spatial memory [13], for example, found that right but not left frontal lesions were associated with price estimation deficits; however, left lesions were substantially smaller than right lesions, and there was a significant correlation between lesion volume and deficit among left- but not right-lesioned patients.

A striking example of complications in the analysis of lesion laterality and volume is found in studies of effects of right and left hemisphere lesions on simple and complex reaction time. In general, reaction time appears to be especially impaired in patients with right hemisphere lesions, and the correlation between lesion volume and reaction time appears to be greater in the right hemisphere [1]. Two recent studies by TARTAGLIONE *et al.* have confirmed these findings. In one [14], the correlation between reaction time and lesion volume was 0.45, for right hemisphere lesions and −0.07 for left hemisphere lesions. In the other [15], subjects were divided into impaired and unimpaired groups, and differences in lesion volume between the groups were much greater for subjects with right hemisphere lesions.

The implications of the volume findings have not been investigated in detail. TARTAGLIONE *et al.* point out that for other neuropsychological measures significant relations with volume are found for left hemisphere lesions, but it remains to be explained why correlations between volume and deficit are different in the left and right hemsipheres, and especially why the correlations are sometimes greater in one hemisphere and sometimes in the other.

We have recently reviewed some of the complexities of studying the consequences of variation in the location of naturally occurring lesions [16], and presented a quantitative model for the analysis of relations among lesion location, size, and behavior [17]. Here, we apply a simple version of the model to the common situation in which test scores of patients with left and right hemisphere lesions are compared. Our intent is to justify a basic difference between our model and traditional methods of analyzing designs of this type, demonstrate the necessity of including lesion volume in any analysis of the effects of lesion location, and investigate some basic properties of the relations among lesion laterality, lesion volume, and measured performance.

The model postulates that for a given neuropsychological function, each point in the brain is associated with an "importance value" that represents the relative importance of the point to the measure of performance. High importance values indicate that a point is relevant to a measure, so lesions involving the point will produce greater deficits; low importance values indicate that a point is unimportant to the behavior, so lesions will produce small deficits. According to the model, the expected deficit resulting from a lesion is equal to the sum of the importance values in the lesioned region. The set of importance values for all points in the brain for some neuropsychological function is called an "importance function".

In previous papers [16, 17] we have shown how importance functions for a variety of neuropsychological measures can be estimated from information about the size and location of lesions in samples of brain-lesioned patients who have been administered neuropsychological tests. In the current paper we consider some consequences of the model for the common research design in which test scores of patients with left and right hemisphere lesions are compared.

The model makes three basic predictions about the consequences of unilateral lesions. The first two concern the main effects of lesion hemisphere and size, and conform to intuition about the effects of brain lesions. Large lesions should produce greater deficits than smaller ones, because they include a greater number of importance values. Lesions in the more important hemisphere should produce greater deficits that those in the less important hemisphere, because the importance values they contain will each be higher.

The third prediction involves the *joint* effect of lesion size and hemisphere in the prediction of deficit. Suppose the importance value of each unit of tissue in the left hemisphere is 5, and in the right hemisphere is 1. Now consider the relationship between lesion size and deficit within each hemisphere. In the left hemisphere, each additional unit of lesioned tissue will contribute 5 units of deficit; in the right hemisphere, each additional unit will contribute 1 unit of deficit. The resulting relationship between lesion size and deficit is illustrated in Fig. 1.

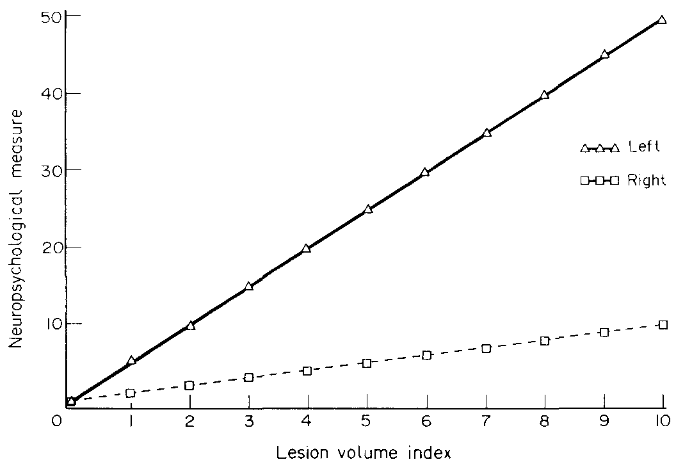

Fig. 1. Hypothetical relationship between lesion volume and neuropsychological performance in patients with left and right hemisphere lesions.

As can be seen in Fig. 1, the third prediction of the model is that, if one hemisphere is more important than the other for a measure, there will be different regressions of deficit on lesion size in the two hemispheres, or equivalently, that the difference between the deficits of left and right hemisphere lesion patients will depend on lesion size. In terms of analysis of variance, this is an *interaction* between lesion size and hemisphere.

The presence of interactions complicates interpretation of main effects. The unilateral lesion research design asks two basic questions about the relationship between lesions and deficit: whether lesions to the left and right hemispheres produce different degrees of deficit, and whether larger lesions produce greater deficits than smaller ones. If, as predicted by the model, lesion size and laterality interact in the prediction of defict, the answer to both questions will be, "It depends". Lesion size may be correlated with severity of deficit in one hemisphere but not the other, and hemispheric differences may exist for large lesions but not for small ones. In the remainder of the current paper we test for the presence of interactions between hemisphere and size of lesions in the prediction of neuropsychological deficits in a sample of unilaterally brain-damaged subjects. In the interest of methodological clarity we will restrict our analysis to the joint effects of lesion volume and hemisphere, and exclude other important variables such as gender and age, which have been integrated with the model in other papers [17].

METHODS

Subjects

Archival data were obtained for 52 patients examined in a neurological clinic who met the following criteria.

(1) A CT scan had been performed.
(2) A unilateral lesion was visible on the CT scan.
(3) The patient was right-handed.
(4) The patient was over 15 years of age.
(5) No history of psychiatric disorder or drug abuse.

The sample included 26 males and 26 females. The mean age was 55 years and the mean time post-lesion was nine months. Etiologies consisted of stroke [41], tumor [8], focal trauma [2] and abscess [1].

Neuropsychological measures

Subjects were administered portions of the Halstead–Reitan Neuropsychological battery as a routine part of their examination. Tests included the Trail Making Test, Parts A and B, Reitan-Kløve Sensory Perceptual Exam, Reitan Indiana Aphasia Screening Exam, Finger Oscillation Tests, and Strength of Grip Test [10]. RUSSELL'S [12] scoring system was used to score the Aphasia Screening Exam. Of the two scores produced (verbal and spatial) only the verbal score was included in the analysis. For the auditory, visual and tactile modalities of the sensory perceptual exam, the total score was the number of errors occurring during unilateral and double simultaneous stimulation. Left and right side performance were scored separately. Finger-Tip Number-Writing and Finger Recognition scores were the number of errors made with each hand. Left and right finger tapping speed was determined as the mean number of taps in a 10 sec interval over five separate trials with each hand. Left and right strength of grip was determined with a hand dynamometer (Stoelting Co.).

CT Analysis

The scans were placed on a light box and the lesion and the inner perimeter of the skull were traced onto tracing paper. The maximum length and width of each slice was measured along the left–right and anterior–posterior axes, and standardized by the maximum length and width of a slice for each subject. The lesioned area was then approximated as the product of the length and width on each slice (i.e. the lesion was approximated by a rectangle) and an index of lesion volume computed by summing the areas across slices. Approximating lesions by rectangles probably systematically overestimates lesion area, but because subsequent analyses are correlational, the error should not influence our results. The hemisphere of the lesion was also noted and coded −1 for the left hemisphere lesions and +1 for right hemisphere lesions.

RESULTS

Table 1 presents means and SD for the left and right hemisphere lesion groups on the neuropsychological measures and lesion volume. Right and left hemisphere lesion volumes were not significantly different.

Table 2 shows the correlations of the measures with lesion volumes for left and right hemisphere lesioned subjects. For five of seven left side measures (e.g. left hand finger tapping), correlations with lesion volume are greater for right than left hemisphere lesions, while for seven of eight right side measures (including aphasia errors) correlations with lesioned volume are greater for left hemisphere lesions. Of the three measures that did not fit the pattern, one (left visual errors) showed no evidence of lateralization at all.

The nature of this interaction effect is illustrated in Figs 2 and 3. Figure 2 is a scatterplot of lesion volume and left tactile errors. Regression lines have been estimated separately for left and right hemisphere lesion subjects. For left hemisphere subjects there is no relationship between lesion volume and number of errors, while for right hemisphere subjects there is a substantial relationship; the intercepts do not differ. Figure 3 shows the same relationship for

Table 1. Means and SD of neuropsychological measures

	Lesion location			
	Left hemisphere		Right hemisphere	
	Mean (SD)	N	Mean (SD)	N
Test				
Strength of Grip (R)	20.6 (15.8)	19	28.3 (15.5)	23
Strength of Grip (L)	27.3 (11.6)	18	14.5 (13.8)	23
Finger Tapping (R)	22.4 (19.5)	21	35.0 (14.9)	21
Finger Tapping (L)	32.5 (13.1)	20	21.3 (17.4)	21
Tactile Errors (R)	3.1 (4.2)	21	0.4 (1.0)	28
Tactile Errors (L)	0.3 (1.1)	21	3.8 (4.1)	28
Auditory Errors (R)	1.3 (1.9)	20	0.6 (1.4)	27
Auditory Errors (L)	0.9 (1.6)	20	2.0 (2.1)	27
Visual Errors (R)	4.4 (6.6)	20	0.8 (2.2)	27
Visual Errors (L)	2.1 (4.7)	20	3.2 (4.2)	27
Finger Recognition (R)	4.4 (6.1)	19	1.3 (2.8)	28
Finger Recognition (L)	1.4 (2.5)	19	6.6 (8.2)	28
Finger-Tip Writing (R)	6.0 (7.0)	19	2.9 (4.4)	27
Finger-Tip Writing (L)	3.5 (4.1)	19	6.6 (7.7)	27
Aphasia Verbal	34.0 (19.5)	21	8.6 (8.5)	25
Volume Index	45.5 (32.9)	24	58.9 (57.2)	28

Table 2. Correlations between neuropsychological measures and lesion volume for left and right hemisphere lesion subjects

	Left side measures		Right side measures	
	Hemisphere of lesion			
Test	Left	Right	Left	Right
	r	r	r	r
Finger Tapping	0.05	0.25	0.23	0.01
Strength of Grip	0.03	0.13	0.04	−0.13
Tactile Errors	0.03	0.49	0.42	−0.22
Auditory Errors	−0.01	0.13	0.15	−0.14
Visual Errors	0.16	0.09	0.37	−0.27
Finger-Tip Writing	0.21	0.42	0.14	0.33
Finger Recognition	0.28	0.12	0.32	−0.14
Aphasia Verbal			0.42	0.02

right tactile errors. Right hemisphere subjects show no relationship between volume and number of errors, while left hemisphere subjects show a strong relationship.

The possibility of interactions in the prediction of deficit was further investigated using hierarchical multiple regression. Results are given in Table 3. First, each neuropsychological measure was regressed on the main effects of volume and hemisphere, but no interaction. The resulting R^2 values are given in the first column of Table 3. The next two columns report the F values of the contribution of lesion volume and hemisphere to the prediction of each measure, with d.f. in the next column. The main effect of volume contributed significantly to

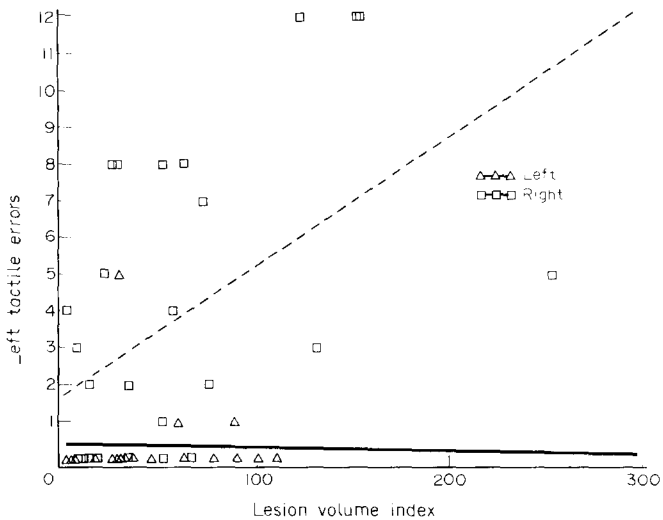

Fig. 2. Relationship between left hand tactile errors and lesion volume in patients with left and right hemisphere lesions.

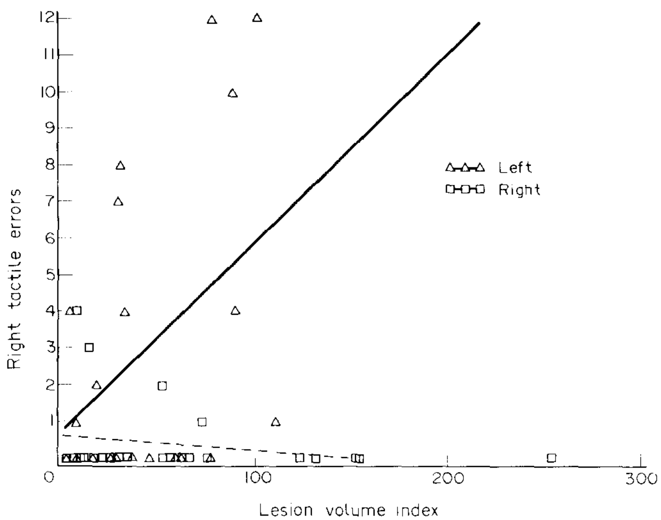

Fig. 3. Relationship between right hand tactile errors and lesion volume in patients with left and right hemisphere lesions.

two regressions, while the main effect of hemisphere contributed significantly to 10, and approached significance ($P=0.06$) in another.

Next, the interaction of volume and hemisphere was added to each regression, (i.e. each neuropsychological measure was predicted from lesion size and hemisphere, as above, *and* the interaction). The fifth column of Table 3 shows the increase in R^2 produced by the addition of the interaction to the previous model. The sixth column gives the F values for

Table 3. Means and SD of neuropsychological measures

	Model							
	Main effect				Interaction			
Test	R^2	F_{vol}	F_{hemis}	df	ΔR^2	F_{inter}	df
Strength							
Right	0.04	0.36	1.43	1,39	0.01	0.25	1,38
Left	0.21	0.96	9.24†	1,39	0.00	0.04	1,38
Tapping							
Right	0.13	0.18	5.67	1,39	0.02	0.96	1,38
Left	0.15	2.03	4.71†	1,38	0.00	0.19	1,37
Tactile							
Right	0.21	0.17	11.71†	1,46	0.12	8.02†	1,45
Left	0.37	13.73†	13.10†	1,46	0.04	2.95*	1,45
Auditory							
Right	0.05	0.23	2.25	1,44	0.02	0.94	1,43
Left	0.10	0.96	3.69*	1,44	0.00	0.12	1,43
Visual							
Right	0.14	0.00	7.04†	1,44	0.10	6.08†	1,43
Left	0.03	0.67	0.55	1,44	0.00	0.24	1,43
Finger Rec.							
Right	0.11	0.01	5.55†	1,44	0.07	3.71*	1,43
Left	0.15	1.63	6.35†	1,44	0.00	0.00	1,43
Finger Writ.							
Right	0.12	1.47	4.49†	1,43	0.00	0.00	1,42
Left	0.19	8.59†	1.67	1,43	0.01	0.49	1,42
Aphasia							
Verbal	0.46	0.00	37.16†	1,43	0.06	5.31†	1,42

*$P<0.10$
†$P<0.05$

the addition of the interaction, with d.f. in the final column. The interaction contributed *additional* variance, beyond volume and hemisphere main effects, at $P<0.05$ in three regressions, and at $P<0.10$ in two others.

DISCUSSION

We have presented a statistical analysis of the joint effects of lesion size and laterality on neuropsychological deficit. The proposed model makes the commonsense, but previously neglected, prediction that the effects of lesion size and hemisphere should be mutually dependent. Analysis of data from brain-injured subjects demonstrated this dependence in the form of statistical interactions between size and laterality in the prediction of deficit.

The results suggest that lesion volume should not simply be ignored in studies of the effects of lesion laterality. Neither is it adequate to demonstrate that lesion volumes do not differ between hemispheres, because the important effects of volume are largely manifest *within* each hemisphere. Analysis of covariance is particularly inappropriate, because the central assumption—equal regression slopes in the groups—will frequently be violated.

Furthermore, the results have implications for studies that examine the main effects of lesion size and laterality in the prediction of neuropsychological deficit. In any analysis of variance, it is axiomatic that main effect should not be interpreted until the possibility of interaction has been ruled out (e.g. [7], p. 173 ff). It appears reasonable to assert that a model including the main effects of volume and hemisphere, and their interaction, should be applied to future studies of this type.

A third consequence of the results concerns the effect of lesion volume. Most studies that have compared lesion volume and laterality in the prediction of deficit have found location to be more important [5]. The results of this study suggest that important effects of lesion size may have been overlooked because they are mainifest in the interaction of size and laterality, rather than in the main effect of size.

In summary, we make several recommendations for future studies of this type. Lesion size should be estimated, and lesion laterality coded with dummy variables (e.g. -1 for left hemisphere lesions, and $+1$ for right hemisphere lesions) so multiple regression may be applied [3]. In addition, the interaction of size and laterality should be computed. Several computer programs for multiple regression will compute the dummy variables and the interaction automatically (e.g. PROC GLM in SAS), or the interaction term can be computed as the product of size and the dummy variable for laterality [3]. A neuropsychological measure can then be regressed on the two main effects and the interaction. If the interaction is *non*-significant at a high level of confidence it can be removed from the model, and the researcher may proceed to interpretation of main effects or ANCOVA; if the interaction cannot be eliminated it should remain in the model, the main effect should be interpreted with caution, and ANCOVA should be avoided. Because the interpretation of main effects depends on the validity of the null hypothesis of no interaction, it is sometimes recommended that interactions be tested at a liberal significance level, such as $P=0.10$ or $P=0.25$, to guard against the possibility of a Type II error [8].

The most complex case, in which mean lesion sizes *and* correlations between size and performance differ between the hemispheres, requires especially cautious interpretation. Descriptive methods, such as computing separate correlations between lesion size and neuropsychological response for left and right hemisphere lesions and the graphical ones that have been employed in this paper, can be applied to understand the nature of the main effects and their interaction. More advanced methods for the analysis of such models are available [6], but are beyond the scope of this paper.

Quantitative analysis of patients with accurately localized lesions has the potential to elucidate functional differences in the human brain to an extent that previously has not been possible. Volume and location of lesions in human brains will never be under strict experimental control, however, so there will always be a need to interpret lesion effects in the presence of extraneous sources of variance. Relatively simple statistical procedures can help extract more scientific knowledge from the vast amount of information that has been made available by modern neuroimaging technology.

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REFERENCES

1. BENTON, A. Reaction time in brain disease: Some reflections. *Cortex* **22,** 129–140, 1986.
2. BLACK, F. W. and BERNARD, B. A. Constructional apraxia as a function of lesion locus and size in patients with focal brain damage. *Cortex* **20,** 111–120, 1988.
3. COHEN, J. and COHEN, J. *Applied multiple regression/Correlation Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1983.
4. GRAFMAN, J., SALAZAR, A., WEINGARTNER, H., VANCE, S. and AMIN, D. The relationship of brain-tissue loss volume and lesion location to cognitive deficit. *J. Neurosci.* **6,** 301–307, 1986.

5. INGLIS, J., RUCKMAN, M., LAWSON, J. S., MACLEAN, A. W. and MONGA, T. N. Sex differences in the cognitive effects of unilateral brain damage. *Cortex* **18,** 257–276, 1982.
6. HUITEMA, B. E. *The Analysis of Covariance and Alternatives.* John Wiley, New York, 1980.
7. KEPPEL, G. *Design and Analysis*, 2nd Edn. Prentice-Hall, Englewood Cliffs, New Jersey, 1982.
8. KIRK, R. E. *Experimental Design* 2nd Edn. Wadsworth, Inc., Belmont, CA, 1982.
9. LEVINE, S. C., HUTTENLOCHER, P., BANICH, M. T. and DUDA, E. Factors affecting cognitive functioning of hemiplegic children. *Devl Med. Child Neurol.* **29,** 27–35, 1987.
10. REITAN, R. M. and WOLFSON, D. *The Halstead–Reitan Neuropsychological Test Battery: Theory and Clinical interpretation.* Neuropsychology Press, Tucson, Arizona, 1985.
11. DELLA ROCHETTA, A. I. Classification and recall of pictures after unilateral frontal or temporal lobectomy. *Cortex* **22,** 189–211, 1986.
12. RUSSELL, E. W., NEURINGER, C. and GOLDSTEIN, G. *Assessment of Brain Damage: A Neuropsychological Key Approach.* John Wiley, New York, 1970.
13. SMITH, M. L. and MILNER, B. Differential effects of frontal-lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia* **22,** 697–705, 1984.
14. TARTAGLIONE, A., BINO, G., MANZINO, M., SPADAVECCHIA, L. and FAVALE, E. Simple reaction-time changes in patients with unilateral brain damage. *Neuropsychologia* **24,** 649–658, 1986.
15. TARTAGLIONE, A., ONETO, A., MANZINO, M. and FAVALE, E. Further evidence for focal effect of right hemisphere damage on simple reaction time. *Cortex* **23**, 285–292, 1987.
16. TURKEIMER, E. Techniques of quantitative measurement of morphological structures of the central nervous system. In *Neuropsychologica Function and Brain Imaging*, E. D. BIGLER, R. A. YEO and E. TURKHEIMER (Editors), pp. 47–64. Plenum Press, New York, 1989.
17. TURKHEIMER, E., YEO, R. A., JONES, C. L. and BIGLER, E. D. Quantitive assessment of covariation between neuropsychological deficit and location of naturally occurring lesions in humans. *J. clin. exp. Neuropsychol., in press.*
18. WEDDELL, R. A., TREVARTHEN, C. and MILLER, J. D. Reactions of patients with focal cerebral lesions to success or failure. *Neuropsychologia* **26,** 373–385, 1988.