Cognitive Bias, Functional Cortical Geometry, and the Frontal Lobes: Laterality, Sex, and Handedness

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Abstract

■ Performance of patients with quadrant lesions on the inherently ambiguous Cognitive Bias Task (CBT) suggests sexual dimorphism in the fundamental aspects of functional cortical geometry, by emphasizing different cerebral axes. In right-handed males, extreme context-dependent and context-independent response selection biases are reciprocally linked to left vs. right frontal systems. In right-handed females, these complementary biases appear to be reciprocally linked to posterior vs. frontal cortices. Frontal lobe functions are more lateralized in males than females due to sexual dimorphism of the left frontal systems. Both in males and females, patterns of CBT scores in non-right-handers with quadrant lesions are opposite to those found in right-handers. This suggests the existence of two functionally and neurally distinct cognitive selection mechanisms. Both mechanisms involve the frontal lobes, but their exact neuroanatomy depends on sex and handedness. ■

INTRODUCTION

Prefrontal cortex is critical for the selection, planning, and temporal organization of cognitive processes (Fuster, 1989; Goldman-Rakic, 1987; Stuss & Benson, 1986). It is implicated in two types of cognitive operations: those guiding behavior by internal representations, e.g., plans, and those ensuring the organism's ability to respond to unanticipated environmental contingencies.

Hypothesis

We hypothesized that in right-handers the left prefrontal system is critical to guiding behavior by a current cognitive context, and the right prefrontal system to the ability to alter the context in response to ongoing events. Each system has access to the universal knowledge base, probably mediated by the posterior cortical systems (Damasio, 1985; Goldman-Rakic, 1987; Goldberg, 1990), from which response selection is made. Yet each relies on a different selection principle: internal context-based vs. external environment-based. The dynamic balance between the two systems may be upset by lateralized prefrontal damage, producing extreme behaviors: perseveration or environmental dependency (Goldberg & Bilder, 1988; Goldberg & Costa, 1986; Goldberg & Tucker, 1979; Lhermitte, 1983; Lhermitte, Pillion, & Sraru, 1985).

In a similar vein, Milner (1982), Milner & Petrides (1984), and Petrides & Milner (1982) implicated the left prefrontal cortex in the control of internally ordered and the right prefrontal cortex of externally ordered events. McCarthy and Warrington (1990) noted that damage to the left, more than right, frontal lobe leads to the failure on tasks requiring "internal generation of strategies and/or control of motor-executive functions" (p. 356).

Theoretical Precursors of the Hypothesis

Traditionally, language lateralization has been viewed as fundamental and that of other cognitive functions as secondary and derivative (Corballis, 1983; Levy, 1974). This view implies the uniqueness of human hemispheric specialization and an evolutionary discontinuity in cerebral organization. Since language is unique to humans, at least in its narrow definition, it effectively precludes the evolutionary approach to hemispheric specialization. While asymmetries exist in other species (Glick, Meibach, Cox, & Maayani, 1979; Glick, Ross, & Hough, 1982; Nottenbohm, 1977), meaningful homologies with humans are not easily derived in this framework. Due to the focus on language, hemispheric research emphasized posterior cortex.

Recently, several novel approaches have been advanced, placing hemispheric specialization in a broader framework and treating language lateralization as a consequence or a special case of a more fundamental principle (Bogen, 1969; Goldberg & Costa, 1981; Goldberg, Vaughan, & Gerstman, 1978; Hamilton & Vermeire, 1988a, 1988b, 1991). By divesting natural language of its cardinal role in hemispheric specialization, this position permits the exploration of evolutionary *continuity* in the development of lateralization and homologies across species. This view has the epistemological appeal of greater consistency with general biological reasoning.

The study was premised on the following broad distinction between cognitive novelty and routinization as the basis for hemispheric specialization (Goldberg & Costa, 1981). The right hemisphere is critical for exploratory processing of novel situations to which none of the representations or strategies pre-existing in a subject's cognitive repertoire is readily applicable. The left hemisphere is critical for processing with reliance on preexisting representations and routinized strategies. The hypothesis is supported by cognitive cross-sectional, cognitive longitudinal, and neurological findings (Goldberg & Costa, 1981).

Tucker and Williamson (1984) further developed this theme in a way particularly relevant to the frontal lobes. Based on an extensive literature review, they argued that the dopamine pathways are somewhat lateralized to the left hemisphere *and* are critical for behavioral stereotypes, and norepinephrine pathways to the right hemisphere *and* are critical for response to novelty.

Further support for the novelty–routinization distinction comes from neural nets. Grossberg (1987) and Carpenter and Grossberg (1987) suggested that separating the "stability" and "plasticity" subsystems enhances the computational efficiency of the net.

Assuming that the novelty–routinization principle reflects the general aspects of hemispheric specialization, how is it expressed at different points of the anterior–posterior cerebral axis? The expression of this principle in the posterior cortex and its relationship to agnosias was discussed by Goldberg (1990). We view the functional lateralization of the frontal lobes proposed here as the anterior expression of this general principle.

RESULTS

To test our hypothesis, we designed the Cognitive Bias Task (CBT), capable of quantifying the impact of cognitive context on response selection. CBT is a multiple choice procedure designed as a *bias (preference)* rather than a *performance (accuracy)* task.

CBT entails designs characterized along five binary dimensions: shape (circle/square), color (red/blue), number (one/two identical components), size (large/small), and contour (outline/filled with a homogeneous color). Thus, 32 stimuli can be generated, and a "similarity index" computed between any two stimuli, ranging from 5 (identical) to 0 (differing along all five dimensions).

A trial involves the presentation of the target alone followed by two choices below, vertically aligned to con-

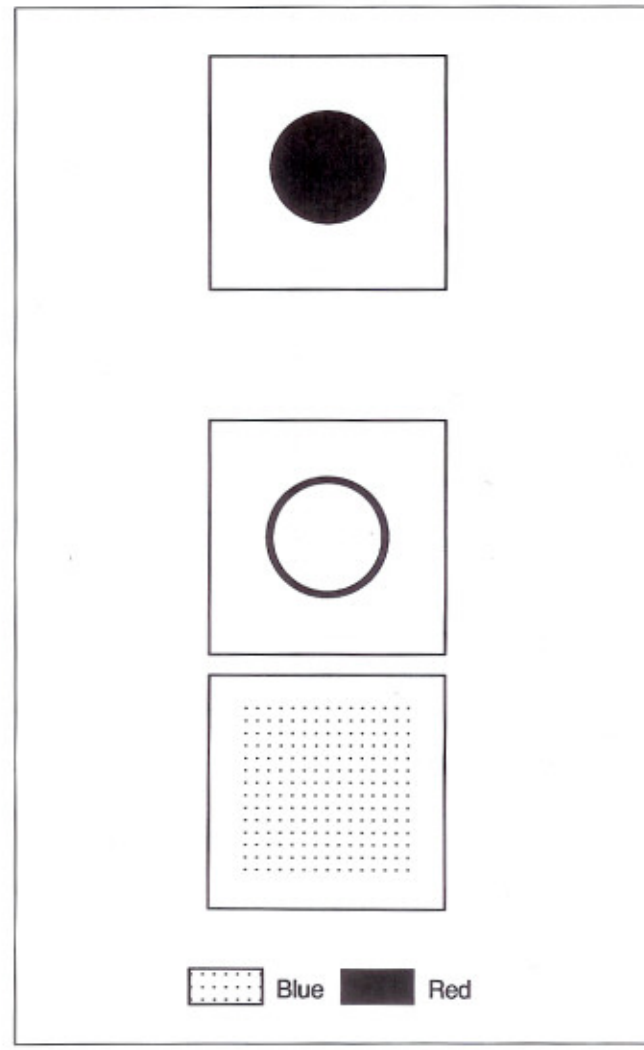

Figure 1. Example of CBT trial.

trol for possible hemi-inattention (Fig. 1). Subjects look at the target and then select one of the two choices that they *like the best*. The experiment is preceded by these instructions:

> You will see cards with different designs. The designs may vary in several respects. You will see a card at the top and two cards below. Look at the top card and choose one of the two cards below that you *like the best*. There are no "correct" or "incorrect" responses. Your choice is entirely up to you. Please, try to choose quickly.

By design, the "similarity indices" between the target and two choices are never equal; thus on each trial subjects must make a choice that is more similar to, or more different from, the target. There are 60 independent trials; the same trial sequence for each subject. All "similarity indices" and target-choice "similarity index" pairs are equally represented and counterbalanced through the sequence.

The "similarity indices" between targets and subject's choices are summed across trials. A high cumulative score implies consistently similar choices—a target-driven response selection bias. A middle-range cumulative score implies that the choices are unrelated to the targets—a target-indifferent selection bias. A low cumulative score implies consistently different choices; in an inverse way it also represents a target-driven selection bias.

It is presumed that the target provides a cognitive context, and we are interested in the degree to which it influences the multiple choice response selection. Since both high and low cumulative scores imply guidance by target properties, both reflect context-dependent response selection. Middle-range cumulative scores imply context-indifferent response selection.

The results of the study will be subjected to two analyses. In the first analysis, we use the raw cumulative scores derived in the above-described fashion. On this scale, ranging from 80 to 220, high and low scores imply a context-dependent and a middle-range score implies context-independent response bias. In group data, however, this scale will not discriminate well between the samples consisting uniformly of context-independent behaviors, or of an admixture of "similar" and "different" context-dependent behaviors.

In the second analysis, we use converted cumulative scores, computed as the absolute deviations of the raw cumulative scores from the raw-score scale midpoint, which is 150. On this scale, ranging from 0 to 70, a high score implies a context-dependent and a low score implies a context-independent response selection bias.

The converted cumulative scores provide a conceptually better measure of the constructs at hand, since they are insensitive to the direction of deviation from raw-score scale midpoint. This also circumvents the problem of averaging across very high and low cumulative raw CBT scores in group data. Still, the raw cumulative scores provide a more direct description of the data, least dependent on our preconceptions about the nature of the task. Very few subjects (patients or controls) scored below midpoint. Therefore, both analyses yield essentially identical results. The one exception to the rule will be discussed below.

Sex Differences in Healthy Right-Handed Subjects

We compared CBT scores in 19 healthy males and 19 females, all strictly right-handed, and matched on age and education (see Methods for the description of handedness assessment). Mean age was 37.6 ± 10.0 in males and 37.7 ± 12.0 in females. Mean education was 15.1 ± 2.5 in males and 14.2 ± 2.6 in females.

The CBT scores were significantly higher in males than

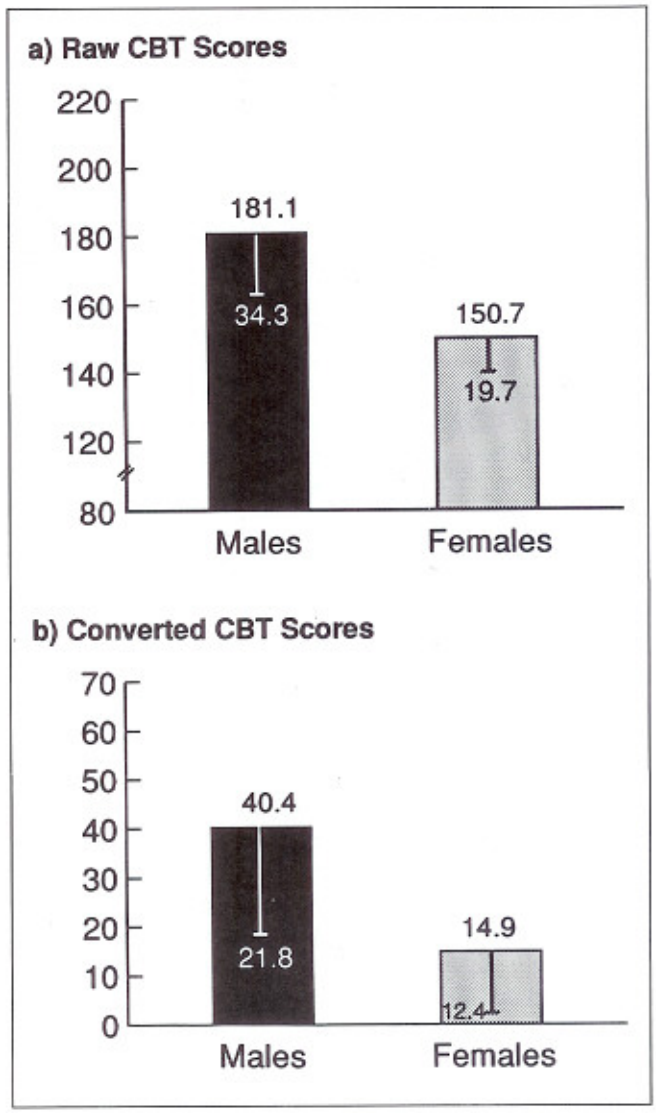

Figure 2. Means and standard deviations for raw (**a**) and converted (**b**) CBT scores in strictly right-handed healthy subjects.

females (Fig. 2a and b). This was true for raw cumulative scores: 181.1 ± 34.3 vs. 150.7 ± 19.7 [$t(28.71) = 3.33$, $p = 0.002$], and converted cumulative scores: 40.4 ± 21.8 vs. 14.9 ± 12.4 ($t = 4.42, p < 0.001$). Right-handed males tend to adopt a more context-dependent response selection bias than right-handed females. The mean converted score was significantly different from 0 (lowest extreme of the scale) in males ($t = 1.85, p < 0.05$) but not females; and different from 70 (highest extreme of the scale) in females ($t = 4.44, p < 0.005$) but not males. Females had lower variance than males for raw ($F = 3.03, p = 0.02$) and converted scores ($F = 3.08, p = 0.02$).

Because of the above sex difference, we decided to consider the two genders separately in all subsequent analyses, even though the initial hypothesis was phrased in a gender-insensitive way.

Effects of Quadrant Lesions in Right-Handed Males

We studied the effects of brain lesions on CBT performance in strictly right-handed males. The sample included five left frontal (LFRM), eight right frontal (RFRM), three left posterior (LPRM), and five right posterior lesions (RPRM). Twenty-one healthy males (HRM) were also studied, matched to patients on age and education. All lesions were lateralized, and did not cross the central sulcus. Regions of interest were outlined with Damasio and Damasio (1989) templates.

In both frontal groups, lesions substantially involved, but were not necessarily restricted to, the dorsolateral areas. They could also affect orbital, operculum, cingulate, and premotor regions. In both posterior groups, lesions substantially involved, but were not necessarily restricted to, the association cortices (see Table 1 for lesion etiology and Fig. 3 for neuroanatomy).

Separate variance t tests were used for all lesion vs. control group CBT score comparisons, instead of ANOVAs, due to the small sample sizes, heterogeneity of group variances, and sample size differences. We also computed nonparametric Kolmogorov–Smirnov two sample tests (Norusis/SPSS Inc., 1986). Since the t test and Kolmogorov–Smirnov analyses yielded virtually identical results, only the former will be presented here. The significance levels are presented without the Bonferroni corrections, since only planned comparisons were made, and their numbers did not exceed the number of degrees of freedom (Keppel, 1991). However, the central findings of the study are sufficiently robust to withstand the Bonferroni correction, which would entail multiplying the significance levels by 4. The findings are summarized in Figure 4a and b.

Raw Score Analysis

The effects of lateralized frontal lesions were opposite: CBT scores increased in RFRM (212.3 ± 4.2), but decreased in LFRM (163.0 ± 4.2), relative to matched HRM (180.3 ± 27.2). Both shifts were significant: $t(22.3) = 5.24$, $p < 0.001$ for the RFRM/HRM comparison and $t(23.0) = 2.78$, $p = 0.01$ for the LFRM/HRM comparison. Obviously, the difference between LFRM and RFRM was more significant: $t(8.61) = 20.68$, $p < 0.001$. Posterior lesions had no, or a minimal, nonsignificant effect in the direction of that of ipsilateral frontal lesions (RPRM = 180.0 ± 35.1; LPRM = 169.3 ± 5.1).

Group variances in RFRM and LFRM were both smaller than in matched controls: $F = 42.5$, $p < 0.001$ for the RFRM/HRM comparison and $F = 42.13$, $p = 0.002$ for the LFRM/HRM comparison. In both frontal lesion groups, CBT scores differed from 150, which corresponds to random performance: $t = 42.3$, $p = <0.001$ for RFRM and $t = 6.95$, $p = 0.002$ for LFRM.

Converted Score Analysis

The effects of lateralized frontal lesions were opposite: CBT scores increased in RFRM (62.3 ± 4.2), but decreased in LFRM (13.0 ± 4.2), relative to matched HR (35.9 ± 18.6). Both shifts were significant: $t(24.4) = 6.1$, $p < 0.001$ for the RFRM/HRM and $t(24.0) = 5.12$, $p < 0.001$ for the LFRM/HRM comparison. Obviously, the difference between LFRM and RFRM was more significant: $t(8.61) = 20.68$, $p < 0.001$. Right posterior lesions had no effect (RPRM = 36.4 ± 26.5), and left posterior lesions had an attenuated effect in the direction of that produced by left frontal lesions [LPRM = 19.3 ± 5.1; $t(12.26) = 3.30$, $p = 0.006$].

Group variances in RFRM and LFRM were both smaller than in matched healthy controls: $F = 20.0$, $p < 0.001$ for the RFRM/HRM comparison and $F = 19.8$, $p < 0.001$ for the LFRM/HRM comparison.

Two control tasks were given in a counterbalanced order to a subset of subjects after CBT (Fig. 5a). They were similar to CBT, but with the explicit instructions to make the "most similar" or "most different" choices. The performance of patients did not differ from that of healthy subjects on these tasks: $t(12.76) = 0.73$, n.s. for the "most similar" and $t(6.80) = 1.13$, n.s. for the "most different" task in patients with frontal lesions; $t(11.89) = 0.62$, n.s. for the "most similar" and $t(6.42) = 0.93$, n.s. for the "most different" task in patients with posterior lesions. Thus the lesions influence response biases rather than abilities.

By design, high CBT scores are "target-driven." To clarify the meaning of middle-range raw (or low converted) CBT scores, the following additional analyses were conducted. For each of the five binary dimensions characterizing the CBT stimuli, the trials with choices discordant for that dimension were selected. Of the 60 trials, 38 were discordant for color, 36 for shape, 36 for number, 38 for size, and 32 for contour. All 60 trials were

Table 1. Lesion Etiology by Group

Group	*n*	*Lesion Etiology*			
		Tumor Excision	*Cerebro-vascular*	*Posttraumatic Excision*	*Temporal Lobectomy*[a]
Strictly Right-handed Males					
Frontal					
Left	5	3	0	2	0
Right	8	3	1	4	0
Posterior					
Left	3	2	0	1	0
Right	5	3	1	1	0
Total	21	11	2	8	0
Strictly Right-handed Females					
Frontal					
Left	5	1	3	1	0
Right	4	3	1	0	0
Posterior					
Left	1	1	0	0	0
Right	4	2	0	1	1
Total	14	7	4	2	1
Non-Right-handed Males					
Frontal					
Left	2	2	0	0	0
Right	2	0	0	2	0
Posterior					
Left	3	0	0	0	3
Total	7	2	0	2	3
Non-Right-handed Females					
Frontal					
Right	3	2	1	0	0
Posterior					
Left	2	0	0	0	2
Right	2	0	0	0	2
Total	7	2	1	0	4

[a]All subjects with temporal lobectomies had the procedure performed for the relief of adult-onset epilepsy. At the time of testing all subjects were seizure free.

discordant for choice position (top or bottom), which comprised the sixth dimension.

For discordant trials, the raw scores for LFRM (the lowest-score male group) were analyzed further. Each LFRM subject had a distinct preference ($p < 0.05$, binomial distribution) on at least one, and on the average 1.80, CBT dimensions.

Then five healthy, strictly right-handed males (matched to LFRM on age and education) were given The Preference Task, which was analogous to CBT in every respect, except on each trial the two choices appeared without a target. The instructions were to choose "the one you like the best." For five out of six binary dimensions the direction of preferences shown by the healthy controls on this task was the same as that exhibited by LFRM on CBT. On one dimension (shape) none of the LFRM subjects exhibited a preference on CBT.

Thus in LFRM, response selection is determined by shared, and probably fairly fixed, sensory preferences, independent of the superimposed cognitive context or task. This produces low converted CBT scores (or raw scores close to scale midpoint). In RFRM response selec-

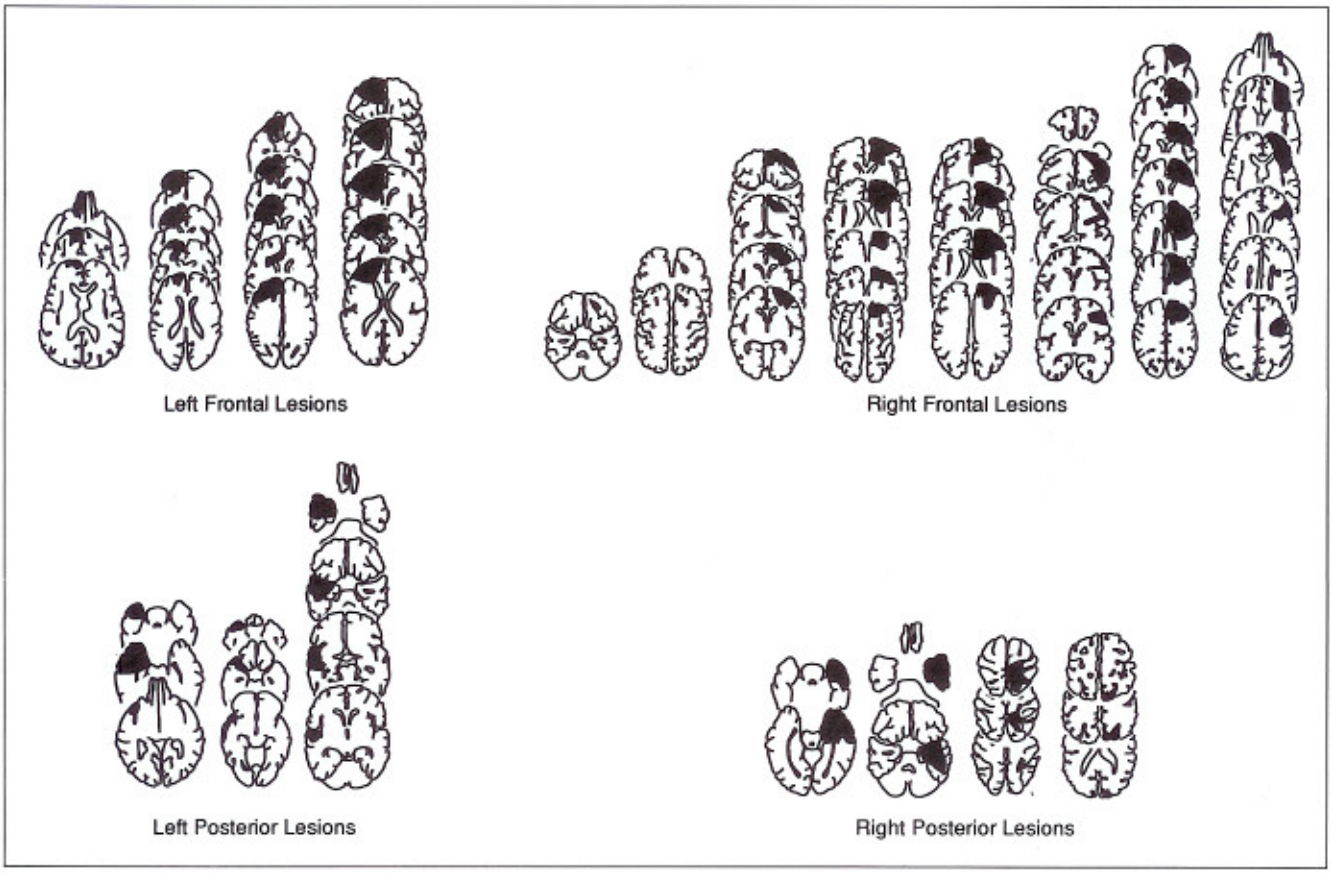

Figure 3. Lesion description in strictly right-handed males. Note: Two scans (one from left frontal lesion group and one from right posterior lesion group) were unavailable. However, detailed written CT/MRI reports were available.

tion is determined by the context-providing targets. This produces high CBT scores. In HRM the scores are intermediate relative to the frontal lesion groups, suggesting a balance between the context-dependent and context-independent factors.

Effects of Quadrant Lesions in Right-Handed Females

We studied the effects of brain lesions on the CBT performance in strictly right-handed females. The sample included five left frontal (LFRF), four right frontal (RFRF), one left posterior (LPRF), and four right posterior lesions (RPRF). Fourteen healthy females (HRF) were also studied, matched to patients on age and education. Lesion anatomy (Fig. 6) was similar to that of the male groups.

Raw Score Analysis

The effects of left and right frontal lesions were similar: CBT scores increased in LFRF (204.4 ± 12.6) and RFRF (214.7 ± 2.1) relative to matched HRF (158.3 ± 16.5). Both shifts were significant: $t(9.36) = 6.45, p < 0.001$ for the LFRF/HRF comparison and $t(14.27) = 12.45, p < 0.001$ for the RFRF/HRF comparison. The effect of right frontal lesions was greater than that of left, but not significantly. Group variances were smaller in RFRF than in LFRF ($F = 37.3, p = 0.01$) and in HRF ($F = 64.3, p = 0.006$).

The effects of left and right posterior lesions were also similar and opposite to those of frontal lesions: CBT scores decreased somewhat in LPRF (138.0) and RPRF (151.7 ± 9.1) relative to matched HRF (158.3 ± 16.5). The effects were not as strong as in frontal lesions. The RPRF/HRF comparison was not significant. No comparison was possible between HRF and the one LPRF patient. When the CBT scores of all posterior-lesioned subjects (149.0 ± 10.0) were compared with those of all frontal-lesioned subjects (209.0 ± 10.5), the effect was significant [$t(8.8) = 10.54, p < 0.001$].

Converted Score Analysis

The effects of left and right frontal lesions were similar: CBT scores increased in LFRF (54.4 ± 12.6) and RFRF

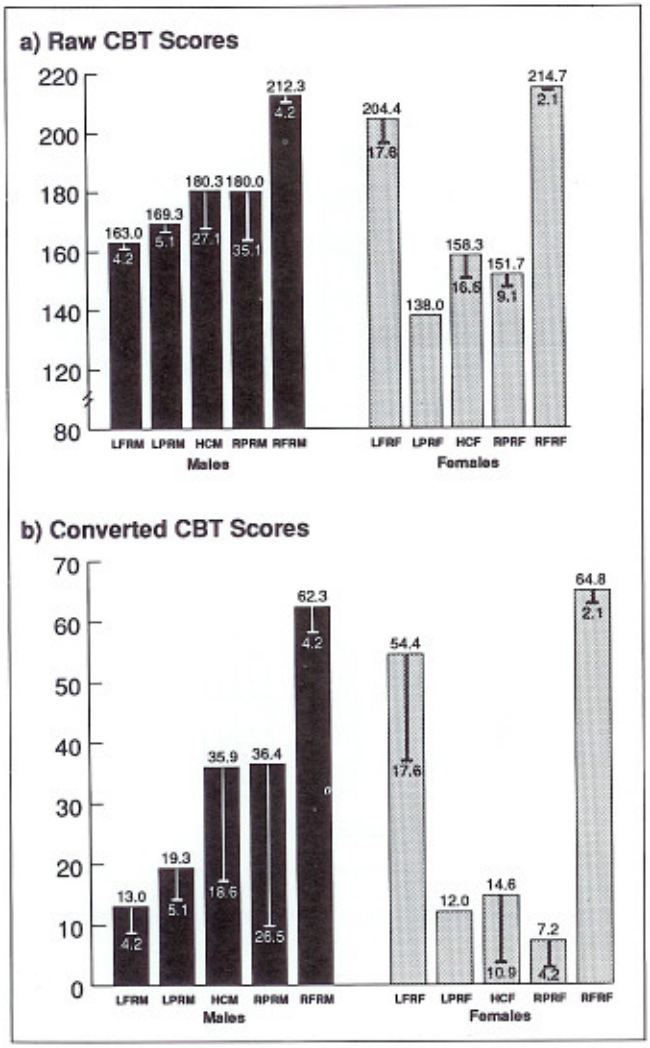

Figure 4. Mean raw (**a**) and converted (**b**) CBT scores in male and female lesion groups. LFRM, left frontal right-handed males ($n = 5$); LPRM, left posterior right-handed males ($n = 3$); HCM, healthy control males ($n = 21$); RPRM, right posterior right-handed males ($n = 5$); RFRM, right frontal right-handed males ($n = 8$); LFRF, left frontal right-handed females ($n = 5$); LPRF, left posterior right-handed females ($n = 1$); HCF, healthy control females ($n = 14$); RPRF, right posterior right-handed females ($n = 4$); RFRF, right frontal right-handed females ($n = 4$).

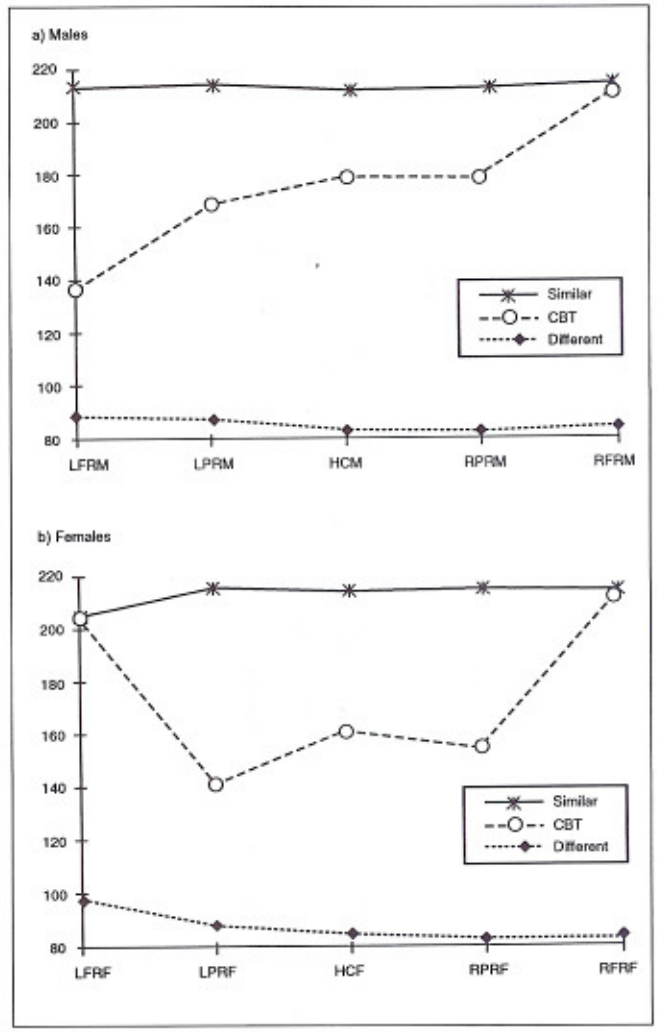

Figure 5. Mean group scores for CBT and the control tasks with explicit instructions in strictly right-handed subjects: (**a**) males; (**b**) females. LFRM, left frontal right-handed males; LPRM, left posterior right-handed males; HCM, healthy control males; RPRM, right posterior right-handed males; RFRM, right frontal right-handed males; LFRF, left frontal right-handed females; LPRF, left posterior right-handed females; HCP, healthy control females; RPRF, right posterior right-handed females; RFRF, right frontal right-handed females.

(64.8 ± 2.1) relative to matched HRF (14.6 ± 10.9). Both shifts were significant: $t(6.3) = 6.3$, $p = 0.001$ for the LFRF/HRF comparison and $t(15.4) = 16.3$, $p < 0.001$ for the RFRF/HRF comparison. The effect of right frontal lesions was greater than that of left, but not significantly. Group variances were smaller in RFRF than in LFRF ($F = 37.25$, $p = 0.01$) and in HRF ($F = 27.9$, $p = 0.02$).

The effects of left and right posterior lesions were also similar and opposite to those of frontal lesions: CBT scores decreased somewhat in LPRF (12.0) and in RPRF (7.2 ± 4.2) relative to matched HRF (14.6 ± 10.9). The effect was not as strong as in frontal lesions. The RPRF/HRF comparison approached significance [$t(13.84) = 2.04$, $p = 0.06$]. No comparison was possible between HRF and the one LPRF patient. When CBT scores of all subjects with posterior lesions were compared with those of all subjects with frontal lesions, the effect was significant [$t(11.39) = 12.77$, $p < 0.001$].

Two control tasks with the explicit instructions to make the "most similar" or "most different" choices were given to a subset of subjects after CBT. The performance of patients and healthy controls did not differ: $t(9.62) = 1.3$, n.s. for the "most similar" task and $t(7.3) = 0.3$, n.s. for the "most different" task (Fig. 5b). Thus, the lesions influence response biases rather than abilities.

For discordant CBT trials, the raw scores for HRF, LPRF, and RPRF (the lowest-score female groups) were analyzed further. LPRF and RPRF were pooled together. Each HRF, LPRF, and RPRF subject had a preference ($p < 0.05$,

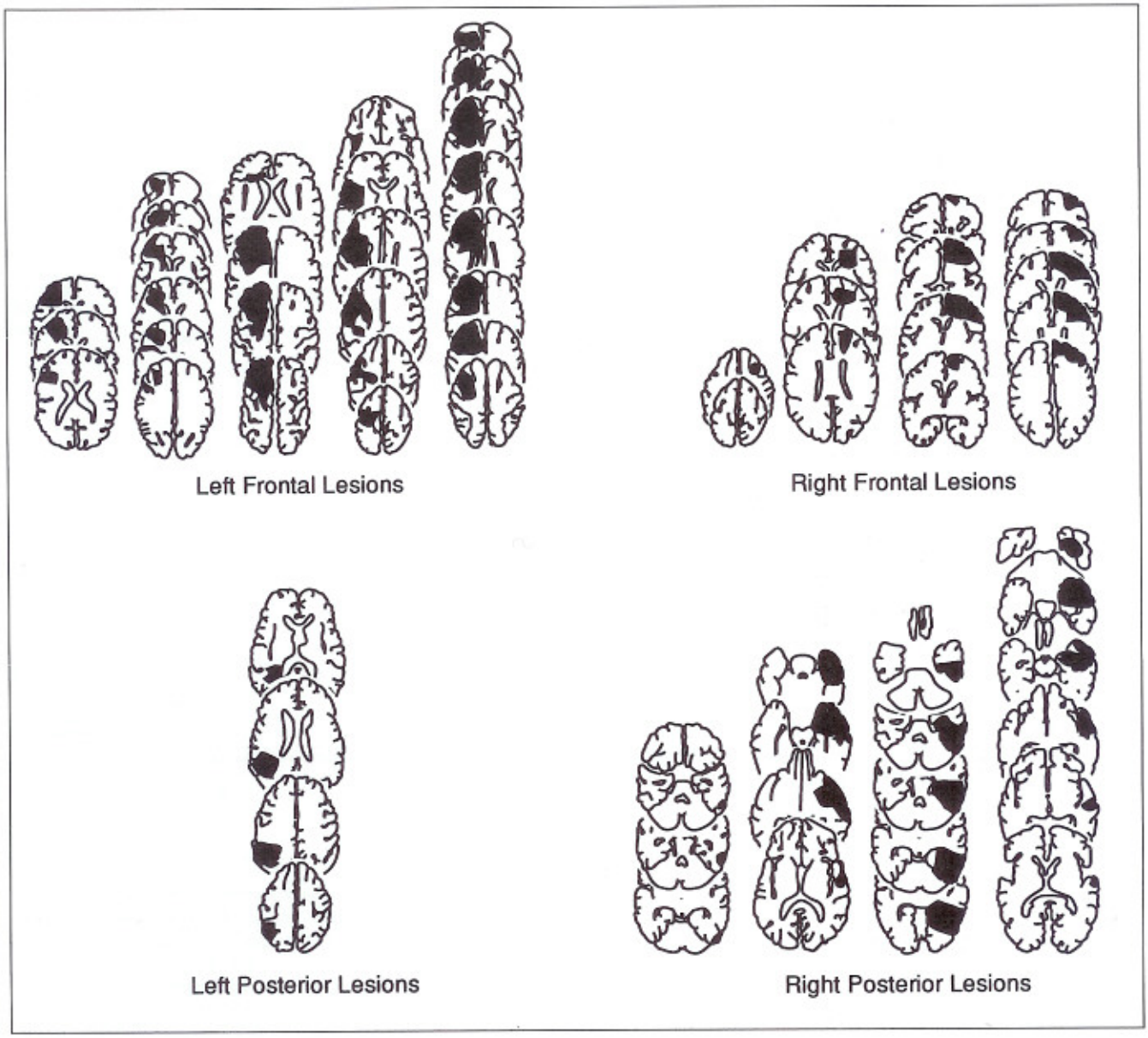

Figure 6. Lesion description in strictly right-handed females.

binomial distribution) on at least one CBT dimension: on the average 1.4 for LPRF/RPRF and 1.33 for HRF.

Then 23 healthy, strictly right-handed females (matched to the above groups on age and education) were given The Preference Task. The preferences shown by the healthy females on this task was the same as those exhibited on CBT by HRF for five out of six dimensions (on one dimension no preference was shown) and by LPRF and RPRF for three out of six dimensions (on three dimensions no preference was shown).

Thus, in HRF, LPRF, and RPRF response selection on CBT is determined by shared, and probably fairly fixed, sensory preferences, independent of the superimposed context or task. This produces low CBT scores. In RFRF and LFRF selection is determined by context-providing targets. This produces high CBT scores.

Comparison of Lesion Effects in Right-Handed Females and Males

We now compare the CBT scores in males and females with quadrant lesions (Fig. 4a and b). Two issues will be addressed: the differential effects of frontal vs. posterior lesions and of left vs. right frontal lesions. Because of the variance and sample size differences across samples, ANOVA could not be performed. Separate variance *t* tests were used (Norusis/SPSS Inc., 1986).

Left–Right vs. Frontal–Posterior Effects

In males ipsilateral lesions shift CBT scores in the same direction relative to healthy controls. Left-hemispheric lesions decrease CBT scores toward context-indepen-

dence. Right-hemispheric lesions increase CBT scores toward context-dependence. In females the lesion effects are best described along the frontal–posterior, rather than the left–right, axis. Frontal lesions (left and right) increase CBT scores toward context-dependence. Posterior lesions (left and right) decrease CBT scores toward context-independence.

In males, the CBT scores for the left frontal and posterior lesion groups combined significantly differ from the CBT scores for the right frontal and posterior lesion groups combined: raw $t(13.55) = 4.59$, $p < 0.001$; converted $t(14.50) = 6.20$, $p < 0.001$. Conversely, the CBT scores for the left and right frontal lesion groups combined do not significantly differ from the CBT scores for the left and right posterior lesion groups combined: raw $t(14.07) = 1.45$ n.s.; converted $t(16.57) = 1.27$, n.s.

In females, the opposite is true. The CBT scores for the left frontal and posterior lesion groups combined do not significantly differ from the CBT scores for the right frontal and posterior lesion groups combined: raw $t(11.70) = 0.59$, n.s.; converted $t(11.91) = 0.82$, n.s. Conversely, the CBT scores for the left and right frontal lesion groups combined significantly differ from the CBT scores for the left and right posterior lesion groups combined: raw $t(8.75) = 10.54$, $p < 0.001$; converted $t(11.39) = 12.77$, $p < 0.001$.

These data are best characterized by the scatter plots in Figure 7a and b. The raw and converted scores revealed virtually identical patterns. Therefore, only the latter are presented.

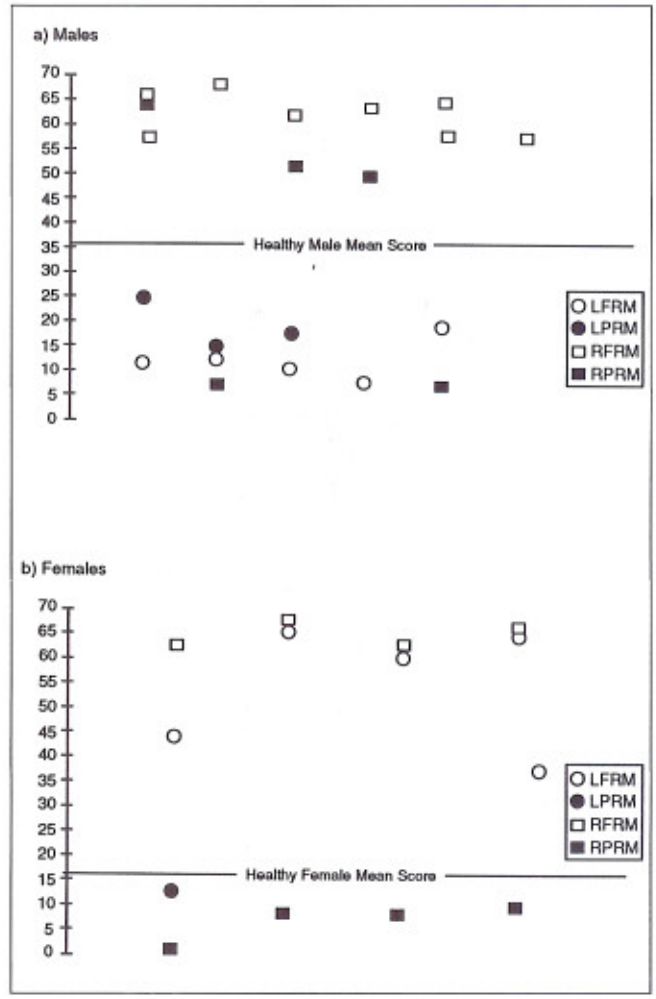

Figure 7. Scatter plot diagrams of converted CBT scores in strictly right-handed subjects: (**a**) males; (**b**) females. LFRM, left frontal right-handed males; LPRM, left posterior right-handed males; HCM, healthy control males; RPRM, right posterior right-handed males; RFRM, right frontal right-handed males; LFRF, left frontal right-handed females; LPRF, left posterior right-handed females; HCP, healthy control females; RPRF, right posterior right-handed females; RFRF, right frontal right-handed females.

Relative Magnitude of Frontal and Posterior Lesion Effects

Both in males and females, the magnitude of the effects produced by frontal and posterior lesions is unequal: the effects of frontal lesions are dramatic, and those of posterior lesions minimal. Does this disparity reflect the true properties of functional cerebral organization, and suggest that the cognitive response selection bias is controlled mostly by the frontal systems? Or is it, at least in part, an artifact of the scales used? For males there is no obvious reason to suspect the latter. For females such an artifact may be at work with respect to the converted scores.

In males, the mean CBT score of the healthy sample is close to the scale midpoint (Fig. 4a). This gives an equal opportunity of expression for the CBT-score decreasing and increasing lesion effects. In females the CBT score of the healthy sample is close to the bottom of the scale (Fig. 4b). This may interfere with the expression of the CBT-score decreasing lesion effects. Although minimal, the posterior-lesion effects are real. All the posterior-lesioned patients have CBT scores, both raw and converted, below the healthy control mean CBT score ($p < 0.031$, binomial distribution).

It is impossible to equally calibrate the male and female scores within the same task, yet one can design a similar (to CBT) task where the healthy female mean score is close to the middle of the scale, and the healthy male mean score shifted proportionately toward the top. If on the new scale the frontal lesion effect still exceeds that of posterior lesions in females, we will conclude that this reflects the true properties of functional cerebral organization. But if the disparity of effect magnitude is an artifact of CBT, then it will disappear on the new task.

We developed CBT2, a task very similar to CBT, but Markovian rather than stochastic. In CBT2 subject's choice on trial i becomes the target on trial $i + 1$. The response bias pattern in lesion and control groups is identical in the two tasks, but the healthy female mean CBT2 score is closer to the middle of the scale.

Left and right frontal lesion effects were similar in

females: CBT2 scores increased in LFRF (196.6 ± 13.8 raw; 33.1 ± 13.8 converted) and RFRF (211.3 ± 9.7 raw; 47.75 ± 9.7 converted) relative to matched HRF (185.7 ± 15.0 raw; 22.2 ± 15.0 converted). Left and right posterior lesion effects were also similar and opposite to those of frontal lesions: CBT2 scores decreased in LPRF (177 raw; 13.5 converted) and in RPRF (166.7 ± 11.4 raw; 9.25 ± 5.5 converted) relative to matched HRF (185.7 ± 15.0 raw; 22.2 ± 15.0 converted).

On CBT2 the frontal and posterior lesion effects in females are of comparable magnitudes. Both significantly change CBT2 scores compared to controls [for frontal lesions $t(18.31) = 2.85, p = 0.01$; for posterior $t(16.85) = 2.65, p = 0.017$], and in opposite directions.

Effects of Lateralized Frontal Lesions in Males and Females

The effects of right frontal lesions are identical in females and males. They increase the CBT scores, suggesting a context-dependent response selection bias. The effects of left frontal lesions are opposite. In males, they decrease the CBT scores, suggesting a context-independent bias. In females they increase the CBT scores, suggesting a context-dependent bias. The difference is significant [$t(4.87) = 6.98, p = 0.001$ for both raw and converted scores].

Effects of Lateralized Posterior Lesions in Males and Females

The effects of left posterior lesions are similar in females and males. They decrease CBT scores, suggesting a context-independent bias. The effects of right posterior lesions are opposite. In males, they increase CBT scores toward a more context-dependent bias. In females, they tend to decrease the CBT score toward a less context-dependent bias. The difference does not reach significance [$t(4.66) = 1.73, p = 0.14$ raw; $t(4.25) = 2.42, p = 0.07$ converted].

Interaction between Sex and Handedness

Sex-Handedness Interaction in Healthy Subjects

We administered CBT to 18 non-right-handed subjects: 7 males and 11 females (see Methods for the description of handedness assessment). Mean age was 33.7 ± 13.8 in males and 34.4 ± 9.6 in females. Mean education was 16.9 ± 1.7 in males and 13.9 ± 2.3 in females.

Significant sex by handedness effect was found for CBT scores (Fig. 8a and b) using an ANOVA covarying age and education [$F(1,52) = 4.48, p = 0.007$ raw; $F(1,52) = 7.64, p = 0.001$ converted]. In strict right-handers the CBT score is higher in males than females: 180.3 ± 27.2 vs. 158.3 ± 16.5 raw; 35.9 ± 18.6 vs. 14.6 ± 10.9 converted. The corresponding CBT scores in non-right-handers are 176.14 ± 31.33 vs. 181.09 ± 28.85 raw; 30.71 ± 26.04 vs. 36.55 ± 20.65 converted. The sex difference is significant in right-handers [$t(28.71) = 3.33, p = 0.002$ for raw and $t(28.58) = 4.42, p < 0.001$ for converted scores], but not in non-right-handers [$t(12.11) = 0.34, p = 0.34$ for raw and $t(10.73) = 0.50, p = 0.63$ for converted scores].

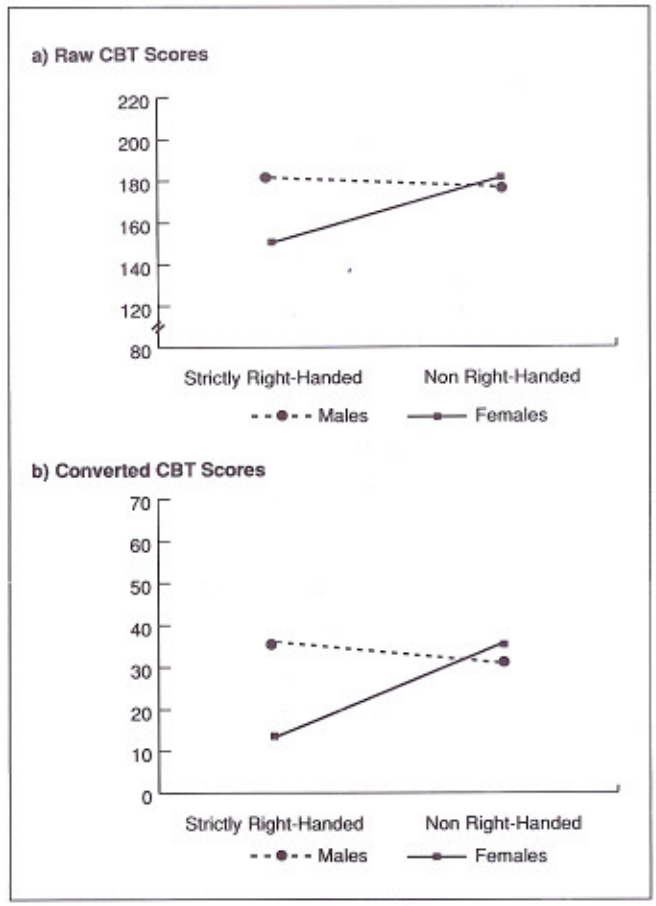

Figure 8. Raw (**a**) and converted (**b**) CBT scores in strictly right-handed and non-right-handed healthy males and females. Strictly right-handed: males $n = 19$ and females $n = 19$; non-right-handed: males $n = 7$ and females $n = 11$.

The effect of handedness on the CBT score is greater in females than males. Female non-right-handers adopt a more context-dependent response bias than right-handers [$t(15.52) = 3.10, p = 0.007$ for raw and $t(14.29) = 3.15, p = 0.007$ for converted score]. Response bias in non-right-handed females is comparable with that of right-handed males. In males the effect of handedness is minimal.

Handedness, Sex, and the Effects of Quadrant Lesions

The data discussed in this section are preliminary due to the small sample sizes. We chose to present them, since they suggest important trends. Left-handed individuals with acquired quadrant lesions are few, and a large sample study may extend in time indefinitely.

We administered CBT to a sample of non-right-handed

subjects with acquired quadrant lesions (see Fig. 9 for neuroanatomical descriptions). The inclusion criteria were the same as for right- handers. The sample included two males with left frontal (LFNRM), three males and two females with left posterior (LPNRM and LPNRF), two males and three females with right frontal (RFNRM and RFNRF), and two females with right posterior lesions (RPNRF). Their raw CBT scores were 160.5 ± 78.5, 151.67 ± 60.14 and 198.5 ± 3.54, 141.5 ± 3.5 and 130.67 ± 36.61, and 192.0 ± 31.11, respectively. Their converted CBT scores were 55.5 ± 14.8, 41.9 ± 33.15 and 48.5 ± 3.5, 8.5 ± 3.5 and 26.67 ± 28.88, and 42.0 ± 31.11, respectively. No females with left frontal, or males with right posterior, lesions were available.

Lesions effects in right-handers and non-right-handers are compared in Figures 10 and 11. The CBT scores of non-right-handed patients are more variable than those of right-handed ($F = 2.46, p = 0.036$ for raw score). This may be due, in part, to the heterogeneity of the non-right-handed group.

Non-right-handers were more likely to consistently select more different choices (cumulative raw score below 150) than right-handers. Of the non-right-handers, 50% (7 out of 14) of patients had cumulative scores below 150 vs. 14% (5 out of 35) right-handers ($\chi^2 = 5.10, p = 0.02$). This was true in males [71.4% non-right-handers vs. 9% right-handers, Fisher's Exact Probability (FEP) = 0.004], but not females (28.6% non-right-handers vs. 21.4% right-handers, FEP = 1.0); and in frontal lesions (71.4% non-right-handers vs. 0% right-handers, FEP = 0.00002), but not in posterior lesions (28.6% non-right-handers vs. 38.5% right-handers, FEP = 1.0). The above- and below-150 scores were represented equally in left- and right-hemispheric lesions in non-right-handers.

An interaction between handedness and right frontal lesion effects is evident both in females and males, for raw and converted scores. In both genders right frontal lesions shift response toward context-dependence in right-handers, and toward context-independence in non-right-handers, relative to healthy controls.

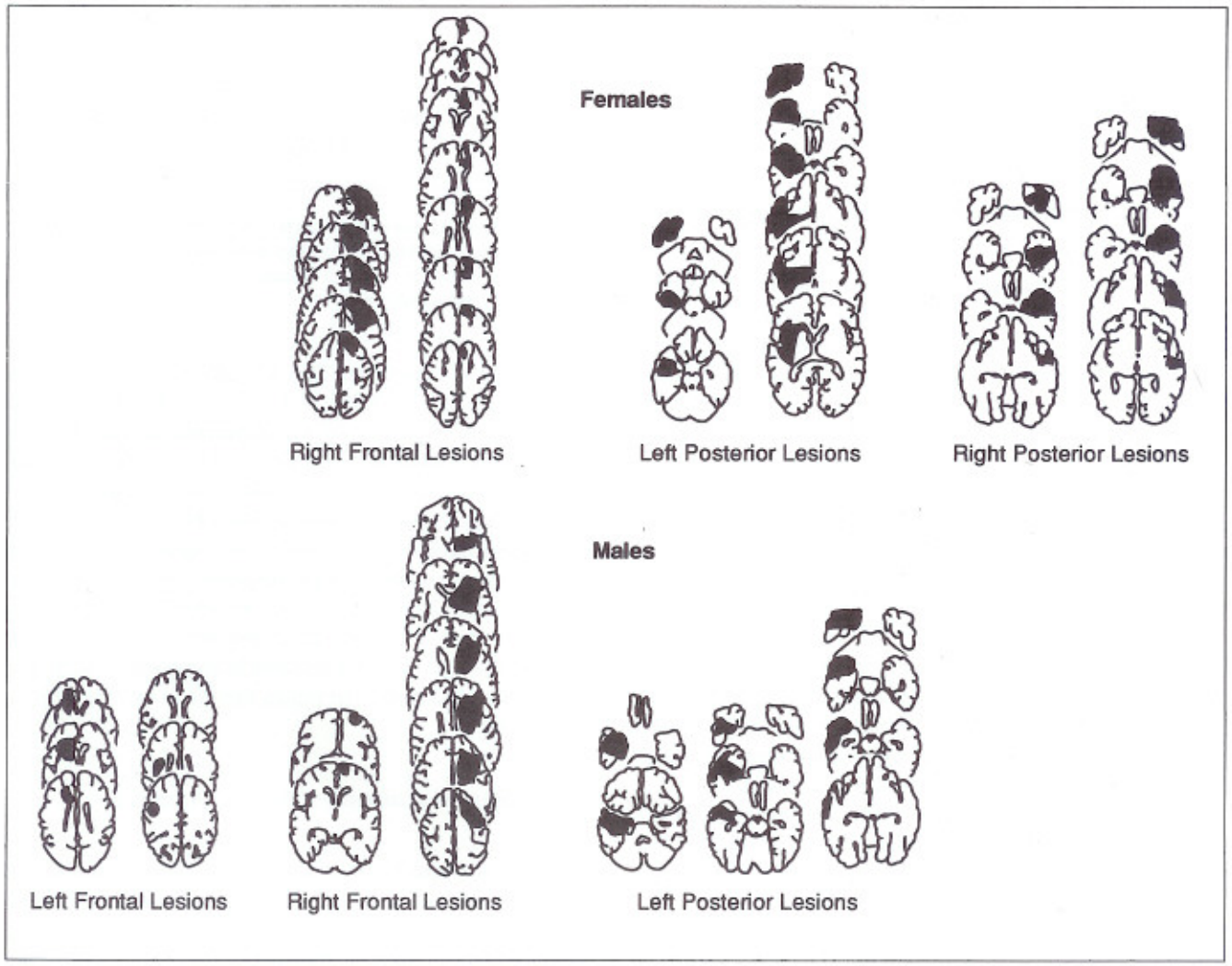

Figure 9. Lesion description in non-right-handed subjects. Note: One scan from the female right frontal group was unavailable. However, a detailed written CT/MRI report was available.

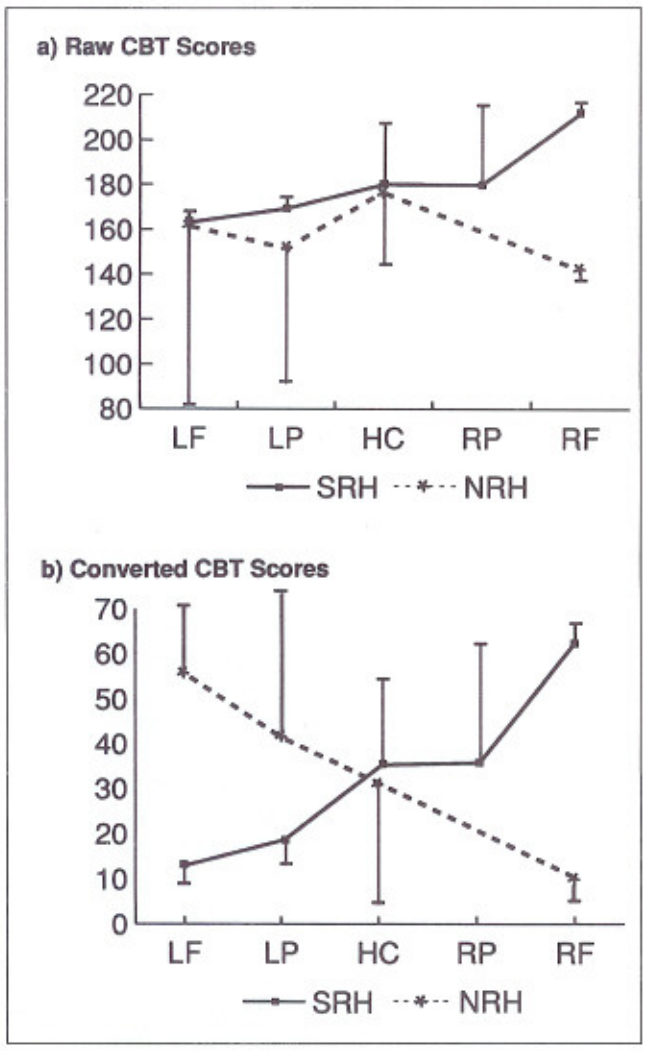

Figure 10. Raw (**a**) and converted (**b**) CBT scores in strictly right-handed (SRH) and non-right-handed (NRH) lesioned males. SRH-LF, left frontal (n = 5); LP, left posterior (n = 3); HC, healthy control (n = 21); RP, right posterior (n = 5); RF, right frontal (n = 8). NRH-LF, left frontal (n = 2); LP, left posterior (n = 3); HC, healthy control (n = 7); RP, right posterior (n = 0); RF, right frontal (n = 2).

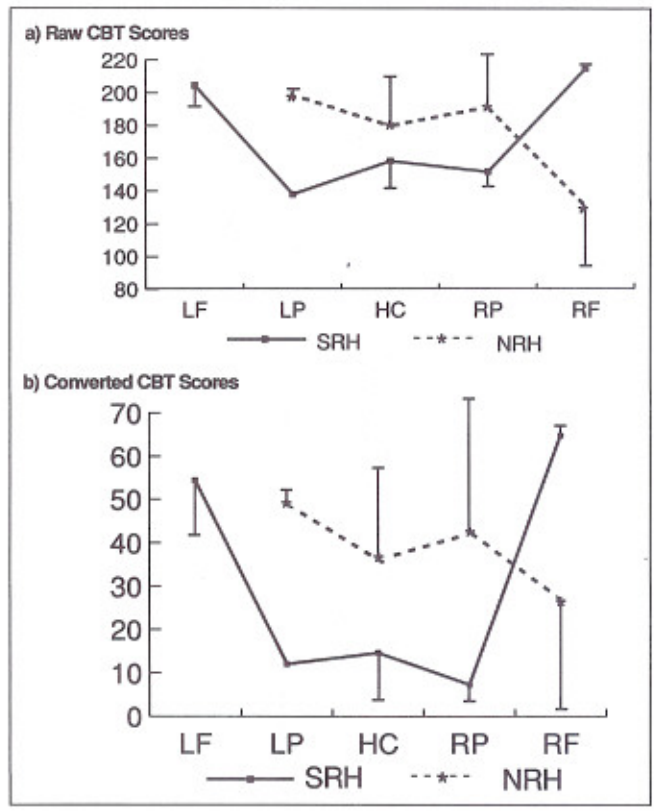

Figure 11. Raw (**a**) and converted (**b**) CBT scores in strictly right-handed (SRH) and non-right-handed (NRH) lesioned females. SRH-LF, left frontal (n = 5); LP, left posterior (n = 3); HC, healthy control (n = 21); RP, right posterior (n = 5); RF, right frontal (n = 8). NRH-LF, left frontal (n = 0); LP, left posterior (n = 2); HC, healthy control (n = 7); RP, right posterior (n = 2); RF, right frontal (n = 3).

The effects of left-hemispheric lesions, both frontal and posterior, can be examined only in males. Mean raw CBT scores are similar in right-handers and non-right-handers: both are shifted toward context-independence relative to healthy controls. Mean converted CBT scores, however, reveal a distinct interaction: response selection bias is shifted toward context-independence in right-handers, and toward context-dependence in non-right-handers.

The reason for this discrepancy is elucidated by individual raw scores examination. Non-right-handed males with left-hemispheric lesions comprise the group with an equal number of extremely high and low raw CBT scores. As a result, the mean raw CBT scores in LFNRM and LPNRM are close to 150 (scale midpoint), and their variability is higher than in any other group. Thus, right-handers with left-hemispheric lesions exhibit a context-independent bias (middle-range raw CBT scores). Among the non-right-handers with left-hemispheric lesions, two forms of a context-dependent bias occur in roughly equal proportions: consistently similar and different choices (high and low raw CBT scores, respectively).

Handedness, Sex, and Functional Cortical Geometry

Not all the quadrant lesion types were available in non-right-handers. Still, visual inspection of Figures 10 and 11 is possible.

In females, quadrant lesion effects on CBT scores are opposite in right-handers and non-right-handers (Fig. 11a and b). In right-handers frontal lesions produce a context-dependent, and posterior lesions context-independent, bias relative to healthy controls. In non-right-handers frontal lesions produce a context-independent and posterior lesions a context-dependent bias. In both right-handers and non-right-handers lesion effects differ along the frontal–posterior, rather than left–right axis, frontal greater than posterior.

In males, lesion effects on the converted CBT scores are opposite in right-handers and non-right-handers (Fig. 10a and b). In right-handers left-hemispheric lesions produce a context- independent and right-hemispheric lesions a context-dependent response bias relative to healthy controls. In non-right-handers left-hemispheric lesions produce a context-dependent and right-hemispheric lesions a context-independent bias. In both right-handed and non-right-handed male groups lesion effects differ along the left–right rather than frontal–posterior axis.

The picture is less clear-cut for the raw CBT scores in males, since in group data raw scores do not discriminate between extremely context-independent behaviors and the admixture of two extremely context-dependent behaviors ("similar" and "different"). When individual cumulative raw CBT scores are examined, it becomes clear that the non-right-handed males with left-hemispheric lesions are very different from their right-handed counterparts.

DISCUSSION

We examined cognitive biases, rather than abilities, in an intrinsically ambiguous task. This may explain the robustness of the observed effects. Assessment of response selection biases may prove to be a sensitive paradigm in cognitive studies.

The constructs of context-dependent and context-independent response biases developed here are still intuitive ones. They require further elaboration and must be instantiated through additional cognitive tasks of various levels of complexity. More precise understanding of underlying neuroanatomy is also required.

Nonetheless, the adaptive value of two contrasting response selection biases is plausible, and their relationship with distinct neural mechanisms is strongly suggested by our findings. Both the concepts and the paradigm presented here have been developed to allow, at least in principle, parallel experimentation across species, and to explore the evolutionary continuities in functional cortical geometry in terms independent of language.

We phrased our original hypothesis in a gender-invariant way, but contrary to our expectations, robust sex differences have emerged in the study. As a result, the hypothesis was confirmed for the males but not females, and the study took on an additional, unanticipated dimension. Below, we will discuss the findings separately in the context of the functional lateralization of the frontal lobes, gender differences, and handedness.

Lateralization of Frontal Lobe Functions in Right-Handed Males

Lateralized prefrontal lesions in right-handed males alter performance in extreme ways: right frontal lesions produce context-dependent and left frontal lesions context-independent responses. Ipsilateral lesions affect CBT performance in similar directions, but the effects of frontal lesions are far stronger than those of posterior lesions. The CBT scores in patients with frontal lesions are characterized by extremely small within-group variances relative to other groups. This indicates that the processes examined here are controlled primarily by lateralized frontal systems, rather than by whole hemispheres, and that lateralized frontal lesions bias performance in extreme ways.

The findings suggest the following functional organization in right-handed males. The left frontal system emphasizes response selection guided by the current cognitive context; with its role diminished, performance becomes less context-dependent. The right frontal system emphasizes context-independent selection; with its role diminished, performance becomes more context-dependent.

The distinction between context-dependent and context-independent selection biases provides a better account of the findings than the more traditional distinctions applied to hemispheric specialization. The analytic–holistic distinction predicts an increase following left-, and a decrease following right-hemispheric damage in the number of stimulus dimensions used by subjects in response selection. The latter effect is predicted also by the verbal–nonverbal distinction, given the nonverbal nature of CBT stimuli. In fact, the opposite happens.

Prefrontal cortex is central for the selection and bringing "on line" goal-appropriate internal representations (Goldman-Rakic, 1987). Context-dependent behaviors require response selections strongly influenced by specific task representations; and context-independent behaviors require selection of stored representations that define the most probable (across various contexts and tasks) responses to given stimuli. Prefrontal cortex is critical in working memory (Goldman-Rakic, 1987). Our findings suggest that in right-handed males working memory is particularly dependent on the left frontal system (see also Goldberg & Podell, 1994).

While both left and right prefrontal systems probably have access to the universal knowledge base, their interpretation of task demands differ, and they emphasize different response selection biases. Both response selection biases confer certain adaptive advantages, and each embodies a different decision-making strategy. Their relative utility may depend upon how much, or how little, the organism "knows" about a particular situation. If much is known, response selection is guided by the task-specific knowledge. If little is known, response selection is guided by what is the most likely adaptive response across many cognitive situations that have at least something in common with the task.

It is tempting to relate the difference between the context-dependent and context-independent response

selection biases to the difference between internally and externally guided behaviors. This reduction is useful, since it clarifies the constructs involved and captures some of their meaning. Yet it is misleading, since it contains an oversimplification. It is important to distinguish between that which is selected, and that which determines selection. In both cases, response is selected from a pre-existing knowledge base and is in that sense "internal"; but selection is determined by different mechanisms. In context-dependent behaviors it is determined by the internal representation of the tasks at hand and in context-independent behaviors by external cues.

Sexual Dimorphism in the Functional Cortical Geometry

Healthy right-handed females and males differ in response biases: it is more context-dependent in males, and more context-independent in females. This supports the notion that the sexual dimorphism of the human brain extends beyond the systems directly linked to reproductive behavior (Goy & McEwen, 1980; McEwen, 1991). The relationship of these findings to previously reported gender differences in cognitive styles (Witkin, Cox, Friedman, Hrishikesan, & Seigel, 1974; Witkin, Dyk, Faterson, Goodenough, & Karp, 1962; Witkin et al., 1973) and abilities (Gouchie & Kimura, 1991; Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Kimura, 1987; Kimura, 1983; Kimura & Harshman, 1984) merits further exploration.

We found robust sexual dimorphism in the neural mechanisms of response selection. It is particularly evident in the effects of lateralized frontal lesions on producing extreme cognitive response selection biases. Furthermore, the overall functional cortical geometry appears to emphasize different axes in the two genders: left–right in males and frontal–posterior in females. We will discuss these two sets of findings separately.

Sexual Dimorphism in the Frontal and Posterior Cortices

In our study, the effects of frontal lesions are asymmetric in males, but symmetric in females. This suggest a greater degree of functional asymmetry in the male than female frontal lobes and parallels the evidence from human studies and animal models.

Prefrontal cortical volumes are asymmetric in male (right greater than left) and symmetric in female human fetuses (deLacoste, Horvath, & Woodward, 1991). So is regional cerebral blood flow activation in self-induced dysphoria: bifrontal in females and left-frontal in males (Pardo, Pardo, & Raichle, 1993).

Animal studies have consistently suggested that gonadal hormones are responsible for a number of sexually dimorphic brain-shaping effects involving hemispheric asymmetries and the frontal lobes. In fetal monkeys, androgen receptor concentration in the frontal lobes is asymmetric in males, but symmetric in females (Sholl & Kim, 1990). Fetal and early postnatal cortical aromatase activity is higher in the monkey male than female prefrontal cortex (MacLusky, Nattolin, & Goldman-Rakic, 1986, Roselli & Resko, 1986). Estradiol receptor concentration is higher in the left hemisphere of male than female rats (Sandu, Cook, & Diamond, 1986), which may account for the sexual dimorphism in cortical thickness (Diamond, 1985; Diamond, Dowling, & Johnson, 1981; Diamond, Johnson, & Ingram, 1975; Diamond, Johnson, Young, & Sing, 1983; Papas, Diamond, & Johnson, 1979). Progesterone binding activity is higher in female than male rat frontal cortex (Maggi & Zucchi, 1987).

Frontal lesions produce sexually dimorphic effects in rats and monkeys. Male, but not female, rats show an asymmetric response to lateralized frontal lesions (Starkstein et al., 1989). Frontal lobe-mediated object reversal discrimination develops earlier in male than female monkeys (Clark & Goldman-Rakic, 1989; Goldman & MacBrown, 1975; Goldman, Crawford, Stokes, & Rosvold, 1974).

In our study, the effects of right frontal lesions are similar in females and males, but the effects of left frontal lesions are sexually dimorphic. Conversely, the effects of left posterior lesions are similar in females and males, but the effects of right posterior lesions are sexually dimorphic, albeit to a lesser extent. It is of interest that animal models suggest gender differences in the degree to which the maturation of various cortical regions is governed by androgens. In gonadectomized male rats the left–right thickness ratio for the frontal, but not occipital, cortex is reversed. In female rats, ovariectomy reverses this ratio for the occipital and parietal cortices (Diamond, 1985).

The precise neurohormonal mechanisms responsible for the sexual dimorphism in the neocortex is unclear. Geschwind (1984) and Geschwind and Galaburda (1985, 1987) hypothesized that the dimorphic organizational effects of testosterone involve the left hemisphere by inhibiting its development. Galaburda et al. (1987) modified this position by proposing that testosterone affects brain lateralization by enhancing the growth of the right hemisphere.

Even accepting these hypotheses in terms of postulated outcomes, the mechanisms remain unclear. Does testosterone mediate growth inhibition or the enhancement of pruning in the left hemisphere; and growth enhancement or the retardation of pruning in the right hemisphere? Testosterone is involved both in neural growth and in neural death (Arnold & Breedlove, 1985).

Left–Right and Frontal–Posterior Axes of Functional Cortical Organization

In males, ipsilateral lesions produce effects of similar direction but different magnitudes, frontal greater than

posterior. Homologous lesions in opposite hemispheres produce opposite effects of comparable magnitudes. In females, the side of the lesion does not matter, but its position along the frontal–posterior axis does. Frontal and posterior lesions produce opposite effects; the former are of greater magnitude than the latter.

It is not clear if the difference in the effect magnitudes in females is inherent in the processes measured, or is an artifact of the procedure used. If response selection is controlled overwhelmingly by the frontal systems in either gender, then the frontal–posterior difference in effect magnitudes is inherent in the processes measured, and should be expected regardless of the procedure used. Further evidence may emerge, however, that in females frontal and posterior lesion effects are of opposite direction but comparable in magnitude, as our own findings suggest.

Such evidence would have far-reaching implications for understanding the scope of sexual dimorphism in the neural mechanisms of cognition. It would suggest robust differences in the general aspects of functional cortical geometry. Indeed, the frontal–posterior functional differences in the left hemisphere are more pronounced in females than males (Kimura, 1983, 1987; Kimura & Harshman, 1984; Mateer, Polen, & Ojemann, 1982). The patterns of regional cerebral blood flow coactivation in a linguistic task are sexually dimorphic: the left Wernicke's and left Broca's areas are coupled in males and the left and right temporal areas in females (Wood, Flowers, & Naylor, 1991). In our study, the patterns of scores suggest that CBT performance is mediated in males with particular reliance on the left hemisphere and on the frontal systems bilaterally in females.

The relationship between our findings and several influential theories of self-regulation merits further examination. Building on earlier work by Pribram and McGuinness (1975), Tucker and Williamson (1984) proposed the existence of two neuroanatomically separate mechanisms in dynamic interaction: arousal and activation. Arousal facilitates orientation to external events and novelty, depends on the noradrenergic system, and is mediated by the right hemisphere. Activation increases informational redundancy (i.e., dependence on pre-existing representations), depends on the dopaminergic system, and is mediated by the left hemisphere.

Denny-Brown and Chambers (1958) described lesion effects that imply similar processes, but different neuroanatomical structures. They noted a reciprocal relationship between the effects of parietal and temporal ablations on the one hand and frontal on the other. The former produce stimulus avoidance and perseveration, the latter stimulus approach and compulsive exploratory behavior.

Peterson, Fox, Posner, Mintun, and Raichle (1988), Posner and Boies (1971), Posner, Inhoff, Friedrich, and Cohen (1987), and Posner, Walker, Friedrich, and Rafal (1984) reported similar findings. Posner and Petersen (1990) proposed a multicomponential attentional system theory. One component is mediated by the posterior parietal areas and another by midline frontal structures.

All these approaches assume, as we do, the existence of cognitively distinct, neuroanatomically separate, internally and externally driven regulatory mechanisms. Yet comparable cognitive dichotomies are mapped by different authors onto different neuroanatomical dichotomies: left–right by Tucker and Williamson (1984), and frontal–parietal by Denny-Brown and Chambers (1958), and Posner and Petersen (1990). Is it possible that one mapping describes the male, and the other female, neurocognitive organization? In most studies on which these theories are based, male and female subjects are pooled in single samples. If the degree of sexual dimorphism is greater than is implicitly assumed by such pooling, then a chance sample gender composition will bias the findings toward a "left-right" or "anterior-posterior" model.

Functional vulnerability of the frontal lobes has been noted in many neurological and psychiatric conditions (Goldberg, 1992). Understanding functional lateralization of the frontal lobes has vast clinical implications. Schizophrenia is more severe in males than females (Bellack & Blanchard, 1993) and depression is more common in females than males (Frank, Carpenter, & Kupfer, 1988; Robins, Kubos, Starr, Rao, & Price, 1984). Left-hemispheric dysfunction has been proposed for schizophrenia (Flor-Henry, 1976; Gur, 1978), right-hemispheric for depression (Flor-Henry, 1976, 1983; Fromm & Schopflocher, 1984), and frontal lobe dysfunction for both (Berman, Zec, & Weinberger, 1986; Weinberger, Berman, & Zec, 1986; Phelps, Mazziotta, Baxter, & Gerner, 1984; Robins et al., 1984). Contextual processing deficit has been proposed for schizophrenia (Cohen & Servan-Schreiber, 1992), and lateralized frontal dysfunction for obsessive-compulsive disorders (Baxter et al., 1987). Is the sexual dimorphism in the epidemiology of major neuropsychiatric disorders related to the sexual dimorphism in the functional cortical geometry reported here? What is the nature of this relationship?

Handedness, Sex, and Functional Cortical Geometry

The sex by handedness interaction in healthy controls reported here parallels earlier work, cognitive and morphometric (Habib et al., 1991; Pringle, Anderson, & Jaffe, 1985; Wittleson, 1985, 1989).

Quadrant lesions produce opposite effects in right-handers and non-right-handers, while preserving the overall cortical functional geometry characteristic of a given sex. In males, left- and right-hemisphere lesions shift the response bias in opposite directions, relative to normal controls. Along the left-right axis, lesion effects in non-right-handed males are the mirror image of those in right-handed males. In females, frontal and posterior lesions shift the bias in opposite directions, relative to

normal controls. Along the frontal–posterior axis, lesion effects in non-right-handed females are the mirror image of those in right-handed females.

Relationships between cognitive styles/abilities and handedness have been described (Witkin et al., 1962; 1973; 1974). No evidence existed, however, for a strong association between handedness and cognitive hemispheric specialization. A strong association would imply that the cognitive functions lateralized to the left hemisphere in right-handers are lateralized to the right hemisphere in left-handers, and vice versa. This could not be demonstrated in earlier studies, leading to a near-consensus that the relationship is inherently weak or nonexistent. It may be, however, that the cognitive constructs and tasks used in the past failed to tap the fundamental properties of hemispheric specialization, because they focused on secondary, derivative, and confounded expressions thereof. To unmask the relationship between handedness and hemispheric specialization, proper cognitive constructs must be defined first.

To our knowledge, the findings presented here offer the first direct evidence of a strong association between handedness and cognitive hemispheric specialization. These findings are important prima facie. They also validate the importance and the fundamental nature of the cognitive constructs introduced in this paper.

It is possible, further, that the relationship between handedness and cortical functional geometry was obscured in earlier research precisely due to its focus on hemispheric specialization. Our findings suggest that in females, handedness interacts with the frontal–posterior, rather than left–right, cortical axis at least on certain tasks. While sex differences in hemispheric asymmetry have been acknowledged (McGlone, 1978, 1980), there has been little appreciation of sex differences in the overall functional cortical geometry. Inquiry into the neurohormonal bases of the emergence of different geometries in the two genders, and their relationship to handedness, may become an important direction of future work.

By necessity, our "non-right-handed" sample was noisy. In addition to clear left-handers, it included various degrees of ambidexterity and familial left-handedness. Given the low prevalence of left-handers with focal brain damage, this strategy was justified as a first approximation. It is fortuitous that the dissociations reported above were as robust as they were, despite the "noise." Still, certain relationships may have been obscured by the heterogeneous nature of our "non-right-handed" samples.

CBT allows two kinds of context-dependent response strategies: "similar-to-the-target" constancy-seeking and "away-from-the-target" novelty-seeking. In our right-handed samples the first strategy predominates, and the second is all but absent. In our non-right-handed samples the two strategies are represented in roughly equal proportions. This raises the possibility that cognition in left-handers is characterized by unique features and that their cerebral organization is not just an attenuated direct or mirror image of the right-handed one, but is in some respects qualitatively different. May it be that the two types of context-dependent response strategies are differentially associated with handedness: familiarity-seeking with right and novelty-seeking with left? Could this account for the reported association of left-handedness with creativity (O'Boyle & Benbow, 1990)?

The "away-from-target" novelty-seeking strategy is rare in humans, but common in nonhuman primates (Mishkin & Delacour, 1975). In humans, right-handedness predominates. In nonhuman primates, right- and left-handedness are present in roughly equal proportions (Collins, 1985). May it be that the association between handedness and cognitive strategy has its evolutionary precursors?

Finally, our findings suggest that females are different from males, and right-handers from left-handers, in fundamental aspects of functional cortical geometry, and not merely in the degrees of expression of invariant principles. While sex and handedness differences have been recognized for a long time, it has been assumed that we all embody the same *principles* of functional cortical organization: distilled in right-handed males and diluted in all the rest. This assumption is probably wrong.

METHOD

Psychometric Properties of CBT

The test–retest reliability of CBT, computed in 15 healthy subjects (seven males and eight females), was high: $r = 0.88$, $p < 0.01$. To test the psychological reality of the five stimulus dimensions, we conducted a scaling experiment with six healthy right-handers (three males and three females). They received 32 trials, each with a target and 6 choices differing from the target by 0–5 dimensions. All subjects were near-perfect at ranking the choices in the order of similarity to the target: Kendall's Concordance $W = 0.94$ $\chi^2 = 906.4$, $p < 0.001$.

Subjects

Subjects were 18–65 years old, without histories of drug/alcohol abuse, or psychiatric illness or symptoms (DSM III-R, 1987). Additional exclusion criteria for healthy subjects were loss of consciousness, or any CNS disorder. For lesioned subjects they were additional CNS disorder, or loss of consciousness due to a previous injury.

All subjects received an individual handedness questionnaire (Briggs & Nebes, 1975) and a first-degree familial handedness questionnaire of our own design. Subjects were considered strictly right-handed if the individual handedness score was 41 or above (out of 48), *and* no first degree familial left-handedness was reported; otherwise subjects were considered non-right-handed (Table 1).

All the patient groups were comparable on WAIS-R IQs

(FIQ, VIQ, and PIQ), Raven's Standard Progressive Matrices (RSPM), and The Token Test (TT) (see Lezak, 1983) (Table 2).

Lesion Types and Lesion Analysis

All lesions were demonstrable on MRI or CT, and verified by a neuroradiologist blind to the patients and purpose of the study. The definition of a lesion was parenchymal tissue excision or destruction. Subjects with space occupying masses, e.g., unoperated tumors, were excluded. Only lesioned subjects with adult-onset diseases or injuries were included. The time range between lesion onset and testing was 3–107.5 months. Table 3 shows lesion etiology. Most subjects with post traumatic injuries received MRI scans to minimize the possibility of non-visualized lesions on CT (Levin et al., 1987).

MRI and CT scans were transformed to standardized templates with demarcated regions (Damasio & Damasio, 1989). Each MRI or CT was matched to one of six standard templates. Using an X/Y plotting method, the lesions were transferred onto the templates. Using overlays, the affected regions could be determined.

When functional neuroimaging data (SPECT, EEG, or brain mapping) were available, they were used to rule out other areas of dysfunction. For example, a patient with a focal, left frontal lesion and a physiological study indicating predominantly right frontal abnormality, or vice versa, would be dropped from the study. Functional neuroimaging data were available on most subjects.

Procedure

Informed consent was obtained from all subjects. Next, Briggs and Nebes's (1975) and familial handedness questionnaires were administered. Lesioned, but not healthy subjects were then given WAIS-R, RSPM, and TT. Next, CBT was administered followed by CBT2. Then the two control tasks with the explicit "similar" and "different" instructions were administered. For lesioned subjects testing was completed within 4 hr. There was a 10–15 min interval between the administration of the standard neuropsychological tests and CBT.

Table 2. Means and Standard Deviations of Demographic Variables in the Lesion Groups

Group	*n*	*Age*	*Education*	*FSIQ*[a]	*RSPM*[b]	*TT*[b]
			Strictly Right-handed Subjects			
Males[c]						
LF	5	42.0(9.2)	15.2(2.3)	85.6(5.7)	53.6(32.2)	50.0(14.7)
RF	8	39.9(9.7)	11.8(3.2)	90.0(9.8)	49.0(32.9)	65.3(32.7)
LP	3	38.3(3.5)	11.7(1.5)	94.3(9.9)	74.0(4.6)	47.8(29.1)
RP	5	40.2(9.4)	13.4(3.0)	86.2(7.4)	48.2(39.6)	59.4(11.5)
Females						
LF	5	40.4(15.4)	14.4(2.3)	94.4(10.1)	60.2(28.8)	48.3(9.2)
RF	4	37.3(9.4)	12.7(1.0)	87.0(5.0)	54.0(14.6)	49.1(4.3)
LP	1	25.0	16.0	104.0	75.0	50.0
RP	4	42.5(7.4)	13.8(2.6)	92.5(14.2)	47.5(44.3)	50.0(0.0)
			Non-Right-handed Subjects			
Males						
LF	2	25.0(9.9)	15.0(4.2)	101.5(13.4)	57.5(38.9)	47.1(12.0)
RF	2	28.5(14.8)	11.0(1.4)	93.5(26.2)	30.5(41.7)	50.0(0.0)
LP	3	34.3(15.4)	12.0(0.0)	80.0(6.3)	51.7(42.5)	48.0(8.6)
Females						
RF	3	40.3(5.7)	13.3(2.3)	93.7(13.8)	56.7(46.5)	49.3(1.1)
LP	2	42.0(2.8)	12.0(0.0)	81.0(1.4)	20.0(9.9)	49.2(0.3)
RP	2	40.0(11.3)	10.5(2.1)	92.0(14.1)	67.5(24.7)	48.9(2.1)

[a]FSIQ, Wechsler Adult Intelligence Scale—Revised Full Scale Intelligence Quotients.
[b]Raven's Standard Progressive Matrices (RSPM) and Token Test (TT) scores are in percentiles based upon normative data.
[c]LF, left frontal; RF, right frontal; LP, left posterior; RP, right posterior.

Table 3. Mean and Standard Deviations of Handedness Variables in the Lesion Groups

Group	*n*	*Individual Handedness*	*Familial Handedness*[a]
		Strictly Right-handed Subjects	
Males			
LF	5	48.0(0.0)	0/5
RF	8	46.5(2.6)	0/8
LP	3	47.7(0.6)	0/3
RP	5	45.8(2.3)	0/5
Females			
LF	5	45.4(2.9)	0/5
RF	4	46.5(3.0)	0/4
LP	1	48.0	0/1
RP	4	46.8(1.9)	0/4
		Non-Right-handed Subjects	
Males			
LF	2	41.0(8.5)	1/2
RF	2	30.0(16.9)	2/2
LP	3	17.7(23.2)	2/3
Females			
RF	3	46.7(2.3)	3/3
LP	2	25.0(32.5)	1/2
RP	2	24.0(33.9)	2/2

[a]The fraction represents the number of group members with familial left-handedness. Non-right-handedness was defined as *either* an individual handedness score below 41 or positive first degree familial left-handedness. Small sample sizes did not allow us to quantify the degree of familial left-handedness in individual subjects; therefore, it was treated categorically.
[b]LF, left frontal; RF, right frontal; LP, left posterior; RP, right posterior.

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