

Hemispheric Specialization in Human Prefrontal Cortex for Resolving Certain and Uncertain Inferences

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Uncertainty is a fact of life that must be accommodated in real-world decision making. Although it has been suggested that the right prefrontal cortex (PFC) has a special role to play in decision making under uncertainty, there is very little hard data to support this hypothesis. To better understand the roles of left and right PFCs in reasoning and decision making in situations with complete and incomplete information, we administered simple inference problems to 18 patients with lateralized focal lesions to PFC (9 right hemisphere, 9 left hemisphere) and 22 age- and education-matched normal controls. The stimuli were systematically manipulated for completeness of information regarding the status of the conclusion. Our results demonstrated a 2-way interaction such that patients with left PFC lesions were selectively impaired in trials with complete information, whereas patients with right PFC lesions were selectively impaired in trials with incomplete information. These results provide compelling evidence for hemispheric specialization for reasoning in PFC and suggest that the right PFC has a critical role to play in reasoning about incompletely specified situations. We postulate this role involves the maintenance of ambiguous mental representations that temper premature overinterpretation by the left hemisphere.

Keywords: decision making, frontal lobes, indeterminacy, lateralization, lesions, reasoning

Introduction

Uncertainty is an unavoidable feature of our relationship with the world. To reason effectively, we must have mechanisms to represent and manipulate indeterminate relations. To date, most work in cognitive neuroscience on reasoning and decision making under uncertainty has been carried out in the context of probabilistic gambling or economic scenarios involving risk/reward evaluations (Bechara et al. 2000; Sanfey et al. 2003; Camille et al. 2004; Glimcher and Rustichini 2004; Hsu et al. 2005; Huettel et al. 2006). However, not all uncertain situations involve risk/reward evaluations. To examine the neural basis of reasoning under uncertainty independent of risk/reward evaluations and to contrast it with reasoning under certain, fully specified, situations, we utilized reasoning tasks involving transitive relations and manipulated the level of determinacy within the argument.

Transitivity is the logical property of transferability, such that the relation A has to B and B to C transfers from A to C ($A = B; B = C; A = C$). The transitivity relation is a basic cornerstone of logic and a critical component of our reasoning abilities. Logical arguments involving transitive relations can be either valid or invalid. Valid arguments (e.g., $A > B; B > C; A > C$) are determinate. For example, given $A > B$ and $B > C$, the relationship between A and C is absolutely determined by the information provided: it follows $A > C$. Invalid arguments can be either determinate or in-

determinate. Determinate invalid arguments (e.g., $A > B; B > C; C > A$) are inconsistent. For example, given $A > B$ and $B > C$, the relationship between A and C is absolutely determined not to be $C > A$ because this contradicts the information provided in the premises. Indeterminate arguments (e.g., $A > B; A > C; B > C$), on the other hand, contain an element of uncertainty or ambiguity. For example, given $A > B$ and $A > C$, not enough information is provided to determine the relationship between B and C. It is possible that $B > C$, $C > B$, or $B = C$, with no basis for preference. Such arguments are also invalid, not because of inconsistency but because there is no fact of the matter as to the relationship between B and C; it is truly indeterminate or uncertain.

Some cognitive theories of reasoning recognize this important conceptual difference and postulate processing differences in reasoning about determinate and indeterminate arguments (see Discussion). We are interested in the neural underpinnings of these conceptual and cognitive differences. In terms of hemispheric lateralization, it is widely accepted that the left prefrontal cortex (PFC) has a critical (Langdon and Warrington 2000; Goel and Dolan 2004; Reverberi et al. 2005)—even dominant (Gazzaniga 2000)—role to play in knowledge-intensive reasoning and decision-making processes. However, the current role of the right PFC seems largely limited to perceptual reorganization (Corballis 2003) and conflict detection/resolution (Goel et al. 2000; Reverberi et al. 2005). There is some intriguing, but inconclusive, evidence suggesting that right PFC may facilitate decision making in situations of incomplete information (Goel and Grafman 2000), by supporting the representation and processing of ambiguous relations (Goldberg et al. 1994; Goel 1995, 2002).

Given this background, we hypothesized differential hemispheric involvement in the processing of determinate and indeterminate relations, with greater involvement of left PFC in the former and right PFC in the latter. Specifically, to better understand the roles of left and right PFCs in reasoning and decision making in situations with complete and incomplete information, we administered simple inference problems to 18 patients with lateralized focal lesions to PFC (9 RH, 9 LH) and 22 age- and education-matched normal controls and analyzed their performance.

Methods

Patient Selection

Patients were selected on the basis of focal unilateral lesions confined to the PFC (see Fig. 1 and Supplementary Fig. 1) and relatively intact sensory, motor, language, and cognitive functions, as determined by neurological and neuropsychological testing (see below). Of the patients, 13 were drawn from a Vietnam head injury population. These patients came from similar socioeconomic and educational backgrounds. They

all received penetrating head injuries during their service in Vietnam in the late 1960s and were tested most recently between 1999 and 2002. Thus, their etiology, injury dates, and recovery periods are similar. Of the other 5 patients, 2 had tumor excisions (one of these was tested 11 years after surgery, whereas one was tested 5 months after surgery), 1 had an aneurysm and was tested 8 years after surgery, and 2 had strokes and were tested 2 and 8 years after the incident. The experimental protocol was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board, and all patients and normal control subjects gave informed consent.

Neuropsychological Assessment

All patients received a neuropsychological assessment. The scores of the most relevant cognitive baseline tests are reported in Table 1. They indicate that the patients' memory and IQ scores are within the normal range.

Lesion Location and Extent

The lesion sites, total volume loss, and intersection of lesion sites with Brodmann Areas (BAs), as determined from patient magnetic resonance imaging (MRI) and CT scans, are specified in summary overlay images in

Figure 1, individual patient images in Supplementary Figure 1, and Supplementary Table 1. Patient MRI scans were acquired on a GE 1.5-T scanner as T_1 -weighted axial 3-dimensional SPGR (radiofrequency-spoiled gradient echo sequence [used by GE]) images of 124 contiguous slices of 256×256 voxels ($0.9375 \times 0.9375 \times 1.5$ mm, echo time = 1.9 ms, time repetition = 8.9 ms) at a flip angle of 20 degrees. Patient CT scans were acquired on a GE Light Speed system as 96 slices of 2.5-mm thickness with an interval of 1 mm. Skull and scalp components were removed using the BET algorithm (Smith 2000) in MEDx (Medical Numerics Inc., Sterling, VA). Patient MRI volumes were imported into ABLe (Medical Numerics Inc.) software (Makale et al. 2002) and displayed as a series of slices in a light box format. Lesions were manually outlined on the slices (by M.T. and checked by J.G.) prior to any behavioral testing. Total lesion volume (in cubic centimeter) (and lesion volume as a percentage of total brain volume) was calculated by voxel count. The patient volume was then normalized to a reference template volume by a 12-parameter affine linear transformation (allowing for translation, rotation, scaling, and shearing). The lesion voxels were included in the registration process. The ABLe reference volume is an MRI of a 27-year-old normal male transformed to Talairach space with a 12-parameter affine linear

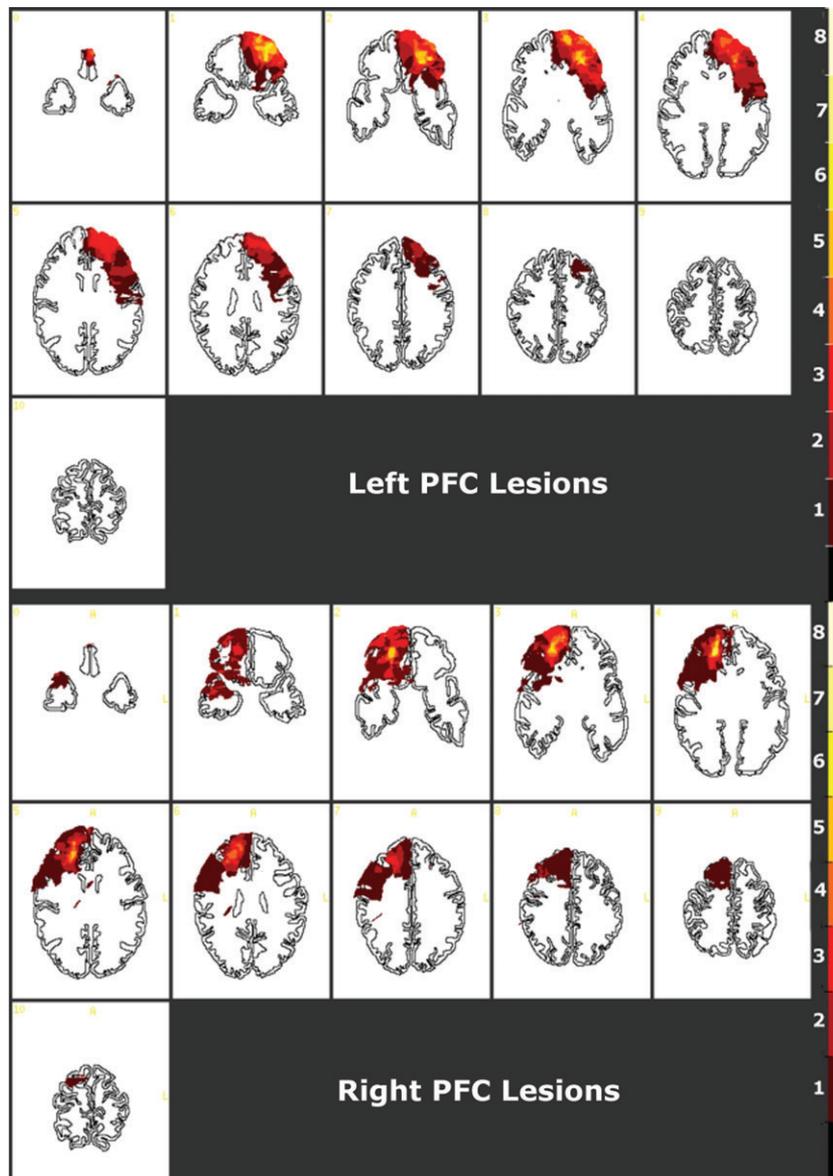


Figure 1. Lesion overlay maps for 15 patients (transverse slices, R = L) displayed on a template transformed to Talairach dimensions. The 11 slices (7–11 mm thickness) are 17 degrees relative to the inferior orbitomeatal line and correspond closely to the Damasio (Damasio H and Damasio AR 1989) transverse brain template (see Methods).

Table 1

Age and education level of all subjects, and cognitive baseline test scores of patients (SD in parentheses)

Measures	Normal controls (<i>N</i> = 22)	Left (<i>N</i> = 9)	Right (<i>N</i> = 9)
Age	49.00 (7.33)	48.50 (10.45)	54.38 (6.42)
Level of education	14.84 (2.35)	15.00 (2.14)	14.67 (2.68)
Volume loss (cc)		48.58 (32.00)	42.57 (32.16)
WAIS-R general		106.78 (20.48)	99.00 (17.03)
WAIS-R verbal		102.32 (16.47)	98.56 (16.73)
WAIS-R performance		111.67 (22.46)	100.10 (18.61)
WMS-R general		98.00 (10.26)	100.43 (14.02)
WMS-R working memory		104.78 (14.70)	102.78 (12.12)
Verbal fluency (FAS)		38.13 (21.36)	46.13 (21.05)
Boston naming task		51.67 (8.56)	52.10 (7.82)
Beck depression inventory		14.00 (11.40)	8.00 (11.17)

transformation. The volume is resliced at 17 degrees relative to the inferior orbitomeatal line, and 11 transverse slices that best match the Damasio (Damasio H and Damasio AR 1989) templates have been selected by a neuroradiologist and interactively labeled with BAs by reference to the Damasio templates. Although the locations of BAs in these templates are approximate, they are widely accepted in the neuropsychology and neurology communities. The registered patient volume was then resliced at a 17-degree cranial angle, and the 11 sections that matched the ABL reference volume (and hence the Damasio templates) were automatically extracted. Because the BAs are premarked on the 11 slices of the ABL reference volume (see above) and the patient brain volume has been registered and resliced to conform to this template, the intersection of lesion with BAs was calculated by a simple voxel-by-voxel comparison.

The summary overlay images (Fig. 1), individual patient images (Supplementary Fig. 1), and Supplementary Table 1 highlight that the regions with the most extensive damage across the 2 patient groups are the medial ventral regions, in particular BA 10 ($M = 14.62$, standard deviation [SD] = 15.60). Eight of the right PFC and 7 of the left PFC patients had lesions encompassing BA 10. In fact, a repeated-measures analysis of variance followed by post hoc tests revealed that percent loss to BA 10 was significantly higher than percent loss to BAs 24, 25, 32, and 46, with a similar but nonsignificant trend ($P < 0.10$) versus BAs 6, 45, and 47, $F_{11,176} = 1.87$, $P < 0.05$. Of the BA regions where percent loss did not differ from BA 10 (BAs 8, 9, 11, 44), BAs 8, 9, and 11 differed significantly only from BA 24, whereas BA 44 did not differ from any other region. Both patient groups had equivalent damage to BA 10 ($t_{16} = -0.02$, not significant [NS]). In fact, there was no statistical difference in average loss in any BA across the 2 patient groups.

Task and Administration

Subjects were engaged in a transitive inference task. Half the items involved explicit spatial relational arguments such as "Mary is ahead of John; John is ahead of Michael; Mary is ahead of Michael," whereas the other half involved nonspatial relational arguments such as "Mary is smarter than John; John is smarter than Michael; Mary is smarter than Michael," that can be mapped onto spatial relations (Van der Henst and Schaeken 2005). As there was no difference in accuracy between spatial ($M = 71\%$, $SD = 16$) and relational ($M = 72\%$, $SD = 18$) arguments ($P = 0.67$), the 2 argument types were collapsed together into one group. All trials involved arbitrary propositions about which subjects would have no beliefs.

We presented 102 trials. To balance for "yes" and "no" responses, half of the arguments were valid ($n = 52$), the other half invalid ($n = 50$) (the reason that these trials were not perfectly balanced is due to a misclassification of one trial during stimuli generation). All valid arguments are necessarily determinate (e.g., Barbers are to the right of the cooks; Postmen are to the right of the barbers; Postmen are to the right of the cooks), requiring a 'yes' response. The invalid arguments can be either determinate (but inconsistent) (e.g., Pens are under the book; The book is under the paper; The paper is under the pens) or indeterminate (Sarah is prettier than Heather; Sarah is prettier than Diane; Diane is prettier than Heather). Within the invalid trials, we balanced for inconsistent and indeterminate trials. Of the 50 invalid trials, 28 trials were determinate (i.e., inconsistent) and 22 trials were indeterminate (again, the

slight discrepancy in the number of inconsistent and indeterminate trials was due to misclassification of a couple of trials during stimuli generation).

Subjects were given an explanation of logical validity along with several examples. Once they understood the concept of validity, they were given the task and instructed (in writing) as follows: "Your task is to determine if the third sentence follows logically from, or is entailed by, the first 2 sentences. If it does follow logically, reply by pressing the designated 'yes' key. Otherwise, press the designated 'no' key. Each trial will remain on the screen until you have responded. Once you have responded, the next screen will appear. Proceed as quickly and as accurately as possible. To begin, press the space bar." Their accuracy scores (see below) make it clear that subjects understood the task instructions.

The task was administered on a computer terminal in a self-paced manner. Trials were presented in 2 blocks of 51 items (for a total of 102), with an opportunity to rest after every 25 trials. Subjects responded by pressing one of 2 keys corresponding to "valid" and "invalid."

Results

Average accuracy rate across all trials was 76% ($SD = 15\%$). (To verify that the data could be analyzed using parametric statistics, we ran a separate Kolmogorov-Smirnov test on determinate and indeterminate trials to confirm normal distribution of the scores. The results confirmed that the distributions of scores did not deviate significantly from normality for either the determinate [$P = 0.24$, NS] or indeterminate [$P = 0.41$, NS] trials). Accuracy scores involving determinate and indeterminate syllogisms (see Fig. 2) were analyzed with a mixed-model analysis of covariance using a 3×2 design involving lesion (left, right, normal control) as a between-subjects variable and determinacy (determinate, indeterminate) as a within-subjects variable. Education (in years) was entered as a covariate, due to its correlation with performance on the reasoning task ($r = 0.48$, $P < 0.05$). The results revealed a significant interaction between lesion and determinacy, $F_{2,33} = 6.82$, $P < 0.01$ (Fig. 2). Pairwise comparisons, taking into account unequal cell sizes (Winer et al. 1991), revealed impaired performance of left PFC patients in determinate trials ($M = 72.0$, $SD = 17.6$) compared with both normal controls ($M = 84.7$, $SD = 14.2$) ($t_{29} = 3.25$, $P < 0.01$) and right PFC patients ($M = 78.8$, $SD = 11.0$) ($t_{16} = 1.76$, $P < 0.05$) (1-tailed t -test as per our a priori hypothesis) and impaired performance of right PFC patients in indeterminate trials ($M = 56.1$, $SD = 22.5$) with respect to both normal controls ($M = 79.0$, $SD = 18.4$) ($t_{29} = 5.54$, $P < 0.01$) and left PFC patients ($M = 73.5$, $SD = 19.8$) ($t_{16} = 3.60$, $P < 0.01$). Specifically, 6 out of 9 patients with left PFC lesions performed more poorly on the determinate trials than the determinate average ($M = 81\%$, $SD = 15$), whereas 7 out of 9 right PFC patients performed more poorly on indeterminate trials than the indeterminate average ($M = 73\%$, $SD = 20$). (In the case of the right hemisphere patients, the lesions of the 2 patients that did not follow the pattern were in the extreme anterior frontal pole [BA 10]. In the case of the left hemisphere patients, the lesions of 2 of the 3 patients that did not follow the pattern were in orbital cortex. The lesion of the third patient encompassed BAs 45, 47, and 10). There was no significant difference in the performance of normal controls on determinate and indeterminate trials, $t_{21} = 1.75$, NS. Of the 22 normal controls, 16 performed better on determinate trials than the determinate average, whereas 13 performed better on indeterminate trials than the indeterminate average.

In addition to education, performance on the reasoning task was also correlated with performance on general IQ (Wechsler

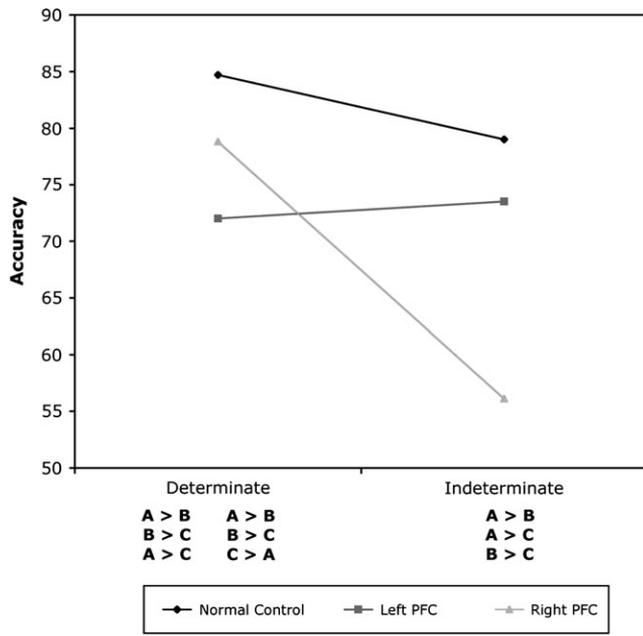


Figure 2. Accuracy scores on 3-term transitive reasoning. A lesion (right PFC, left PFC, normal controls) by determinacy (determinate, indeterminate) interaction shows a crossover double dissociation in the performance of left and right PFC patients in determinate and indeterminate trials.

Adult Intelligence Scale-Revised (Wechsler 1981) (0.85, $P < 0.001$), general memory (0.71, $P < 0.01$) and working memory (0.58, $P < 0.01$) components of Wechsler Memory Scale-Revised (Wechsler 1987), verbal fluency (FAS) (Spreen and Strauss 1991) (0.54, $P < 0.05$), and the Boston naming task (Kaplan et al. 1983) (0.63, $P < 0.01$). There was no correlation between performance on the reasoning task and total cortical volume loss, depression score Beck Depression Inventory (Beck 1987), or age. To control for the above factors, we excluded the normal controls (for whom these scores were not available) and carried out a 2×2 mixed-model ANCOVA involving lesion (left, right) as a between-subjects variable and determinacy (determinate, indeterminate) as a within-subjects variable and entered the above 6 factors (that correlated with reasoning) as covariates. Again, the results demonstrated a significant 2-way interaction between determinacy and lesion, $F_{1,8} = 13.10$, $P < 0.01$, driven by a significant difference in accuracy between patients with right and left PFC lesions in indeterminate ($t_{16} = 7.67$, $P < 0.01$) and determinate ($t_{16} = 2.32$, $P < 0.05$) trials. This 2-way interaction indicates a double dissociation (Shallice 1988) between left and right PFCs in the ability to reason about determinate and indeterminate transitive relations, respectively.

Determinate trials are either valid or inconsistent, thus requiring either a 'yes' or a 'no' response, whereas indeterminate trials always require a 'no' response. It is therefore possible that the double dissociation reported above is confounded by an unequal distribution of trials that required 'yes'/'no' responses across determinate and indeterminate conditions. To rule out this possibility, we reanalyzed the data using a mixed-model ANCOVA using a 2×3 design involving lesion (left, right) as a between-subjects variable and determinacy (valid, inconsistent, indeterminate) as a within-subject variable. The results again revealed a significant interaction between lesion and determinacy, $F_{2,16} = 7.46$, $P < 0.01$ (see Supplementary Fig. 2). Pairwise comparisons revealed that on indeterminate trials, patients with lesion to

right PFC performed worse (56.1%) than patients with lesion to left PFC (73.5%). This pattern was reversed for valid determinate items (i.e., those requiring a 'yes' response) such that patients with lesion to left PFC performed worse (71.5%) than patients with lesion to right PFC (79.8%). Finally, for inconsistent determinate items (i.e., those requiring a 'no' response), patients with lesion to left PFC performed comparably (75.8%) to patients with lesion to right PFC (76.6%). These figures confirm that the interaction is not driven by an imbalance in 'yes' and 'no' responses between determinate and indeterminate trials.

Discussion

The results show a double dissociation between left and right PFCs and the ability to reason about determinate and indeterminate transitive relations. There are no obvious explanations for these results involving preferences, risk, or reward evaluation given the nature of the stimuli or the verbal nature of the material (see WAIS-R verbal scores in Table 1). Neither can the results be explained in terms of the imbalance in 'yes' or 'no' responses on indeterminate and determinate trials (see Results above). We propose to explain the results in terms of the interplay between left hemisphere's propensity to overinterpret information (Gazzaniga 2000) and the right hemisphere's capacity to "temper" this overinterpretation by supporting ambiguous or uncertain mental representations (Goel and Vartanian 2005).

Cognitive theories of transitive reasoning postulate the construction and inspection of a mental representation depicting the state of affairs described in the argument (Huttenlocher 1968; Johnson-Laird 1994). The inspection of the model requires a check for consistency, and if that is satisfied, a process equivalent to a validity confirmation algorithm is run. In determinate trials, where complete information is available, a fully specified unambiguous mental representation is constructed. The inconsistent trials will fail the consistency check, resulting in a "not valid" response. Where there is no consistency violation, the task is to recognize and confirm the validity of the inference, allowing a valid response.

This type of "validity confirmation" is an ideal task for Gazzaniga's left hemisphere "interpreter" (Gazzaniga 2000; Wolford et al. 2000). We conceive of this interpreter as a pattern matcher that makes sense of the environment by locking onto and extrapolating patterns (logical, statistical, causal, etc.). It abhors uncertainty and automatically fills in any gaps in the available information, often prematurely or incorrectly. When it is damaged, one would expect an overall degradation in the ability to recognize logical patterns apparent as a specific impairment in resolving valid determinate trials (but not indeterminate trials, where there is no pattern to match). The left PFC lesion patients were impaired specifically in this way. Consistent with this finding, a series of lesion (Goel et al. 2004; Reverberi et al. 2005) and neuroimaging (Goel et al. 2000; Acuna et al. 2002; Goel and Dolan 2003; Knauff et al. 2003) studies implicate a system involving left PFC in reasoning tasks. The good performance for both patient groups on inconsistent trials suggests that the conflict/inconsistency detector in both patient groups has been largely spared. This is consistent with imaging and patient studies that implicate medial dorsal and right dorsolateral prefrontal cortex systems in conflict/inconsistency detection during reasoning [Goel et al. 2000, Goel and Dolan 2003]. Both of these regions are largely intact in our patients [see Fig. 1].

In contrast, indeterminate trials require the construction and inspection of multiple models corresponding to the various possibilities (Johnson-Laird 1994) and a further integration of these models into a single ambiguous model highlighting the indeterminacy of the conclusion (Van der Henst and Schaeken 2005). Thus, performance differences between determinate and indeterminate arguments can be explained in terms of greater cognitive resources required to construct and maintain multiple representations (Johnson-Laird 1994) and/or the requirement to integrate them into an ambiguous or indeterminate model (Van der Henst and Schaeken 2005). It is possible that the right PFC provides the additional cognitive resources (working memory, attention) for maintaining and manipulating the additional representations. However, this interpretation is weakened by the following facts: 1) there are no cognitive baseline differences in the left and right patient groups, and these measures were entered as covariates in our analysis; 2) increasing the number of mental representations that need to be considered (thus cognitive load) in determinate syllogisms increases activation in left (not right) PFC (Waechter and Goel 2005); and 3) the postulation of greater working memory and attentional processing is simply inconsistent with what is known about the ventral aspects of right PFC (Bechara et al. 1998; Gazzaniga 2000; Gilbert et al. 2005), the region of maximal lesion overlap in our patients. Thus, a simple increase in cognitive load cannot explain the results.

We believe that the key to understanding the poor performance of the right PFC patients in indeterminate trials is the requirement of constructing an ambiguous representation that preserves the uncertainty inherent in the arguments. Consistent with previous suggestions (Goel and Grafman 2000), and recent fMRI data (Paulus et al. 2001; Huettel et al. 2005), our results point to structural differences in the capacity of left and right PFCs for encoding and manipulating certain types of representations (see also Goldberg et al. 1994; Beeman and Bowden 2000). In particular, the left PFC is more adept at constructing determinate, precise, and unambiguous representations of the world, whereas the right PFC is more adept at constructing and maintaining fluid, indeterminate, vague, and ambiguous representations (Goel 1995, 2002).

If subjects are able to build and actively maintain an ambiguous representation for indeterminate trials, they can use it to temper or “inhibit” premature interpretations by the left PFC. If, however, a right PFC lesion impairs this ability, then the left hemisphere interpreter will impose a particular interpretation on the problem representation (Gazzaniga 2000; Wolford et al. 2000), rendering it determinate. Any specific interpretation of the indeterminate trials will increase error rates by one third, corresponding roughly to the level of impairment in the performance of the right PFC patients.

These results show that lesions to PFC can lead to deficits in reasoning about certain and uncertain relations—even in the absence of risk-reward evaluations—but with very different hemispheric profiles. This has several implications. First and foremost, it provides compelling evidence for a hemispheric specialization model, over a left hemispheric dominance model, of human reasoning. Given indeterminacy is part of our interaction with the world, the right PFC has a critical role to play in real-world reasoning by supporting the encoding and processing of ambiguous representations and preventing over-interpretation by the left hemisphere. Second, it also speaks to existing explanations that implicate bottom-up mediation of cognition by emotions in decision making under uncertainty in

tasks like the Iowa gambling task (IGT) (Bechara et al. 2000). Insofar as patients with right ventral PFC (including BA 10) lesions make poor choices on the IGT (Tranel et al. 2002; Clark et al. 2003), and the IGT involves a “stacked” deck that creates an initial mental set that must subsequently be overturned (Fellows and Farah 2005), breaking the mental set (i.e., switching decks) will be hindered by any disruption in the ability to form flexible representations of the task. The fluid representational capability of the right PFC that we are postulating provides an alternative common explanation for reasoning with uncertain relations both in our paradigm and some risk/reward evaluation paradigms.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

Notes

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