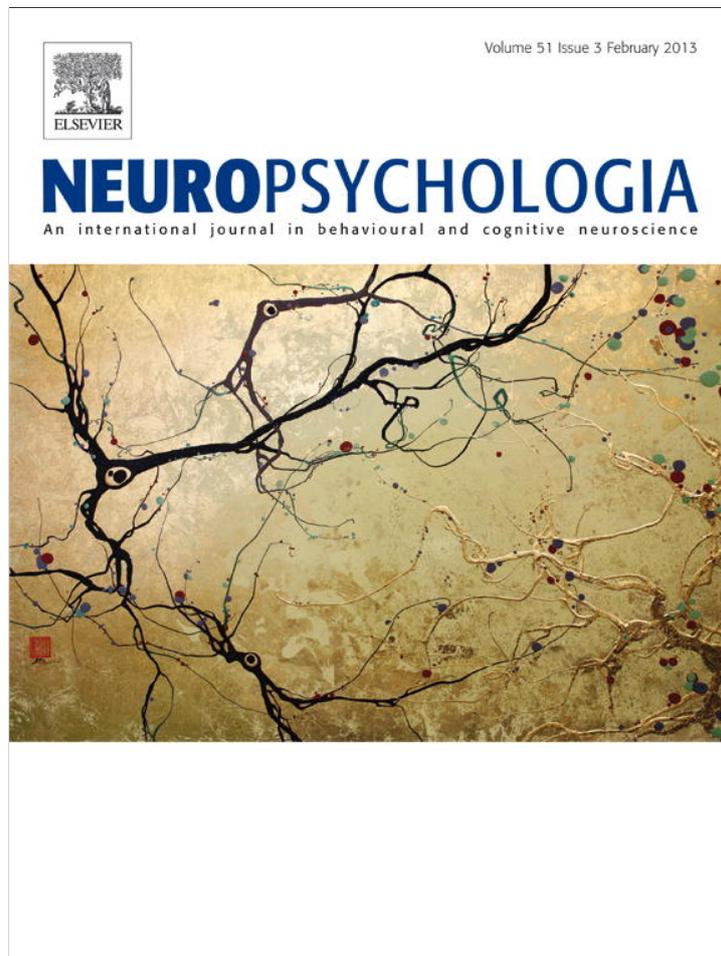


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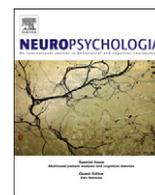
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## Transitive inference reasoning is impaired by focal lesions in parietal cortex rather than rostralateral prefrontal cortex

Randall L. Waechter<sup>a,\*</sup>, Vinod Goel<sup>b,c</sup>, Vanessa Raymond<sup>d,e</sup>, Frank Kruger<sup>f,g</sup>, Jordan Grafman<sup>h</sup>

<sup>a</sup> Windward Islands Research and Education Foundation (WINDREF) & Department of Bioethics, School of Medicine, St. George's University, Grenada, West Indies

<sup>b</sup> Department of Psychology, University of Hull, UK

<sup>c</sup> Department of Psychology, York University, Toronto, Ontario, Canada M3J 1P3

<sup>d</sup> Department of Radiology, Johns Hopkins University, Baltimore, MD, USA

<sup>e</sup> Department of Medicine, Imperial College, London, UK

<sup>f</sup> Department of Molecular Neuroscience, George Mason University, Fairfax, VA, USA

<sup>g</sup> Department of Psychology, George Mason University, Fairfax, VA, USA

<sup>h</sup> Traumatic Brain Injury Research Laboratory, Kessler Foundation Research Center, NJ, USA

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## ABSTRACT

Transitive inference reasoning involves the examination and comparison of a given number of relational pairs in order to understand overall group hierarchy (e.g.,  $A > B$ ,  $B > C$ ,  $C > D$ ; therefore is  $A > D$ ?). A number of imaging studies have demonstrated the role of the parietal cortex for resolving transitive inferences. Some studies also identify the rostralateral prefrontal cortex as being critical for “relational integration” processes supporting transitive reasoning. To clarify this issue, we carried out a transitive inference study involving neurological patients with focal lesions to the rostralateral prefrontal ( $n=5$ ) or parietal cortices ( $n=7$ ), as well as normal controls ( $n=6$ ). The patients and controls were statistically matched on age, education, pre-injury IQ, general memory, working memory, and performance/full IQ, though the rostralateral patients did score significantly higher than the normal controls on verbal IQ. Results indicate that patients with focal lesions to the parietal cortex were impaired in the task relative to both the patients with focal lesions to rostralateral prefrontal cortex and the control group, and there was no difference in task performance between the rostralateral prefrontal and the control groups. This result continued to hold after controlling for verbal IQ as a covariate. These findings point to a critical role for the parietal cortex, rather than the rostralateral prefrontal, in transitive inference. Since the groups performed similarly on a working memory task, working memory cannot fully account for the result, suggesting a specific role of parietal cortex in transitive inference.

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### 1. Introduction

Many of the decisions humans make involve comparing numerous pieces of information. For example, in determining which students will be offered admission to College, entrance officials may rank order the students from highest to lowest SAT score. The process of examining and comparing a given number of relations in order to understand overall group hierarchy is commonly referred to as transitive inference. For example, given that  $A > B$ ,  $B > C$ ,  $C > D$ , a reasoner will understand that  $A > D$  without being explicitly told so. This process is a cornerstone of logic and may have its origins in the need for socially organized species to infer dominance relations (Delius and Siemann, 1998).

A number of neuroimaging studies have examined the neural correlates of transitive inference reasoning over the past 15 years (Acuna, Eliassen, Donoghue, & Sanes, 2002; Fangmeier & Knauff, 2009; Fangmeier, Knauff, Ruff, & Sloutsky, 2006; Goel & Dolan, 2001; Goel, Gold, Kapur, & Houle, 1998; Goel, Makale, & Grafman, 2004; Goel, Stollstorff, Nacic, Kuntson, & Grafman, 2009; Heekers, Zalesak, Weiss, Ditman, & Titone, 2004; Knauff, Fangmeier, Ruff, & Johnson-Laird, 2003; Knauff, Mulack, Kassubek, Salih, & Greenlee, 2002; Prado, Van Der Henst, & Noveck, 2010; Ruff, Knauff, Fangmeier, & Spreer, 2003; Wendelken & Bunge, 2009). These studies report varied activation in a number of brain areas, including the right and/or left lateral prefrontal cortex (BA 9, 10, 44, 45, 46, 47), medial frontal cortex (BA 8, 33), bilateral superior parietal cortex (BA 7, 39, 40), bilateral inferior/middle temporal lobes (BA 20, 21, 22, 31, 37, 38), bilateral middle occipital lobes (BA 17, 18, 19) and premotor cortex.

A recent qualitative review of the neuroimaging literature argues that much of this variation in brain activity may be explained in terms of task variables such as the presence or

\* Corresponding author.

E-mail address: [randallwaechter@hotmail.com](mailto:randallwaechter@hotmail.com) (R.L. Waechter).

absence of content, conflict, and determinacy. Moreover it identifies a bilateral parietal network with task specific frontal lobe involvement (as a function of content, conflict, and indeterminacy) as underlying transitive inference (Goel, 2007). A more recent quantitative meta-analysis of imaging studies of logical reasoning finds consistent activation in a bilateral parietal and lateral frontal lobe network including bilateral middle frontal gyrus (BA 6), bilateral precuneus (BA 7), left angular gyrus (BA 39) and left intraparietal sulcus (BA 40) associated with transitive reasoning (Prado, Chadha, & Booth, 2011). However, at least two imaging studies have concluded that right anterior medial/rostralateral (BA 10) prefrontal cortex (not parietal cortex) is critical for the “relational integration” processes involved in transitive inference (Fangmeier et al., 2006; Wendelken & Bunge, 2009).

Patient data on transitive inference tasks are scarce. Some early studies examined the effect of focal lesions to the temporal lobes on transitive inference tasks (Caramazza, Gordon, Zurif, & DeLuca, 1976; Read, 1981). Only three studies have examined the effect of frontal lobe deficits on transitive inference.

Vartanian, Goel, Tierney, Huey, and Grafman (2009) compared 14 patients with the frontal variant of frontotemporal dementia (FTD) and 21 normal controls on familiar and unfamiliar transitive inference items. They found that patients with frontal variant FTD were more impaired on transitive reasoning trials containing content that they had beliefs about (e.g. London is north of Cairo), but not trials containing content that they could not have had any beliefs about (e.g., the library is north of the Roth center) compared to the control group. These results are consistent with the importance of a frontal-temporal brain network for resolving inferences that people have beliefs about (Goel, 2007).

Koscik and Tranel (2012) examined performance of patients with ventromedial prefrontal cortex (vmPFC) damage ( $n=15$ ) to patients with damage in other brain areas (with the foci in medial temporal cortex) ( $n=36$ ), and neurologically normal participants ( $n=44$ ) on a transitive inference task consisting of an ordered set of arbitrary patterns (using a non-verbal training paradigm). They found that damage to the vmPFC resulted in a deficit in the ability to use transitive inference, and this deficit was not driven by deficient learning of relationships between items, extrapolation to novel pairings in general, or differences in reinforcement or punishment during a training phase (Koscik & Tranel, 2012).

Waltz et al. (1999) examined the performance of frontotemporal dementia patients with primarily prefrontal damage ( $n=6$ ), and primarily anterior temporal damage ( $n=5$ ) against neurologically intact individuals ( $n=7$ ) on transitive inference tasks, which varied in their level of difficulty. Difficulty was determined by the ordering of the premise pairs. Linear or chained ordering (Sam taller than Nate; Nate taller than Roy) corresponded to Level 1 difficulty while nonlinear/scrambled ordering (Beth taller than Tina; Amy taller than Beth) corresponded to Level 2 difficulty. Waltz et al. (1999) reported that frontotemporal dementia patients with primarily prefrontal cortex damage were significantly impaired in determining the validity of scrambled (Level 2) transitive inference problems, compared to patients with mostly temporal lobe damage and normal controls. The frontal patients did not perform any worse than the temporal patients and normal controls when the relational complexity associated with the task was lowest (i.e., Level 1), that is, when the premises were chained. This study has contributed to the claim that prefrontal cortex is necessary for resolving transitive inference.

No studies of transitive inference involving neurological patients with focal lesions specifically to rostralateral prefrontal cortex and/or parietal cortex are reported in the literature. To address this gap in the patient literature, and the seeming inconsistency in the imaging literature regarding the roles of rostralateral prefrontal cortex and parietal cortex in transitive inference, we conducted a study designed to directly compare the

performance of patients with focal lesions to rostralateral prefrontal cortex and parietal lobes with that of normal controls on transitive inference tasks. If the rostralateral prefrontal cortex is necessary for transitive inference, as predicted by the imaging studies of Fangmeier et al. (2006) and Wendelken and Bunge (2009), we would expect the rostralateral prefrontal-damaged group to be impaired on the task. If the parietal lobes are necessary for transitive inference, as predicted by a majority of the imaging studies and meta-analyses (Goel, 2003; Goel, Buchel, Frith, & Dolan, 2000; Goel & Dolan, 2001, 2003; Knauff et al., 2003; Prado et al., 2010, 2011) we would expect the parietal-damaged group to be impaired on the task.

2. Method

2.1. Patient selection

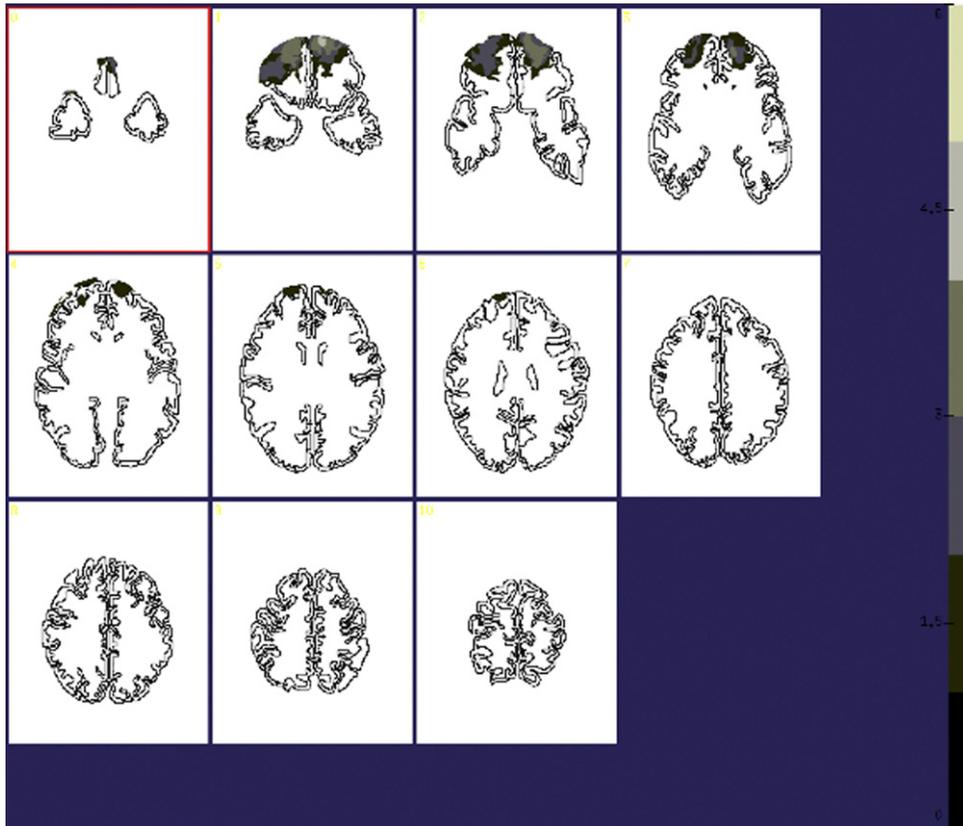
All participants were male and selected from the Vietnam Head Injury Study (Phase 3). Both patients and controls served in the Vietnam War during the late 1960s and early 1970s. The patients all received penetrating head injuries during their service in Vietnam. Thus their etiology, injury dates, and recovery periods are similar. The normal controls did not receive any head injuries during their service. All participants had relatively intact sensory, motor, language, and cognitive functions, as determined by neurological and neuropsychological testing (see below).

The inclusion criteria for the frontal lobe-damaged group were focal lesions to rostralateral prefrontal cortex, primarily BA 10 (bilaterally). Due to a lack of patients with damage strictly to BA 10, we included those with mostly BA 10 damage and limited damage to other frontal areas (BA 9, 11, 12, 45, 46, and 47) (see Table 1 and Fig. 1, which report lesions in other BA areas with a minimum of 5% damage). The final rostralateral prefrontal group consisted of 5 patients, whose percent damage to bilateral BA 10 ranged from 10% to 31%. Importantly, none of these patients had lesions outside of the frontal lobes.

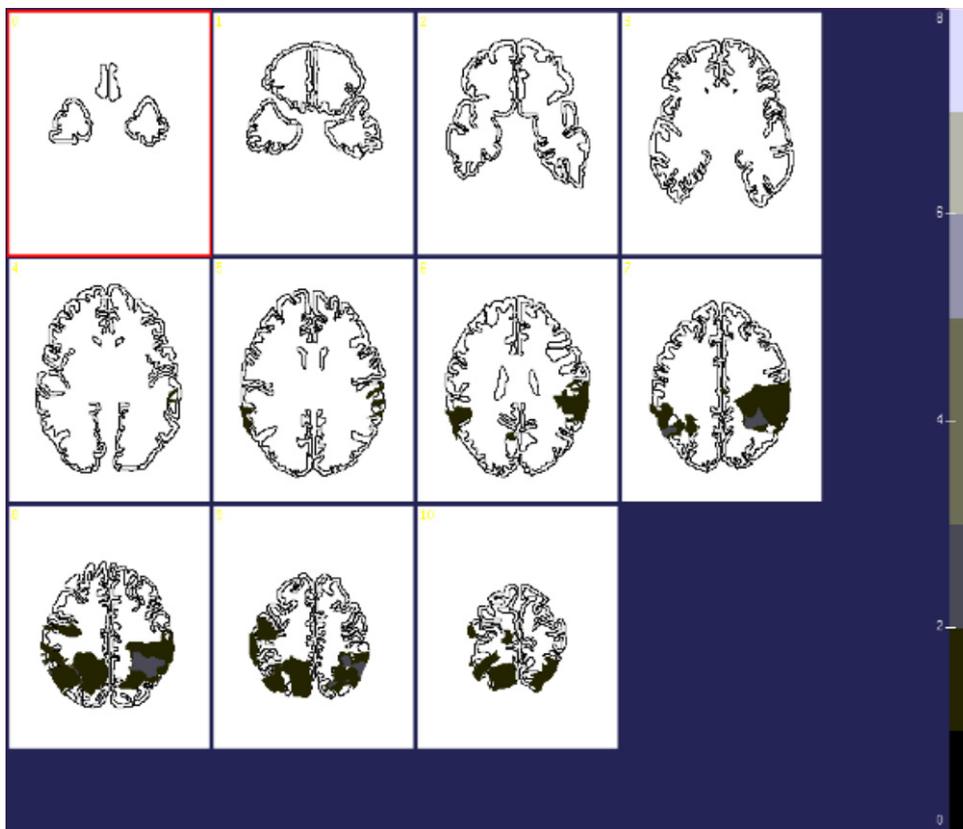
The parietal group was selected based on focal damage primarily to BA 7 and 40 (bilaterally). Again, given only two patients with damage limited to strictly BA 7 and 40, we included those with limited damage to other parietal areas (BA 1–2–3, and 39) (see Table 1 and Fig. 2, which report lesions in other BA areas with a minimum of 5% damage). The final parietal group consisted of 7 patients, whose percent damage

**Table 1**  
Percent damage to Brodmann areas and percent accuracy on the transitive inference task for each patient (Pat. no.) (hemisphere of BA 10 or BA 7/40 damage).

Brodmann Area	Frontal lobes							Parietal lobes				Accuracy on task	
	10	9	11	12	44	45	46	47	7	40	1-2-3		22
<b>Rostralateral prefrontal patients (N=5)</b>													
Pat. 0267 (L)	31	-	14	30	-	-	-	-	-	-	-	-	.896
Pat. 1364 (L)	31	7	-	-	-	-	-	-	-	-	-	-	.625
Pat. 1585 (R)	27	-	7	5	-	9	-	-	-	-	-	-	.688
Pat. 2309 (Bi)	10	-	-	8	-	8	-	10	-	-	-	-	.833
Pat. 3013 (R)	29	6	6	-	-	-	-	7	-	-	-	-	.458
<b>Parietal patients (N=7)</b>													
Pat. 0408 (R)	-	-	-	-	-	-	-	-	7	-	-	19	.583
Pat. 1061 (R)	-	-	-	-	-	-	-	-	4	6	-	-	.417
Pat. 1288 (L)	-	-	-	-	-	-	-	-	2	42	-	6	.667
Pat. 1298 (R)	-	-	-	-	-	-	-	-	-	12	-	10	.625
Pat. 2341 (L)	-	-	-	-	-	-	-	-	13	9	-	13	.229
Pat. 3054 (Bi)	-	-	-	-	-	-	-	-	5	3	8	-	.375
Pat. 3081 (R)	-	-	-	-	-	-	-	-	17	-	-	-	.521



**Fig. 1.** Overlay of brain areas damaged across the 5 patients in the rostralateral prefrontal patient group. Color indicates the number of patients with lesions in that area. Images are flipped: Left=Right and Right=Left.



**Fig. 2.** Overlay of brain areas damaged across the 7 patients in the parietal patient group. Color indicates the number of patients with lesions in that area. Images are flipped: Left=Right and Right=Left.

**Table 2**  
Demographic and neuropsychological mean (SD) scores across the three participant groups.

Measures	Normal controls (N=6)	Rostrolateral patients (N=5)	Parietal patients (N=7)
Age	61.0 (4.5)	58.4 (2.7)	57.7 (2.0)
Education	13.7 (1.4)	14.6 (2.1)	16.2 (2.9)
Pre-injury AFQT-7A	53.3 (30.7)	55.8 (21.9)	43.9 (30.0)
Total cm <sup>3</sup> all damaged areas	–	29.3 (27.3)	22.7 (17.2)
WAIS verbal IQ	94.7 (7.6)*	110.2 (8.7)*	95.9 (12.2)
WAIS performance IQ	98.3 (9.1)	103.5 (4.7)	100.7 (21.1)
WAIS full IQ	96.3 (8.5)	106.3 (4.8)	99.5 (15.9)
WMS overall general memory	99.8 (12.2)	117.5 (21.9)	95.4 (15.1)
WMS working memory	95.5 (10.0)	99.3 (8.4)	89.0 (14.7)

AFQT-7A: Armed Forces Qualification Test percentile rank; WAIS refers to Wechsler Adult Intelligence Scale-III; WMS refers to Wechsler Memory Scale-III.

\*  $p = .05$  (Tukey HSD post-hoc tests).

to bilateral BA 7 and 40 ranged from 7% to 44%. Importantly, none of these patients had lesions outside of the parietal lobes.

The study also included a group of  $N=6$  healthy control participants, who were matched to the patient groups in age, education, pre-injury IQ, general memory, working memory, and performance/full IQ, though the rostralateral patients did score significantly higher than the normal controls on verbal IQ (see below).

All patients and healthy controls gave informed consent for participation in the study. The experimental protocol was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board.

## 2.2. Neuropsychological assessment

Pre-injury general intelligence of the participants was assessed via the Armed Forces Qualification Test (AFQT-7A), which is administered to individuals upon entry into the military. The AFQT-7A has been extensively standardized within the U.S. military and correlates highly with WAIS IQ scores (Grafman et al., 1988). Analysis revealed no significant differences in pre-injury AFQT-7A percentile rank scores between the control, rostralateral prefrontal and parietal patient groups (Table 2).

All study participants received a neuropsychological assessment, the scores of which are reported in Table 2. The scores indicate that the participants' memory and IQ are generally within the normal range. Analysis of variance (ANOVA) was used to examine differences in demographic and neuropsychological scores between the rostralateral prefrontal, parietal, and normal control groups. There were no significant differences between the groups in mean age, number of years of education, total cm<sup>3</sup> volume loss in damaged areas (for the patient groups), WAIS-III performance IQ, WAIS-III full IQ and Wechsler overall general memory and working memory scores (Table 2). There was a significant difference between the groups in WAIS-III verbal IQ scores,  $F(2,17)=4.05$ ,  $p < .05$ . Tukey HSD post-hoc analysis indicated that the rostralateral prefrontal group had a higher WAIS-III verbal IQ score than the control group (mean difference = 15.5,  $p < .05$ ). Thus, we incorporated the WAIS-III verbal IQ score as a covariate in our results analysis, as discussed below.

## 2.3. Determination of lesion location and extent

The lesion sites, total volume loss, and intersection of lesion sites with BAs, as determined from patient computerized tomography (CT) scans, are specified in summary overlay images in Figs. 1 and 2. The CT scans were acquired on a GE Light Speed Plus CT scanner in helical mode (150 slices per subject, field of view covering head only). Images were reconstructed with an in-plane voxel size of .4.4 mm, overlapping slice thickness of 2.5 mm, and a 1 mm slice interval. Skull and scalp components were removed using the BET algorithm in MEDx (Medical Numerics Inc., Sterling, VA, USA). Patient CT volumes were imported into ABL (Medical Numerics Inc.) software (Makale et al., 2002) and displayed as a series of slices in a light box format. A trained neuropsychiatrist manually traced the lesions on all relevant slices. The tracings were then reviewed by J.G., who was blind to the results of the neuropsychological testing. Lesion location and volume were determined from the CT images using the Analysis of Brain Lesion software (Makale et al., 2002; Solomon, Raymont, Braun, Butman, & Grafman, 2007) contained in MEDx v3.44 (Medical Numerics) with enhancements to support the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Total lesion volume (in cubic centimeters) 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 ABL reference volume is an MRI of a 27-year-old normal male transformed to Talairach space with a 12-parameter affine linear transformation. The volume is resliced at 17° relative to the inferior orbitomeatal line, and 11 transverse slices that best match the Damasio (Damasio & Damasio, 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° 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 (Figs. 1 and 2), highlight that the regions with the most extensive damage across the 2 patient groups are the bilateral rostralateral prefrontal cortex, in particular BA 10, and the bilateral parietal cortex, in particular BA 7, 40. There were no significant correlations between overall lesion size (CC volume loss) or total percent of brain damaged and accuracy or reaction time scores on the transitive inference task administered in the study.

One concern with traumatic injury patients is in regard to contre-coup brain injury associated with significant force and trauma. However, there is no strong evidence that penetrating traumatic brain injury due to shell fragments, which is the cause of damage among most of our patient population, routinely results in counter-coup effects (Grafman & Salazar, 1987). Certainly our CT scan analysis only rarely gave such hints. While we cannot eliminate the possibility of any microscopic damage (only an autopsy could do that), based on CT scan data, we believe that most of the energy imparted from the penetrating brain wounds occurred at the point of entry and along the missile path.

## 2.4. Task and administration

Participants were asked to engage in a computer administered four-term transitive inference task. Since four-term inference tasks can be overly demanding for patients, only three terms were necessary to resolve the inference problems. The use of the fourth term increased difficulty by allowing for the possibility of multiple models. This was deemed desirable as previous studies indicated maximal involvement of the rostralateral prefrontal cortex (BA 10) for the most difficult items (Christoff et al., 2001; Kroger et al., 2002; Ramnani, & Owen, 2004). Thus this task can be described as a "four-term transitive inference task with three relevant terms."

A total of 48 inference problems (24 valid and 24 invalid) were presented (see Appendix A). Of the 24 invalid trials, 12 were inconsistent, and 12 were indeterminate. This distribution allowed for a balance of yes/no responses while presenting an adequate number of each of the trial types. The stimuli were further divided into 27 chained (Level 1 difficulty) problems and 21 scrambled (Level 2 difficulty) problems as defined by Waltz et al. (1999). When the terms are presented in chained/linear/sequential order (Level 1 difficulty), reasoners are able to construct a linear/sequential spatial map of the arguments and simply evaluate the conclusion against the representation, as in the following example:

Mary is taller than Fiona;  
Mary is taller than Carol;  
Fiona is taller than Rosemary;  
Mary is taller than Rosemary? (correct response: "yes/valid")

However, when the terms are presented in scrambled/non-sequential/non-linear order (Level 2 difficulty) Reasoners must "flip" the spatial representation or consider two relations simultaneously in order to resolve the inference, as in the following example:

Fiona is smarter than Rosemary;  
Mary is smarter than Carol;  
Mary is smarter than Fiona;  
Rosemary is smarter than Mary? (correct response: "no").

While individual names were repeated in some of the item premises in an effort to hold content constant across valid, indeterminate, and inconsistent forms, there was no repetition of complete trials. As the premises do not apply to specific, known "Marys" and "Rosemarys," there is no reason to expect carry over from one trial to another.

Participants 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 decide if the conclusion follows logically from the premises as per the examples. If you think the argument is VALID, press the 'c' key. If you think the argument is NOT VALID, press the 'm' key." Participants proceeded through the problems at their own pace, and were given a maximum of 40 s to respond to each trial. After 40 s, the program automatically proceeded to the next item and non-responses were scored as incorrect. The difficulty (Level 1 versus Level 2) and validity of the inferences was

randomly assigned in a fixed sequence that ran identically for all participants. Participant reaction time (RT) from presentation onset of the full inference chain and accuracy scores were measured for analysis.

### 2.5. Data analyses

Given the small sample sizes of the patient and control groups, we first performed an exploratory data analysis of the accuracy scores on the transitive inference task. Visual examination of normal Q–Q plots in conjunction with Kolmogorov–Smirnov (K–S) tests of normality all indicated that the chained (Level 1) accuracy scores were normally distributed (K–S  $p=.349$ ). These same tests indicated that the scrambled (Level 2) accuracy scores were also normally distributed (K–S  $p=.928$ ). We then performed an exploratory data analysis of the reaction times on the transitive inference task. Visual examination of normal Q–Q plots in conjunction with Kolmogorov–Smirnov tests of normality all indicated that the chained (Level 1) and scrambled (Level 2) reaction times were normally distributed (K–S,  $p=.813$  and  $p=.748$ , respectively). Finally, a Levene's Test of Equality of Error Variances indicated that variance in both chained ( $p=.441$ ) and scrambled ( $p=.712$ ) accuracy scores was equivalent across the control and patient groups. This equivalence in error was confirmed when post-hoc results with a Games–Howell test were similar to post-hoc results obtained with Tukey HSD tests as discussed in the results section below. Given the results of these normality tests, we proceeded with standard parametric analysis for the rest of the results.

## 3. Results

A repeated measures analysis (General Linear Model) with Group (rostrolateral prefrontal, parietal, control) as the independent variable and Difficulty (chained, scrambled) as the repeated measures variable revealed a main effect of Group on the accuracy scores,  $F(2,17)=4.21$ ,  $p=.037$ . There was also a trend for a main effect of Difficulty on accuracy scores,  $F(1,17)=3.91$ ,  $p=.068$ , with all of the groups showing lower scores for scrambled versus chained items (Table 3). Given the small sample sizes in our study and the desire to minimize Type I error, we used Tukey HSD post-hoc analysis to examine the differences in accuracy scores between the groups, given its ability to control family-wise error and to decrease the per-comparison error rate (Sato, 1996). This analysis indicated that the parietal patient group scored significantly lower than the control group on all the inference problems (i.e., both chained and scrambled items combined: mean difference =  $-.21$ ,  $p=.047$ ). The parietal patient group also scored lower than the rostrolateral prefrontal patient group on all the inference problems, although this difference only emerged at a trend level (mean difference =  $-.18$ ,  $p=.058$ ). There was no significant difference in accuracy scores between the rostrolateral prefrontal and normal control groups on all the inference problems (mean difference =  $-.03$ ,  $p=1.00$ ). Finally, there was no interaction of Group  $\times$  Difficulty,  $F(2,17)=.76$ ,  $p=.49$ , suggesting that no patient group was particularly more impaired on the more difficult (Level 2) transitive inference items.

We ran similar repeated-measures analysis to examine effects on mean RTs from presentation onset of the full inference chain to participant's responses across all of the transitive inference items. This analysis revealed no significant difference in RTs for scrambled

(Level 2) versus chained (Level 1) items,  $F(1,17)=3.02$ ,  $p=.104$  (Table 3). Further, there was no significant main effect of Group on RT,  $F(2,17)=.96$ ,  $p=.41$ , nor an interaction of Group and Difficulty,  $F(2,17)=.93$ ,  $p=.42$ . We also examined RT data for correctly-answered items only, and this analysis revealed a significant main effect for Difficulty,  $F(1,17)=18.9$ ,  $p=.001$ , with all of the groups showing higher RTs for chained (Level 1) versus scrambled (Level 2) items. Similar to the RT results for all items, there was no Group by Difficulty interaction and no main effect of Group.

We then ran another repeated measures analysis with Group (rostrolateral prefrontal, parietal, control) as the independent variable and Difficulty (chained, scrambled) as the repeated measures variable, including WAIS verbal IQ as a covariate, given that it was the only demographic/neuropsychological variable that showed a significantly different score between the groups. With this covariate included in the model, the estimated accuracy scores across all the inference problems (i.e., both chained and scrambled items combined) was .489 (parietal patients), .626 (rostrolateral prefrontal patients), and .707 (normal controls). There were no significant interactions between Difficulty and WAIS verbal IQ score,  $F(1,14)=.333$ ,  $p=.574$  or Difficulty and Group,  $F(2,14)=.889$ ,  $p=.435$ . There was also no significant main effect of Difficulty,  $F(1,14)=.152$ ,  $p=.703$ , or WAIS verbal IQ,  $F(1,14)=.899$ ,  $p=.360$ . However, there was a significant main effect of Group,  $F(2,14)=3.84$ ,  $p=.049$ . Thus, the significant difference between the groups on the accuracy scores for the transitive inference task held when the WAIS-III verbal IQ scores were included in the model.

## 4. Discussion

The purpose of this study was to examine the roles of the rostrolateral prefrontal cortex versus the parietal cortex in resolving transitive inference problems. The results indicated that the parietal patients were significantly impaired on the transitive inference task compared to normal controls, and were impaired on the transitive inference task compared to the rostrolateral prefrontal patients, albeit at a trend level. There was no significant difference on the task between the rostrolateral prefrontal patients and the normal controls. The results suggest that the parietal cortex, rather than the rostrolateral prefrontal cortex, is necessary for transitive inference. This finding is consistent with many previous imaging studies and two meta-analyses that point to the importance of the parietal lobes for transitive reasoning (Goel, 2003; Goel et al., 2000; Goel & Dolan, 2001, 2003; Knauff et al., 2003; Prado et al., 2010, 2011).

These results are also consistent with Vartanian et al. (2009) in that their frontal temporal dementia patients were not impaired in transitive inference arguments involving propositions that participants did not have beliefs about. There is also no apparent conflict between our results and those of Kosciak and Tranel (2012), in that their reasoning impaired group had lesions in ventral medial prefrontal cortex (not rostrolateral prefrontal

**Table 3**  
Mean percent accuracy (SD) and reaction times (SD) (in seconds) for 27 chained (Level 1) and 21 scrambled (Level 2) transitive inference items across the three participant groups.

Measures	Difficulty	Normal controls (N=6)	Rostrolateral patients (N=5)	Parietal patients (N=7)	All participants (N=18)
Accuracy	Chained	.74 (.10)	.68 (.23)	.56 (.17)	.65 (.18)
	Scrambled	.65 (.16)	.66 (.13)	.40 (.19)	.55 (.20)
	All items	<b>.70 (.09)*</b>	<b>.67 (.18)**</b>	<b>.49 (.16)***</b>	.62 (.17)
RT	Chained	18.1 (4.7)	23.9 (3.8)	21.5 (10.1)	20.9 (7.3)
	Scrambled	18.7 (4.9)	24.9 (4.8)	24.7 (11.1)	22.6 (8.2)
	All items	18.4 (4.3)	24.3 (3.7)	22.9 (10.4)	21.9 (7.3)

\* Parietal patients < normal controls,  $p=.047$  (Tukey HSD post-hoc tests).

\*\* Parietal patients < rostrolateral patients,  $p=.058$  (Tukey HSD post-hoc tests).

\*\*\* Rostrolateral patients = normal controls,  $p=1.00$  (Tukey HSD post-hoc tests).

cortex) and their control patient group had lesions concentrated in temporal medial cortex (rather than parietal cortex).

Interestingly, the performance of our patients with frontal lobe lesions does not replicate the results reported by [Waltz et al. \(1999\)](#). As noted in the Section 1, their frontal dementia patients were selectively impaired in the difficult, Level 2 (scrambled) inference condition. Despite the use of very similar stimuli to [Waltz et al. \(1999\)](#), neither our accuracy nor RT data support a selectively impaired performance in resolving scrambled versus chained transitive inference problems by patients with lesions to the prefrontal cortex. There are several possible reasons for this discrepancy.

First, [Waltz et al. \(1999\)](#) included frontotemporal dementia patients in their study, and were not able to specify focal brain areas within the frontal lobes that were impacted by the disease. Thus, their results may have been driven by damage to the dorsolateral and/or dorsal medial regions rather than the rostralateral prefrontal cortex (BA 10).

Second, [Waltz et al. \(1999\)](#) refer to the importance of working memory for resolving Scrambled (Level 2) transitive inferences but do not provide working memory measures for their patients. However, both the temporal and frontal patients in their study scored relatively low on the WAIS-III full IQ (prefrontal  $96 \pm 6.4$ ; temporal  $94.8 \pm 8.0$ ). This is consistent with our parietal patient group ( $99.5 \pm 15.9$ ), but generally lower than our rostralateral prefrontal group ( $106.3 \pm 4.8$ ). It is possible that the frontal dementia patients in [Waltz et al. \(1999\)](#) may have experienced widespread frontal cortex damage, including the DLPFC, which would have negatively impacted this working memory brain circuit ([Cohen et al., 1997](#)), and performance on the transitive inference task.

There is evidence for a connection between working memory capacity and at least some forms of transitive inference reasoning ([Libben & Titone, 2007](#)). However, the fact that the parietal patients showed impairment on the transitive inference task despite similar WMS-III working memory scores between the three groups in the present study suggests a critical role for parietal cortex in transitive inference, over and above general working memory requirements. Given that the parietal lobes are known to be critical for spatial manipulation ([Cohen et al., 1996](#)), and that a significant theory of logical reasoning postulates the construction and manipulation of spatial mental models in logical inference ([Johnson-Laird, 1986](#); [Mani & Johnson-Laird, 1982](#)), it is plausible that this is the function that the parietal lobes are serving.

While [Waltz et al. \(1999\)](#) discuss relational integration in conjunction with overall frontal lobe functioning; other researchers (e.g., [Fangmeier et al., 2006](#); [Wendelken & Bunge, 2009](#)) have recently focused upon BA 10 (right medial anterior prefrontal and right rostralateral prefrontal, respectively) as the specific frontal region critical for “relational integration”. While we do not question the activation of BA 10 in these studies, in light of our current results and published meta-analyses ([Goel, 2007](#); [Prado et al., 2011](#)), we believe that the association between rostralateral prefrontal (BA 10) and the general function of “relational integration” may be premature. It is important to try to understand possible methodological differences that may account for these diverging results.

[Fangmeier et al. \(2006\)](#) used fMRI to examine brain activation during a nonlinguistic transitive inference task. They differentiated between the neural activations associated with the presentation of the first premise, the presentation of the second premise and its integration with the first, and evaluation of the conclusion. While bilateral parietal lobe activation was involved in all conditions, they noted the recruitment of right anterior medial PFC (BA 10) in the premise integration condition, and concluded that this region is specifically responsible for the combination and coordination (i.e., integration) of premises ([Fangmeier et al., 2006](#)).

[Wendelken and Bunge \(2009\)](#) also used fMRI to examine participants' ability to engage in explicit transitive inference tasks

using nonlinguistic/pictorial stimuli. They examined the full reasoning process, rather than the individual components, as above. In comparing a three-term relational inference condition with a two-term relational baseline condition they reported activation in bilateral parietal lobes and right rostralateral prefrontal cortex (BA 10). They concluded that the rostralateral prefrontal cortex (BA 10) activation is the “most prominent locus of activation during transitive inference” (p. 843).

First, while both studies report activation in BA 10, they do so in different conditions. [Fangmeier et al. \(2006\)](#) report it specifically, and only in, a premise integration condition, while [Wendelken and Bunge \(2009\)](#) report it in the main effect of reasoning. But perhaps more importantly, these two studies differ from other studies of transitive reasoning in the neuroimaging literature by virtue of using nonlinguistic stimuli. In particular, the indicated spatial relations were actually *exemplified* or embodied in the stimuli presentation rather than simply being stated in a proposition.

The linguistic presentation of the task as used in the present study (and many imaging studies) involves the simultaneous (or sequential) presentation of premises and conclusion, requiring participants to carry out at least the following steps: (1) map from the propositional representation that preserves the structural properties of linguistic strings in which the premises are stated to a representation that preserves/exemplifies the spatial relations that are stated in the proposition; (2) hold the transformed representations of premises in working memory, aided by external stimuli representation (all premises remained on the screen for the duration of the task) and integrate them (the retention of the integrated representation is not aided by external stimuli presentation); and (3) resolve the inference.

The stimuli and presentation methods used by [Fangmeier et al. \(2006\)](#) and [Wendelken and Bunge \(2009\)](#) placed different task requirements on participants. In the [Fangmeier et al. \(2006\)](#) study, participants had to: (1) hold explicitly presented/exemplified spatial relations in working memory (the stimuli did not remain on the screen for the duration of the task); (2) integrate the two premises while holding them in working memory, but with no external visual aid (the stimuli did not remain on the screen for the duration of the task); and (3) resolve the inference. The first two steps here differ considerably from those required in our task.

The [Wendelken and Bunge \(2009\)](#) task material and presentation placed still different task requirements on participants: (1) their participants were also presented with exemplified spatial relations, as above, but they did not have to hold them in working memory (because they were continuously present in the external stimuli); (2) integrate the premises (again aided by external stimuli); and (3) resolve the inference. It is possible that these differing task requirements have important consequences for the strategy and neuronal resources employed by participants.

One obvious possibility is that where linguistic stimuli are used, greater effort and resources are required to map the stimuli onto spatial mental models as a prerequisite to solution ([Johnson-Laird, 1986](#); [Mani & Johnson-Laird, 1982](#)). This requires the parietal cortex ([Cohen et al., 1996](#); [Goel & Dolan, 2001](#); [Knauff et al., 2003](#); [Zacks, 2008](#)). In the case of the pictorial stimuli, this mapping has already been done in the task presentation, rendering the involvement of parietal cortex less critical and perhaps shifting processing to the prefrontal cortex.

In summary, our results suggest that the parietal cortex is necessary for enabling transitive inference. When the task contains additional elements including content that we have beliefs about, conflict, indeterminacy, differential working memory loads, or spatial versus linguistic presentation of information, then other key cortical sectors including various regions within the prefrontal cortex will become important.

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**Appendix A. Transitive inference items presented in the study**

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Chained (Level 1) Items

Mary is smarter than Carol	Mary is smarter than Carol	Mary is smarter than Carol
Mary is smarter than Fiona	Mary is smarter than Fiona	Mary is smarter than Fiona
Fiona is smarter than Rosemary	Fiona is smarter than Rosemary	Fiona is smarter than Rosemary
Mary is smarter than Rosemary?	Carol is smarter than Fiona?	Rosemary is smarter than Mary?
Mary is smarter than Fiona	Mary is smarter than Fiona	Mary is smarter than Fiona
Fiona is smarter than Rosemary	Fiona is smarter than Rosemary	Fiona is smarter than Rosemary
Mary is smarter than Carol	Mary is smarter than Carol	Mary is smarter than Carol
Mary is smarter than Rosemary?	Carol is smarter than Fiona?	Rosemary is smarter than Mary?
Mary is taller than Fiona	Mary is taller than Fiona	Mary is taller than Fiona
Mary is taller than Carol	Mary is taller than Carol	Mary is taller than Carol
Fiona is taller than Rosemary	Fiona is taller than Rosemary	Fiona is taller than Rosemary
Mary is taller than Rosemary?	Carol is taller than Fiona?	Rosemary is taller than Mary?
Natalie is healthier than Lucy	Natalie is healthier than Lucy	Natalie is healthier than Lucy
Lucy is healthier than Samantha	Lucy is healthier than Samantha	Lucy is healthier than Samantha
Lucy is healthier than Gloria	Lucy is healthier than Gloria	Lucy is healthier than Gloria
Natalie is healthier than Samantha?	Samantha is healthier than Gloria?	Samantha is healthier than Natalie?
Natalie is healthier than Lucy	Natalie is healthier than Lucy	Natalie is healthier than Lucy
Lucy is healthier than Gloria	Lucy is healthier than Gloria	Lucy is healthier than Gloria
Lucy is healthier than Samantha	Lucy is healthier than Samantha	Lucy is healthier than Samantha
Natalie is healthier than Samantha?	Samantha is healthier than Gloria?	Samantha is healthier than Natalie?
Jessica is faster than Nicole	Peter is lazier than Mat	Nick is messier than William
Jessica is faster than Melanie	Peter is lazier than Clyde	Nick is messier than Wesley
Melanie is faster than Valerie	Clyde is lazier than Henry	Wesley is messier than Liam
Jessica is faster than Valerie?	Peter is lazier than Henry?	Nick is messier than Liam?
Patricia is smaller than Maxine	Felix is bigger than Randy	Jane is tinier than Hanna
Patricia is smaller than Candy	Felix is bigger than David	Jane is tinier than Jackie
Candy is smaller than Elaine	David is bigger than Allen	Jackie is tinier than Meghan

Patricia is smaller than Elaine?	Felix is bigger than Allen?	Jane is tinier than Meghan?
John is brighter than Greg	Nina is nastier than Susan	Natasha is prettier than Laura
Greg is brighter than Andre	Susan is nastier than Audrey	Laura is prettier than Sandy
Greg is brighter than Patrick	Susan is nastier than Lisa	Laura is prettier than Gertrude
John is brighter than Andre?	Nina is nastier than Audrey?	Natasha is prettier than Sandy?
Robert is littler than Joel	Ronald is larger than Richard	Camilla is slimmer than Daisy
Joel is littler than Winston	Richard is larger than Bob	Daisy is slimmer than Meredith
Joel is littler than Del	Richard is larger than Frans	Daisy is slimmer than Courtney
Robert is littler than Winston?	Ronald is larger than Bob?	Camilla is slimmer than Meredith?
Scrambled (Level 2) Items		
Lucy is healthier than Gloria	Lucy is healthier than Gloria	Lucy is healthier than Gloria
Natalie is healthier than Samantha?	Samantha is healthier than Gloria?	Samantha is healthier than Natalie?
Lucy is shorter than Samantha	Lucy is shorter than Samantha	Lucy is shorter than Samantha
Lucy is shorter than Gloria	Lucy is shorter than Gloria	Lucy is shorter than Gloria
Natalie is shorter than Lucy	Natalie is shorter than Lucy	Natalie is shorter than Lucy
Natalie is shorter than Samantha?	Samantha is shorter than Gloria?	Samantha is shorter than Natalie?
Lucy is shorter than Gloria	Lucy is shorter than Gloria	Lucy is shorter than Gloria
Natalie is shorter than Lucy	Natalie is shorter than Lucy	Natalie is shorter than Lucy
Lucy is shorter than Samantha	Lucy is shorter than Samantha	Lucy is shorter than Samantha
Natalie is shorter than Samantha?	Samantha is shorter than Gloria?	Samantha is shorter than Natalie?
Lucy is shorter than Gloria	Lucy is shorter than Gloria	Lucy is shorter than Gloria
Lucy is shorter than Samantha	Lucy is shorter than Samantha	Lucy is shorter than Samantha
Natalie is shorter than Lucy	Natalie is shorter than Lucy	Natalie is shorter than Lucy
Natalie is shorter than Samantha?	Samantha is shorter than Gloria?	Samantha is shorter than Natalie?

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