

Frontal and Parietal Lobe Activation during Transitive Inference in Humans

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Cortical areas engaged in knowledge manipulation during reasoning were identified with functional magnetic resonance imaging (MRI) while participants performed transitive inference (TI) on an ordered list of 11 items (e.g. if $A < B$ and $B < C$, then $A < C$). Initially, participants learned a list of arbitrarily ordered visual shapes. Learning occurred by exposure to pairs of list items that were adjacent in the sequence. Subsequently, functional MR images were acquired as participants performed TI on non-adjacent sequence items. Control tasks consisted of height comparisons (HT) and passive viewing (VIS). Comparison of the TI task with the HT task identified activation resulting from TI, termed 'reasoning', while controlling for rule application, decision processes, perception, and movement, collectively termed 'support processes'. The HT-VIS comparison revealed activation related to support processes. The TI reasoning network included bilateral prefrontal cortex (PFC), pre-supplementary motor area (preSMA), premotor area (PMA), insula, precuneus, and lateral posterior parietal cortex. By contrast, cortical regions activated by support processes included the bilateral supplementary motor area (SMA), primary motor cortex (M1), somatic sensory cortices, and right PMA. These results emphasize the role of a prefrontal-parietal network in manipulating information to form new knowledge based on familiar facts. The findings also demonstrate PFC activation beyond short-term memory to include mental operations associated with reasoning.

Introduction

One of the more remarkable traits of highly encephalized animals is their ability to manipulate knowledge flexibly to deduce novel facts. The cognitive process of internally creating new knowledge by manipulating prior information can be operationally termed reasoning. Transitive inference (TI; if $A < B$, $B < C$, then $A < C$) represents a form of reasoning that humans appear to solve by internally manipulating a holistic representation rather than through formal logic (Acuna *et al.*, 2002). Functional imaging during TI can identify cortical regions underlying reasoning-related processes and internal knowledge formation.

The dorsolateral prefrontal cortex (PFC), among other cortical areas, has been implicated in short-term memory and executive functions, including reasoning (Holyoak and Kroger, 1995; Damasio, 1998). PFC neurons discharge selectively to task stimuli and can continue discharging across a delay even if the stimulus is absent (Quintana *et al.*, 1988; Funahashi *et al.*, 1990; Rao *et al.*, 1997). PFC also becomes engaged during object-location conjunctions, learned associations and rule formation (di Pellegrino and Wise, 1991; Rao *et al.*, 1997; Asaad *et al.*, 1998; Rainer *et al.*, 1998; White and Wise, 1999), processes not readily associated with memory function. Further, patients with frontal lesions have difficulty drawing inferences, applying rules (Milner, 1963; Luria, 1966; Delis *et al.*, 1992; Waltz *et al.*, 1999) and cannot solve TI problems (Waltz *et al.*, 1999). Finally, brain imaging studies have linked PFC to non-mnemonic functions

(Postle *et al.*, 1999; Christoff *et al.*, 2001; Goel and Dolan, 2001), also suggesting a role in executive processes. PFC may be engaged in reasoning and problem solving simply by keeping information about task features readily available; however, it may also be a critical site for manipulating and integrating facts to create new knowledge.

Similar to PFC, posterior parietal neurons have putative short-term memory activity (Koch and Fuster, 1989; Quintana and Fuster, 1992). In addition, parietal neurons exhibit discharge modulation during spatial processing, such as converting among different coordinate frames (Georgopoulos *et al.*, 1984; Galletti *et al.*, 1993; Andersen, 1997; Duhamel *et al.*, 1997; Rushworth *et al.*, 1997). Posterior parietal activation also occurs during a number comparison task requiring participants to decide whether a given number was larger or smaller than 65 (Pinel *et al.*, 2001). PFC is interconnected with parietal areas (Jones, 1969; Pandya and Kuypers, 1969; Jones and Powell, 1970); thus, these two cortical regions probably cooperate not only to hold information, but also to integrate and transform it for various problem solving activities.

In this regard, frontal and parietal areas become activated during arithmetic and spatial mental operations (Roland and Friberg, 1985; Pinel *et al.*, 2001), as well as during analytic reasoning (Prabhakaran *et al.*, 1997), syllogistic deduction, and probabilistic reasoning (Osherson *et al.*, 1998). However, these cognitive actions involve several mental operations that may be difficult to parcellate. By contrast, the premises and solutions in TI are well specified when stimuli are arranged linearly (e.g. $A < B < C$). A TI task using three items reported robust posterior parietal activation (Goel and Dolan, 2001); however, a three-item TI task can be solved without integrating premises (Bryant and Trabasso, 1971; McGonigle and Chalmers, 1992; Zentall and Sherburne, 1994). We examined brain regions that became active as participants solved problems on an ordered list of 11 items, preventing them from using strategies based on the first and last items of the list. Tasks controlling for support processes allowed us to test the hypothesis that mental fact manipulation during problem solving engages PFC and posterior parietal cortex. This work has been published in abstract form (Acuna *et al.*, 1998).

Materials and Methods

Participants

Fifteen participants (six women and nine men; one left-handed male, all others right-handed, 18–24 years) were recruited from the Brown University community. By self-report, all had normal neurologic function and did not have any bodily ferromagnetic materials. Each participant gave written informed consent according to guidelines established and approved by the Brown University Human Subjects Committee and the Beth Israel-Deaconess Medical Center Committee on Clinical Investigations (the MR imaging was done in the facilities of the Department of Radiology, Beth Israel-Deaconess Medical Center), and each received

modest monetary compensation. Behavioral data obtained during learning and application of the reasoning rule in the TI task for these 15 participants, and for 10 others not examined for the MR work, are reported elsewhere (Acuna *et al.*, 2002). The entire experiment was divided into three phases: the first phase entailed learning the order of a list of visual stimuli; the second entailed reasoning (TI) with the list items; and the third phase involved obtaining functional MR images during TI and the control tasks. On a single day, a participant learned an ordered sequence of stimuli (Phase 1) and demonstrated the ability to reason in the TI task (Phase 2). Functional MR scans were acquired 1 day later (Phase 3), and these data form the basis of the current report.

Behavioral Testing

The day before MR scanning, participants were pre-screened for ability to perform TI on an ordered list of 11 arbitrary, visually presented shapes (Fig. 1A). The participants' goal was to choose, given two items from the list, the one occurring closest to one end of the sequence, item K in Figure 1A. The colors of the stimuli from A to K were: red, yellow, purple, dark blue, lime green, brown-orange, fuchsia, light blue, white, orange and green. None of the stimulus attributes – size, chromaticity, luminance and perceptual color differences (Robertson, 1977) – varied systematically across the sequence. When regressed on item position in the sequence, no stimulus attributes was significantly described by a linear fit (Acuna *et al.*, 2002), thereby indicating that they could not be used as an alternative to solving the problems instead of via TI (Acuna *et al.*, 2002). During Phase 1, participants learned the order of the items by trial and error; pairs of shapes that were adjacent in the list were shown in a random order and participants were instructed to choose the item occurring closer to the rightmost end of the list (e.g. given D versus E, choose E). They determined the correct answer merely by the feedback received on trials. After participants learned the sequence to criterion, they proceeded to Phase 2, when TI was tested by presenting non-adjacent (NA) pairs of list items (e.g. D versus F, Fig. 1B). Three types of TI trials were presented in blocks: NA items with one, two or three intervening items (NA1, NA2, NA3). Participants never received feedback on TI trials, so that the only way to determine the correct answer was to refer to the knowledge acquired during the learning phase.

Three main results emerged from the learning and TI psychophysics testing phases [reported in greater detail in Acuna *et al.* (Acuna *et al.*, 2002)]. First, reaction time (RT) increased as learning took place, suggesting that as the relative locations of items were learned, participants incorporated location into a unified representation that took increasingly longer to recall as more items entered the representation. This finding is similar to previous list-learning studies (Sternberg, 1967). Secondly, we found that during TI there was a graded effect of number of intervening items on RT. Thus, NA3 pairs elicited the shortest RT, NA1 pairs elicited the longest RT of the three types of TI trials, and NA2 pairs were intermediate. Thirdly, percent correct was inversely correlated with RT, indicating that NA1 pairs were the most effortful according to both RT and proportion correct. In the present study, we presented NA1 pairs during MR imaging to maximize participants' cognitive processing time and to use a reduced set of behavioral conditions to ensure suitability and practicality for undertaking functional MR experiments.

Tasks during Functional MRI

General

Participants performed three tasks during acquisition of functional MR images: a task requiring reasoning by using TI, a visual height comparison of stimulus pairs (HT), and passive viewing of visual stimulus pairs (VIS). A custom-written program run from a Macintosh IIci (Apple Computer Corp., Cupertino, CA) controlled the stimulus delivery and timing for all tasks. Before acquiring MR images, general instructions were read to each participant regarding the three tasks, though the participants already had previous experience with each task. For each task, participants used a mirror mounted on the head coil to view pairs of stimuli chosen from a list of 11 items (TI and HT tasks, Fig. 1A) or six other similar stimuli (VIS, not illustrated) back-projected onto a tangent screen. The stimuli were centered in each participant's field of vision and the lights in the MR room were turned off during MR imaging. In all tasks, the stimulus display consisted of a white circular (1.6 cm diameter) fixation point centered on

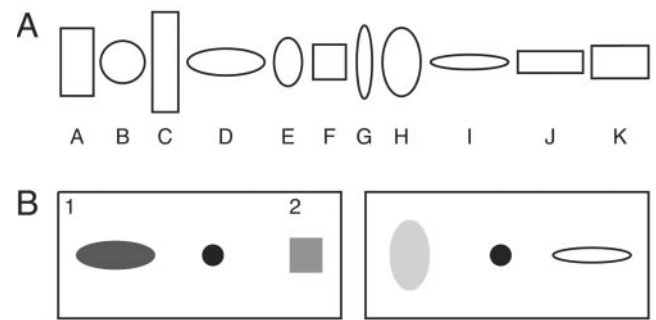


Figure 1. Transitive inference task. (A) Eleven stimuli of different shapes and hues comprised the stimulus set for the TI sequence. During learning and testing, stimuli were shown in pairs; the entire sequence was never viewed. The letters below each shape are presented here merely for explanatory purposes. For any given pair, the correct choice was the stimulus closest to K, so that A was never correct, K was always correct, and whether an intermediate item was correct depended on its relative position in the sequence. (B) Display configuration of stimuli in the MR scanner. The circle in the center served as the fixation point and the flanking stimuli were items from the sequence (stimuli were in color as described in Materials and Methods). Participants were instructed to maintain central fixation throughout the trial and to press a button to indicate stimulus selection during TI or height comparison trials. The stimuli were displayed for 3 s, after which a new trial began. (1) Example of a TI pair. (2) Example of a height comparison pair.

a black background with two test stimuli on either side of it (Fig. 1B shows stimulus outlines). Participants fixated the central dot during the functional MR data acquisition period, and they were required to respond as quickly as possible in each TI or HT trial by pressing one of two MR-compatible, fiber-optic pushbuttons held in each hand. Participants were instructed to press the pushbutton in their left hand if the left stimulus was correct, and vice versa for the right stimulus. The occurrence of a left or right button press was recorded for offline analysis. Short-term memory demands were minimized by presenting the two test stimuli simultaneously and by not having delay periods between stimulus presentation and responses.

Transitive Inference Task

All participants were prescreened for ability to perform the TI task to criterion using the item list schematically illustrated in Figure 1A. During functional MRI data acquisition, participants were presented with NA1 stimulus pairs, which had one intervening sequence item (Fig. 1B₁). As mentioned, these pairs commonly elicited the longest RT during performance of the TI task (Acuna *et al.*, 2002). The 'correct' stimulus, that is, the one closer to the rightmost end of the sequence (item K in Fig. 1A), randomly appeared to the left or right of the fixation point. Feedback regarding a participant's choice on TI trials was never provided, either during the testing phase on the previous day or during the functional MRI data acquisition. In addition, since physical attributes of the stimuli had no relationship to correctness, participants had to manipulate prior knowledge to determine the correct choice.

Height Comparison Task

Participants chose the taller of two stimuli during the HT task. The HT task employed the same stimuli as those used for the TI task, with the taller stimulus appearing randomly in the left or right position. Participants responded by pressing the left or right pushbutton corresponding to the decision of whether the left or right stimulus was taller. No feedback was provided regarding the choice.

The HT task controlled for visual processing, rule application, decision processes and button pressing. We chose the height rule because items in the sequence can be ordered in a linear fashion according to height, similar to the linear ordering of the arbitrary, memorized sequence used in TI. The critical difference between the two rules of 'choosing taller' or 'choosing later in sequence' is that a height comparison can be solved perceptually whereas the reasoning needed in the TI task requires manipulation of known information (the learned, arbitrary order of items).

Passive Visual Task

The passive viewing task required participants to fixate on the central point during appearance of stimulus pairs. Participants held, but did not press, the buttons and were instructed not to perform any comparisons between stimuli. To prevent participants from covertly practicing comparisons used in the TI and HT tasks, we used six novel oval and rectangular shapes that were comparable in size and color to those employed in the learned list. The stimuli used in the VIS task had no relationship to the learned order of the stimuli used for the TI and HT tasks, thereby controlling only for visual processes.

Experimental Design

The total functional MRI data acquisition time lasted 18 min, during which participants performed 10 sets of trials requiring TI, 10 sets of trials requiring height comparisons in the HT task, and 10 sets of trials passively viewing stimuli in the VIS task. We used a Latin square design to order the task sets. Each 36 s task set, or measurement, began with a visually presented instruction for 6 s and then 10 trials (TI, HT or VIS task) each 3 s long. Twelve functional brain volumes were acquired during each task set. For the TI task sets, the instruction displayed the words 'Choose the later one,' with 'later' referring to rightmost element in the sequence, as participants had practiced on the previous day. For the HT task sets, the instruction read 'Choose the taller one,' and for the VIS task sets, it read 'Just watch'. Instructions appeared in black letters on a white background. During each trial, the fixation point and two test stimuli were displayed (Fig. 1B). In total, participants performed 100 trials of each task while in the scanner.

MR Imaging

Anatomical and functional MR images were acquired with a Vision Magnetom MR system (Siemens Medical Systems, Erlangen, Germany) equipped for echo-planar imaging and operating at 1.5 T. Participants lay supine on an automated gurney for insertion into the MR system bore. The head rested within a circularly polarized quadrature head coil that was used for radio-frequency transmission and reception. Each participant's head was approximately centered in the magnetic field of the MR system by aligning the nasion with a laser cross-hair projection before transport into the MR system bore. Head movement was minimized by cushioning and mild restraint, and participants were instructed to refrain from moving the head and speaking during MR imaging.

Inhomogeneities in the magnetic field introduced by the participant were minimized with a standard two-dimensional head shimming protocol. We then acquired a three-dimensional, high-resolution anatomical data set (Siemens' magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, $T_R = 10$ ms, $T_E = 64$ ms, inversion time = 20 ms, 1 mm isotropic voxels). Echo planar images (EPI) were acquired in a transverse plane roughly parallel to the body of the corpus callosum using blood-oxygenation-level-dependent imaging (Kwong *et al.*, 1992). Fifteen slices were sampled from the superior convexity to the approximate level of the Sylvian fissure. Each slice was 5 mm thick and encompassed a field of view of 240 mm with a 128^2 image matrix; voxels had an in-plane resolution of 1.875×1.875 mm for a volume of 17.6 mm³. The imaging sequence for the functional data used a $T_R = 3$ s and a $T_E = 64$ ms.

Data Analysis

The MR images were transferred to Silicon Graphics workstations and manipulated and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996; Cox and Hyde, 1997). A total of 360 echo-planar volumes were acquired during the experiment in sets of 12 volumes (a 36 s measurement, see above). The first two volumes in each measurement were discarded due to T_1 saturation effects (i.e. transient equilibration of longitudinal magnetization at the beginning of each measurement). This left a total of 300 EPI volumes that were analyzed for brain activation. Each participant's MPRAGE and EPI image series were co-registered using the positioning coordinates from the scanner system. The MPRAGE anatomical image was normalized to the standardized space of Talairach and Tournoux (Talairach and Tournoux, 1988) using tools provided in AFNI. Following motion correction (see below) the EPI image set was also transformed to standardized space by adoption of the landmarks defined in the MPRAGE dataset.

Motion Correction

Each participant's EPI images were co-registered to the first EPI volume in the experiment using a six-parameter rigid body transformation (Cox and Jesmanowicz, 1999). After the co-registered EPI images were normalized to standard space (see above) the dataset was resampled to an isotropic resolution of 2 mm. This normalized and resampled EPI dataset was then smoothed using an isotropic 4 mm Gaussian kernel. The normalized, resampled and smoothed EPI dataset was then analyzed as described below to obtain functional brain activation maps.

Deconvolution Analysis

Deconvolutions were performed separately on each participant's EPI data on a voxel-by-voxel basis to estimate the hemodynamic response during performance of each of the three behavioral tasks. We used deconvolution to estimate the average EPI signal of the time series, any linear drift, and hemodynamic response functions for the three behavioral tasks. Unlike correlation analysis, deconvolution allows the simultaneous estimation of contributions from multiple input stimulus functions (or reference waveforms or functions). The first three reference waveforms were specified by the behavioral tasks. These reference waveforms were composed of ones and zeros with the number of entries totaling the number of EPI acquisitions analyzed in the experiment (300). In the behavioral waveforms, we placed ones at the point corresponding to the first volume of a block of a particular behavioral task with zeros elsewhere. Thus, a single reference waveform indicated, by the placement of ones, the beginning of each block of a certain behavioral task (VIS, HT or TI). Then, considering all blocks of a particular task together, the deconvolution algorithm estimated a scaling factor for this reference waveform for the second through tenth volume of the particular behavioral task. This was repeated for each task, to yield 27 separate fit coefficients, nine for each of the three behavioral tasks. The remaining six reference waveforms were specified by the output parameters of the motion correction algorithm, x , y and z translation, and roll, pitch and yaw rotations. A single fit coefficient was calculated for each movement correction parameter. These six waveforms allowed removal of trends in the EPI signal related to head movement. These head movement related coefficients were not analyzed further. In total, 35 fit coefficients were calculated from the data, 27 estimated the contributions of behavioral performance in nine time points, six estimated contributions of head movements, and two estimated the average and linear drift in the EPI signal.

Activation Calculation

The scaling coefficients from the deconvolution were used to determine the degree of brain activation for a particular task as follows. On a voxel-by-voxel basis, the fit coefficients for time points two to 10 of a given behavioral task block were divided by the average EPI signal and multiplied by 100 to arrive at a baseline normalized percent change (%-change) value. These nine %-change values were assessed with a two-way mixed effects analysis of variance (ANOVA) with task and participant as independent variables. In the first level of analysis, the degree of brain activation in each condition was determined by the outcome of a one-sample t -test comparing the distribution of %-change for a particular task (VIS, HT and TI) with zero. Two second-level contrasts compared the activation between conditions directly, HT versus VIS and TI versus HT.

Following these statistical tests, we thresholded the activation data in three ways in order to remove non-brain regions of the statistical images and correct for multiple comparisons. First we excluded non-brain voxels, and then we masked the activation maps with P -value and cluster size thresholds. In order to exclude non-brain voxels, we averaged the EPI reference volume (acquisition 0) from the motion correction step from each participant. This average EPI image was used to exclude from further analysis regions that did not represent the brain or that had signal dropout due to magnetic field inhomogeneities (e.g. near the sinuses). We masked the output of the ANOVA by filtering out regions of the image where the average EPI image was less than three standard deviations below the mean of the average EPI. In order to correct the statistical maps of brain activation (output of the ANOVA) for multiple comparisons, we selected voxel-level and cluster-level thresholds to additionally mask the

data. We selected a voxel-level threshold of $P \leq 0.005$ for initially viewing the activation maps. Following a strategy commonly employed with AFNI, we then performed Monte Carlo simulations (2500 iterations, 5.2 mm radius, 4 mm smoothness) which estimated the frequency of clusters of voxels with a P -value of ≤ 0.005 for cluster sizes of one to 46 voxels. These simulations indicated that in order to achieve a corrected P -value of < 0.05 we should exclude from the statistical activation maps any cluster having < 29 contiguous voxels. Thus, the %-change activation maps were thresholded with a t -value of 3.045 ($P < 0.005$) and a cluster size of ≥ 29 voxels ($P < 0.05$).

Rationale for Statistical Comparisons

A paired comparison approach was utilized to isolate the functional MRI activation of interest, in this case, related to reasoning. With this approach, we could control for visual processing, rule application, decision processes, and movement that occurred during the TI task but were not directly related to reasoning. Thus, three comparisons were planned: comparing functional MR signals during the TI task to those occurring during the HT task (TI-HT), and comparing the HT task to the VIS task (HT-VIS).

TI-HT

Reasoning, as implemented in the TI task, comprises several processes. Minimally, TI occurs together with perception and recognition, rule application ('choose the stimulus closest to K in the sequence'), decision and choice processes, and a motor action. To control for these support processes that are related to task performance, but which might also yield changes in functional MRI signals, we compared the MRI signals occurring during the TI task to those occurring during the HT task. Thus, the TI-HT comparison should yield functional MRI activation most related to the reasoning required in the TI task, without the associated support processes.

HT-VIS

Comparing functional MRI signals obtained during the HT task to the activation obtained during the VIS task should yield signals related to support process such as rule application ('choose the taller stimulus'), decision and choice, and button pressing, but not activation due to perception of stimuli.

Anatomic Parcellations

In an attempt to attribute activation to specific regions of the brain, we identified the maximum percent signal change within each cluster and obtained the coordinates in standardized space Talairach space (Talairach and Tournoux, 1988) of each maximum. These coordinates were used to identify the corresponding Talairach atlas labels as defined in the Talairach Daemon (Collins *et al.*, 1995; Lancaster *et al.*, 2000) and implemented in AFNI. For clusters that spanned multiple atlas regions, we reported the maximum percent signal change within each distinct atlas region that a cluster penetrated.

Results

Behavior

During the functional MRI experiment, all participants performed TI and HT tasks at a level far exceeding chance performance. The mean performance level during the TI task was 92% (range 80–99%); the mean performance level during the HT task was 99% correct (range 97–100%). This performance level was comparable to that observed during the behavioral testing phase (Acuna *et al.*, 2002).

Brain Activation Patterns

We carried out two comparisons: TI-HT, which revealed activation related to integrating information and reasoning, and HT-VIS, which revealed cortical regions related to support processes such as rule application and decision making. Overall, TI-HT produced more active voxels than HT-VIS. In both comparisons, activation appeared in multiple clusters.

Frontal Cortex

Activation in frontal cortex during TI, as compared to the height task, occurred in several frontal clusters across both hemispheres, including dorsolateral portions of the superior, middle and inferior frontal gyri, in addition to cingulate and medial frontal activation (Table 1, Figs 2 and 3). In contrast, frontal activation during height comparison (HT-VIS) included only the precentral and medial frontal gyri (Table 2). The largest activation cluster in frontal cortex during TI-HT occurred in the right middle frontal gyrus, whereas during height comparison the precentral gyrus showed the largest activation cluster (Table 2).

TI activation in the right superior frontal gyrus most likely corresponded to Brodmann's area (BA) 6, and this activation was divided into two distinct clusters, one located medially and the other more laterally on the gyrus (Figs 2 and 3). The left superior frontal gyrus did not reveal activation with the TI-HT comparison. Transitive inference activation in the middle frontal gyrus, on the other hand, encompassed a larger region and also appeared bilaterally (Figs 2 and 3). The right middle frontal gyrus activation occurred in one cluster that likely encompassed regions corresponding to BA 8, 9 and 46. Most of the active voxels in this cluster appeared in BA 9 and 46, though the voxel having the highest intensity of activation occurred in BA 8. In the left middle frontal gyrus, activation occurred in two clusters. The larger of these two clusters included BA 8, 9 and 46, while the smaller one most likely corresponded to BA 6. Inferior frontal gyrus activation occurred only in the left hemisphere; this cluster was situated largely in BA 8 and 9.

Frontal activation during the height task (HT-VIS, Table 2) occurred in the precentral gyrus (BA 4) and bilaterally in the medial frontal gyrus. The left precentral gyrus activation likely corresponded to BA 4, but this cluster extended into the postcentral gyrus as well. The right precentral gyrus activation included portions of BA 4 and 6. The medial portion of the middle frontal gyrus likely corresponded to BA 6, consistent with the supplementary motor area.

Parietal Cortex

Large activation clusters occurred in posterior parietal cortex during TI-HT. The peak activation likely occurred in BA 7, but the activation appeared also to include portions of BA 5 and 40. The parietal activation seen in Figures 2 and 3 can be subdivided into several clusters, with two clusters occurring laterally on the left and right superior parietal lobules, and a region of medial activation that encompassed the precuneus gyrus of both hemispheres. Note that in the right hemisphere in particular, activation occurred largely ventral and posterior to the intraparietal sulcus (Figs 2 and 3).

The HT-VIS comparison activated three areas in the parietal cortex, all in the left hemisphere. Activation occurred in the left postcentral gyrus and in the left superior and inferior parietal lobules. The largest cluster of activation occurred medial to the intraparietal sulcus, likely corresponding to BA 7.

Other Activated Regions

In addition to the frontal and parietal activations already discussed, TI yielded more activation than the HT task in the insular cortex bilaterally, the right mid-cingulate gyrus, right thalamus and left caudate nucleus. The HT-VIS comparison also activated the thalamus bilaterally, left putamen and left insular cortex. The passive viewing task yielded small clusters of activation when compared to the height task, one in a region posterior to the right paracentral lobule, most likely corresponding to BA 5

Table 1
Activation during TI-HT

Location (BA)	Zone	Extent (μ l)	Coordinates			Percent change
			x	y	z	
Frontal lobe						
R MFG (8, 9, 46, 6)	PFC, PMA	5256	-49	-23	38	0.71
R insula (13)	insula	1208	-31	-21	10	0.43
L insula (13)	insula	4904	29	-17	10	0.37
L MFG (8, 9)	PFC		38	-8	30	0.42
L MFG (8, 9, 46)	PFC		49	-23	38	0.68
R SFG/cingulate (6, 8, 24, 32)	preSMA, anterior cingulate	2704	-1	-11	50	0.63
L MFG (6)	FEF	976	27	9	60	0.36
R SFG (6)	FEF	480	-23	-5	54	0.34
L SFG (6, 8)	preSMA	400	11	-9	48	0.44
R central operculum (6)		232	-57	3	10	-0.52
Parietal lobe						
L, R precuneus (7)		33 200	1	73	54	1.13
L SPL (7)			21	65	56	0.88
L IPL (39, 40)	GSM, GA					
R SPL (7)			-28	62	47	1.30
R IPL (39, 40)	GSM, GA					
R cingulate (31/23)		440	-19	19	44	0.14
Subcortex						
R thalamus	medial dorsal	2288	-3	11	14	0.51
L caudate	body	808	15	5	24	0.18
L caudate	tail	376	21	31	14	0.31

The first column indicates the location of the cluster and the Brodmann areas (BA) that were likely included in a cluster; the second column indicates functional areas that the cluster included, and the subsequent columns list cluster volume, coordinates of maxima, and percent change of the voxel that underwent maximum change. A solid line separates identifiable clusters. Abbreviations: L, left; R, right; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule; IPL, inferior parietal lobule; PFC, prefrontal cortex; preSMA, pre-supplementary motor area; PMA, premotor area; SMA, supplementary motor area; FEF, frontal eye fields; GA, angular gyrus; GSM, supramarginal gyrus.

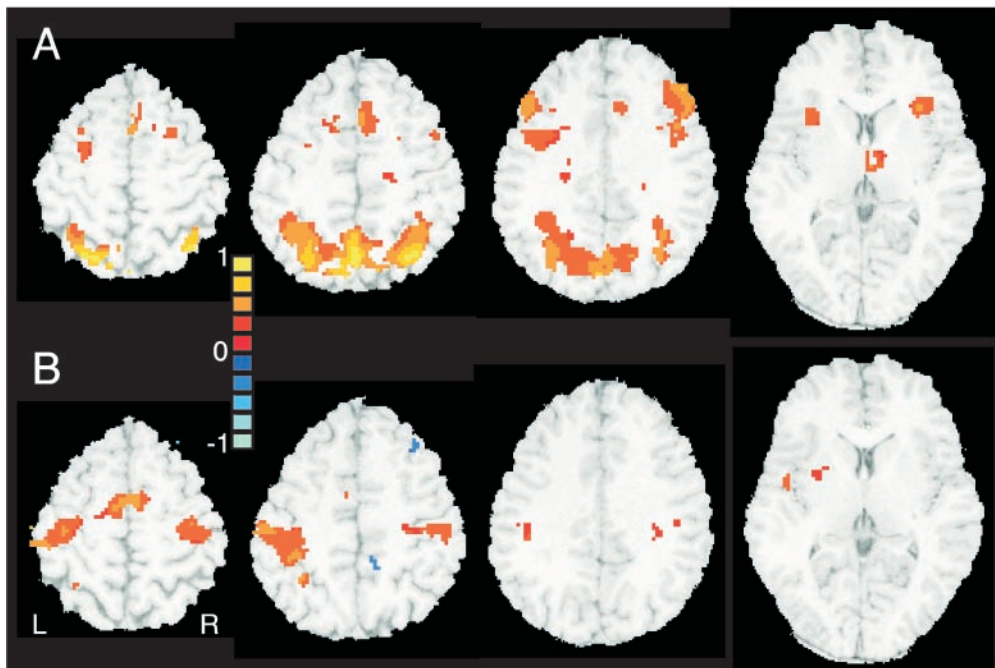


Figure 2. Group activation patterns for the TI-HT (A) and the HT-VIS (B) contrasts. Percentage-change statistical maps are overlain onto representative axial T_1 -weighted slices. Note activation in prefrontal and posterior parietal cortices for the TI-HT comparison (A) and its general absence for the HT-VIS comparison (B). TI-HT yielded activation in frontal and parietal motor areas, a pattern that was not as evident in the HT-VIS comparison. See text for additional details about statistical procedures and activated areas. Relative increase in activation are depicted in orange and yellow; relative decreases in activation are depicted in blue.

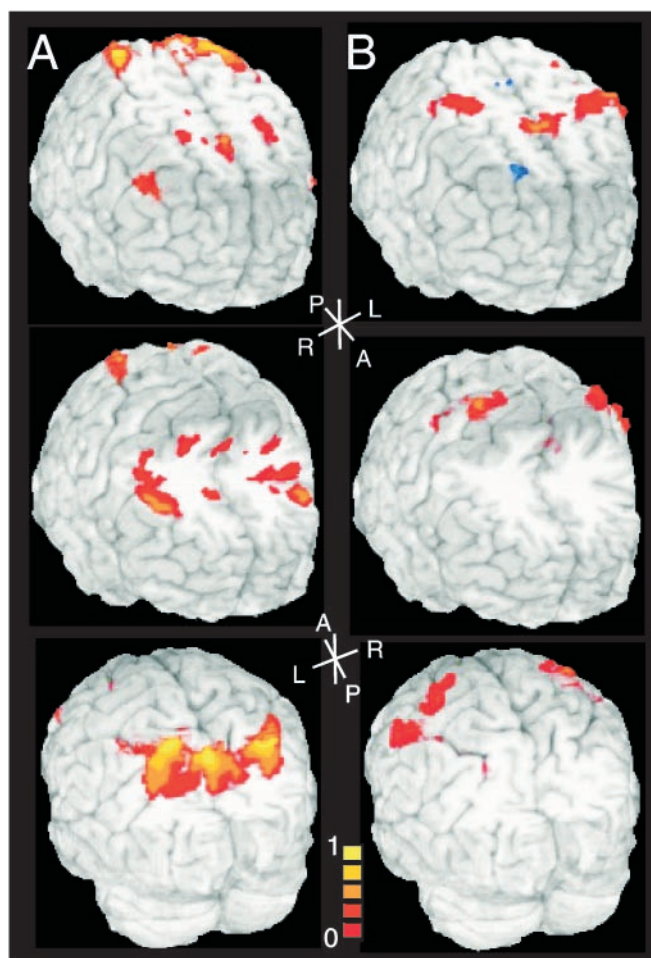


Figure 3. Percentage-change activation patterns across the group for the TI-HT (A) and the HT-VIS (B) contrasts. Activation is illustrated on rendered T_1 -weighted brain images. Note orientation marks; row 3 images have a different vantage point than images in rows 1 and 2. Other details as in Figure 2. The scale for relative activation decreases is not depicted but conforms to that of Figure 2.

and another in the right superior frontal gyrus, probably in BA 8. In the TI-HT comparison, a small group of voxels in the right precentral gyrus showed stronger activation in the height task than during TI; this region was probably located in BA 6.

Discussion

Functional MRI revealed cerebral cortical activation during a reasoning task that required deriving new knowledge by manipulating learned facts. We found different activation networks during TI and rule application, reflecting the relative selectivity of brain areas for reasoning or support processes. Most notably, bilateral PFC, preSMA, BA 8 and insular cortex exhibited activation during TI but not during a height comparison. In addition, large activation clusters occurred bilaterally in the posterior parietal cortex during TI, but during height comparison these were very much reduced and occurred only in the left hemisphere (Figs 2 and 3).

PFC has been closely tied to working memory and to a set of mental actions labeled as executive functions. While there is ample evidence for PFC involvement in short-term memory (Funahashi *et al.*, 1990; Fuster, 1997; Owen *et al.*, 1998), our findings emphasize its role in manipulating information. For example, the process of integrating information can be considered

a specific executive function of PFC (Christoff *et al.*, 2001). Our behavioral findings show that TI is solved by actively searching a unified mental model, similar to identifying geographic relationships of nations by mentally visualizing a map, rather than by using formal logic to act upon separate pairs of items (Woocher *et al.*, 1978; Acuna *et al.*, 2002). Figural and analytic reasoning also activate PFC (Prabhakaran *et al.*, 1997), as do inductive reasoning tasks (Goel and Dolan, 2000), and multi-step problem solving (Roland and Friberg, 1985; Baker *et al.*, 1996; Koechlin *et al.*, 1999).

The posterior parietal and dorsolateral frontal regions activated during TI in the present study are comparable to those seen during a TI task that used three ordered items (e.g. $A > B > C$; Goel and Dolan, 2001). However, the present task activated BA 9 and 46 on the right hemisphere (Table 1), whereas the three-term task activated BA 9 only on the left hemisphere not (Goel and Dolan, 2001). One possible explanation for this discrepancy in lateralization of hemispheric activation for similar mental operation might relate to differences in the list lengths that might have fundamentally changed the nature of the task. Test pairs in our TI task did not include list endpoints, that is, the first or last items of the list, whereas those in the Goel and Dolan (Goel and Dolan, 2001) work did. Endpoint items are special cases in an ordered list, since comparisons involving these items can be solved without regard to any other item (e.g. given $A < B < C$, A is always the smallest). Thus, multiple premises do not necessarily have to be integrated to solve a three-term task correctly (Bryant and Trabasso, 1971; McGonigle and Chalmers, 1992; Zentall and Sherburne, 1994). In a three-term ordered list, every pair of items includes an endpoint, and this may result in different underlying cognitive mechanisms. Another difference between the two tasks is that Goel and Dolan (Goel and Dolan, 2001) presented stimulus relations as sentences, while the present TI task used visual shapes of different colors. It is possible that manipulating relations among visual shapes may have activated the right PFC, while relational manipulations with verbal material preferentially activates the left PFC.

Further evidence that dorsolateral PFC becomes active when facts must be integrated derives from a study in which participants carried out a Raven's Progressive Matrices task (Christoff *et al.*, 2001). In this task, participants inferred how sample stimuli differed from each other visually and then applied those differences to another set of stimuli. Active areas during this task included the right BA 9/46 and left BA 10 when two relations among stimuli had to be integrated and applied to a new set of stimuli. Interestingly, posterior parietal cortex did not exhibit activation during these tasks, possibly because it was feature-based and did not have a strong spatial imagery component.

Posterior Parietal Cortex

Transitive inference yielded extensive activation in the posterior parietal cortex (Figs 2 and 3). Left posterior parietal cortex also became engaged during height comparison, but its activation was greatly reduced. Previous studies have found left inferior parietal activation during mathematical tasks (Rickard *et al.*, 2000) and analogy judgments (Wharton *et al.*, 2000), mental operations that also require manipulating knowledge internally. Judgments regarding whether a number is larger or smaller than a referent also elicit robust posterior parietal activation (Pinel *et al.*, 2001). In contrast, Goel *et al.* (Goel *et al.*, 1998) found that language-based reasoning activated the left frontal but not parietal cortex. It is not evident, however, whether this difference relates to the linguistic issues or to the specific type

Table 2
Activation during HT-VIS

Location of foci	Zone	Extent (μ l)	Coordinates			Percent change
			x	y	z	
Frontal lobe						
L, R MFG (6)	SMA	1856	3	5	54	0.49
R MFG (8)		256	-29	-31	52	-0.645
Parietal lobes						
R pre/postcentral gyrus (4, 3, 1, 2, 5)	M1, S1, SPL	4776	-35	17	68	0.91
L precentral/postcentral gyri (6, 4, 3, 1, 2)	PMA, M1, S1	7208	35	25	70	0.72
L postcentral gyrus (3, 1, 2)	S1		54	20	49	0.58
L SPL (7)			34	34	44	0.45
L SPL (7)		296	33	49	46	0.45
L SPL (7)		280	25	59	44	0.46
L central operculum (13)		320	43	5	8	0.343
R postcentral (5)		312	-1	37	52	-0.458
Subcortex						
L thalamus	posterior, ventral	976	17	19	18	0.255
R thalamus	posterior, ventral	416	-7	15	14	0.237
L putamen		360	25	1	4	0.242

Conventions are as in Table 1. M1, primary motor cortex; S1, primary somatic sensory cortex; S2, secondary somatic sensory cortex.

of reasoning required. In our psychophysical study of TI, we concluded that determining sequence relationships can be viewed as a partially spatial operation, so that parietal activation may, in part, be due to spatial-like operations used during TI. Several lines of evidence have demonstrated posterior parietal activation during mental rotation (Bonda *et al.*, 1995; Cohen *et al.*, 1996) and other tasks requiring spatial operations (Haxby *et al.*, 1991; Andersen, 1997; Rushworth *et al.*, 1997). Furthermore, given that PFC and posterior parietal cortex are reciprocally connected (Jones, 1969; Pandya and Kuypers, 1969; Jones and Powell, 1970), these areas may be expected to cooperate during demanding knowledge-manipulation tasks.

Other Frontal Areas

Transitive inference also engaged preSMA and portions of dorsolateral BA 8, while SMA, M1, and somatic sensory cortex were active with rule processing and motor actions (HT-VIS). PMA was active in both TI and the height comparison task. Activation of M1 and somatic sensory cortex in the HT-VIS comparison is not surprising because the passive viewing task only controls for visual input, not movement or somatic sensory feedback from having pressed a response button. Imaging studies have shown PMA activation during mental rotation (Cohen *et al.*, 1996) and imagined motor actions (Sanes, 1994; Stephan *et al.*, 1995; Porro *et al.*, 1996). In addition, premotor neurons can be selective for instructions, movements, attention (di Pellegrino and Wise, 1993a,b), and can even have visual receptive fields (Graziano *et al.*, 1994), indicating that premotor activation in our task may be related to one of several processes engaged during high-level motor computations.

Previous studies have indicated that preSMA and SMA have different functional roles (Hikosaka *et al.*, 1996; Matsuzaka and Tanji, 1996; Boecker *et al.*, 1998). We also found that these two areas could be dissociated by their relative activation for TI reasoning or support processes. While preSMA became

activated during TI, SMA did not, and the converse occurred for the height comparison task (Tables 1 and 2; Fig. 3). PreSMA has been suggested to have a motor executive role (Boecker *et al.*, 1998) or participate in updating motor programs (Shima *et al.*, 1996). Goel and Dolan found preSMA activation related more to rule application than to inference, and attributed this activation to anticipating a response (Goel and Dolan, 2001). By contrast, participants in our task were told to respond as soon as possible after stimulus onset, so anticipation is not a likely explanation for preSMA activation in this case. Our results suggest that preSMA may have a wider role in cognition, since reasoning activated this area.

Activation of SMA in the HT-VIS comparison, in turn, may result from one of several support processes (Matsuzaka *et al.*, 1992; Halsband *et al.*, 1994; Tanji, 1994). These include rule application, decision processes and movement, among which the present data cannot distinguish.

Design Considerations and Alternative Interpretations

The height comparison task was chosen for several reasons. First, it was a rule that could be applied to the same set of stimuli, thereby controlling for perceptual differences as well as controlling for comparisons, decision-making processes, and choice. Second, the stimuli in the TI list could be ordered linearly along one dimension using either the height rule or the TI rule, which other rules such as choosing ovals over rectangles would not have done. Thus, the height comparison controlled for relating stimuli along a linear dimension. However, the limitations of the height comparison task are that it appeared to be less effortful than TI, according to accuracy and RT (Acuna *et al.*, 2002), and that it also did not require recall from long-term memory, which the TI task did.

Differences in Task Difficulty

Previous studies have found conflicting results when they

examined directly the effect of increasing task difficulty on PFC activation. For example, one study demonstrated that increasing the difficulty of letter recognition by visually degrading them does not necessarily increase PFC activation; if anything, activation may decrease (Barch *et al.*, 1997). Alternatively, a study that examined the effect of task difficulty when participants performed a perceptual match-to-sample task using faces found that PFC activation was highest when the sample pictures were most degraded (Grady *et al.*, 1996). However, the increase in activation may have been related to a different type of processing in the most difficult version of the task as compared to the perceptual processing in the easier conditions (Grady *et al.*, 1996). At the most difficult levels, the processing may involve integrating and mentally manipulating the degraded features as participants decide whether the features match the sample face. In this case, although the TI tasks and the perceptual face matching task appear different on the surface, they may rely on similar cognitive processes. Psychophysical TI data (Woocher *et al.*, 1978; Acuna *et al.*, 2002) suggest that individual list items are integrated into a holistic mental representation, and both the current TI task as well as the difficult version of the face matching task (Grady *et al.*, 1996) may tap into a process of reasoning about stimuli to come to a decision. Finally, in a study that did not rely on degradation of visual stimuli to operationalize difficulty, activation during a semantic task was compared to easy and difficult non-semantic processing (Demb *et al.*, 1995). The rationale was that if the left inferior PFC in particular were equally active during an abstract/concrete categorization whether it was compared to easy or to difficult non-semantic processing, it would indicate that this area is unaffected by task difficulty. The semantic task consisted of categorizing nouns as abstract or concrete; in the easy non-semantic processing, participants determined whether words were printed in uppercase or lowercase; finally, in the difficult non-semantic processing task, participants determined whether the first and last letters of a word were in ascending or descending alphabetical order (Demb *et al.*, 1995). The results revealed that left PFC was equally active during semantic processing regardless of the difficulty of the non-encoding task to which it was compared. Nevertheless, it is possible that PFC would have altered its activation if the difficulty of the semantic task itself had been varied systematically. Further complicating matters is the inherent difficulty in comparing results across different behavioral paradigms; thus, it is unclear how much a generalized effect of difficulty caused PFC activation in the TI task as compared to the height task. A related, and also unresolved, question is the neural instantiation of difficulty. For example, it may be that the same information processing algorithm is used to solve easy and difficult versions of a task, but that difficult tasks recruit more neurons to carry out each step. Thus, difficulty *per se* may not be separable from neurons that carry out a task, but the difficult version of the task may activate a larger region of neocortex, which is also easier to detect with current neuroimaging methods. The underlying computational algorithm by which the brain solves the task, however, may be identical in both the easy and difficult versions of the task.

Differences in Long-term Memory Recall

Transitive inference and height comparison also differ in retrieval from long term memory; while TI requires recalling the learned facts in addition to remembering a rule, the height comparison requires only recall of the rule to choose the taller item. It has been found previously that PFC can be active during retrieval (Tulving *et al.*, 1994a,b; Fletcher *et al.*, 1996; Rugg *et*

al., 1996). It is likely that part of the process of solving TI involves scanning through the list of items to determine their relative locations in the sequence, and to then choose the item occurring closer to end of the list (Acuna *et al.*, 2002). This type of scanning may be similar to scanning through memory for a paired associate, and it may have activated the left PFC in the present study. A previous study has found left PFC activation when participants recalled abstract, verbal paired associates (e.g. 'Near-Close'), but not during recall of verbally presented, concrete pairs of nouns ['Arm-Muscle' (Fletcher *et al.*, 1996)]. However, the stimulus items in Fletcher *et al.* (Fletcher *et al.*, 1996) were verbal, which may have contributed to activation during retrieval. A study of nonverbal paired associates found activation of PFC during encoding, but not retrieval (Klingberg and Roland, 1998), indicating that retrieval of nonverbal paired associates does not necessarily activate PFC.

It has also been suggested that right PFC, as well as parietal areas, become active when episodic memories are recalled, while left PFC is active during semantic retrieval (Tulving *et al.*, 1994a,b). If episodic memory recall were causing right PFC activation, participants would have to recall the precise trials of the previous day's learning phase during which they learned the relevant adjacent stimulus pairs to solve each TI problem. Furthermore, they would have to recall several episodic memories, since at least two adjacent stimulus pairs would be required to solve each TI problem presented during scanning. In addition, learning the adjacent stimulus pairs was slow and effortful, requiring 850 trials on average (Acuna *et al.*, 2002). Thus, it seems unlikely that participants recalled the precise trial during which they learned the item pairs needed to solve any given TI problem.

TI represents only one type of reasoning; however, the activation found in the present study suggests a role for PFC beyond working memory, specifically as part of a neocortical network that manipulates facts to infer new knowledge.

Notes

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