

# Hierarchical Organization of Scripts: Converging Evidence from fMRI and Frontotemporal Degeneration

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**The present study examined the organization of complex familiar activities, known as “scripts” (e.g., “going fishing”). We assessed whether events in a script are processed in a linear-sequential manner or clustered-hierarchical manner, and we evaluated the neural basis for this processing capacity. Converging evidence was obtained from functional neuroimaging in healthy young adults and from behavioral and structural magnetic resonance imaging (MRI) data in patients with focal neurodegenerative disease. In both studies, participants judged the order of consecutive event pairs taken from a script. Event pairs either were clustered together within a script or were from different clusters within the script. Controls judged events more accurately and quickly if taken from the same cluster within a script compared with different clusters, even though all event pairs were consecutive, consistent with the hierarchical organization of a script. Functional magnetic resonance imaging associated this with bilateral inferior frontal activation. Patients with progressive nonfluent aphasia or behavior-variant frontotemporal dementia did not distinguish between event pairs from the same cluster or from different clusters within a script. Structural MRI associated this deficit with significant frontal cortical atrophy. Our findings suggest that frontal cortex contributes to clustering events during script comprehension, underlining the role of frontal cortex in the hierarchical organization of a script.**

**Keywords:** fMRI, frontal, frontotemporal dementia, narrative, organization

## Introduction

Our days are filled with complex, multistep activities. We “make a sandwich” for lunch with ease, and we encounter little difficulty “going grocery shopping.” The cognitive flexibility necessary to generalize activities like these to a wide variety of different circumstances and settings—and still attain important goals like getting fed—is an important attribute of human behavior. We refer to complex, familiar activities such as these as “scripts,” and each of the component activities constituting a script as an “event.” A script may depend in part on sensory input and memory representations, and these help guide behavior in specific circumstances (Godbout and Doyon 1995; Gallese et al. 1996; Rizzolatti et al. 1996; Sirigu et al. 1996, 1996; Crozier et al. 1999). In this study, we focus on the organization of events within a script because this provides important insights into the crucial human attributes of cognitive control and problem solving. There has been considerable controversy concerning the processing of scripts in a linear-sequential or a clustered-hierarchical manner and the neuroanatomic basis for this processing. Yet empirical evidence directly comparing these approaches is sparse. In this report, we describe a novel

technique that directly contrasts linear and hierarchical processing of scripts and provide converging evidence about the neuroanatomic substrate for hierarchical processing from functional magnetic resonance imaging (fMRI) studies of healthy adults and imaging correlates of performance in patients with focal neurodegenerative disease.

Some models of script organization propose a linear-sequential structure in which the representation of events within a script are sequentially ordered associations (Hue and Erickson 1991; van der Meer et al. 2002). Such an approach suggests a serial access mechanism directly linked to the chronological order and sequence in which events occur. In one approach, we take advantage of prior experience and order items based on domain familiarity, such as ordering the days of the week. Neuroimaging in healthy adults describes frontal as well as parietal activations in studies that involve ordering with these materials (Fulbright et al. 2003; Cohen Kadosh et al. 2008; Ischebeck et al. 2008). We can also order items on the basis of the meaning of each individual item, such as knowing that a car engine must be started before we can drive the car on the road. Alternately, we keep track of where we are in the ordered list by a working memory mechanism that maintains a previous item in an active state during selection of a subsequent item and then checks this against an anticipated item remaining to be ordered (Botvinick and Plaut, 2006b; Botvinick and Watanabe 2007). An imaging study evaluating a linear-sequential approach to the ordered presentation of 4 shapes using a 1-back procedure found posterior–superior frontal activation (Schubotz and von Cramon 2001). Likewise, these investigators demonstrated difficulty with serial order in patients with lesions in ventral frontal regions (Schubotz et al. 2004).

An alternate approach has emerged from the seminal observations of Lashley (1951) and Miller et al. (1960). This perspective emphasizes a hierarchical or clustered organization of complex material that directs a script toward some outcome or goal (Zalla et al. 2003; Fiebach and Schubotz 2006; O’Reilly and Frank 2006; Tettamanti and Weniger 2006; van Schie et al. 2006). Smaller subroutines within a script can be managed in a flexible manner while the overall goal remains the focus of behavior, and this facilitates adaptation to a variety of unanticipated external inputs. A script may be stored as a single memory unit containing hierarchically organized clusters of interconnected events (Newell 1990). Events may be clustered within a script, and events within a cluster share more associative elements than events taken from different clusters (Black and Bower 1979; Lichtenstein and Brewer 1980; Schank 1982; Cooper and Shallice 2006; Koechlin and Hyafil 2007). From this perspective, there is a superordinate-to-subordinate flow of information, where subordinate events are nested

within superordinate structures in a multilevel script structure. In another approach, the overall goal of the script as well as the specific events may be maintained at a single representational level, where the associativity strength between events is the primary determiner of a script's organizational structure (Botvinick and Plaut 2006a; Botvinick 2008). These approaches hold in common the view that organizational resources help link events with a closer association within the same cluster relative to other events that are less closely associated. This critical feature distinguishes hierarchical or clustered organization from a linear-sequential form of organization.

Much descriptive evidence associates difficulty organizing scripts with frontal lobe damage. Patients with frontal lobe damage were found to have difficulty ordering events, generating a sequence of events, and performing action sequences (Godbout and Doyon 1995; Sirigu et al. 1996). This deficit has been attributed in part to executive resource limitations seen in patients with frontal lobe damage (Godbout et al. 2004). In another study attempting to assess hierarchical organization, patients with frontal brain damage were asked to identify the boundaries of "small events" and "large events" within a script. Patients differed from controls only when judging the boundary of large events (Zalla et al. 2003), and this was attributed to a deficit recognizing clusters of action sequences. Consistent with these findings, an fMRI study found inferior frontal activation for temporal ordering of scripts compared with category membership judgments of scripts and words (Knutson et al. 2004). During coherence evaluations of brief stories, chronological assessments revealed bilateral frontal-parietal recruitment compared with emotional assessments (Ferstl et al. 2005). Across this body of work, there is no experimental evidence directly comparing linear-sequential and clustered-hierarchical approaches with meaningful materials such as scripts.

Another approach has examined hierarchical organization using language materials. fMRI recruitment of left inferior frontal cortex during sentence processing thus has been attributed in part to the hierarchical organization of syntactically mediated material (Friederici and Kotz 2003; Heim et al. 2003; Cooke et al. 2005). Evidence to support this claim comes from similar activations during acquisition of a hierarchically organized artificial grammar (Bahlmann et al. 2008). Damage to left inferior frontal cortex resulted in greater difficulty organizing phrases in a sentence, whereas damage to dorsolateral prefrontal cortex yielded greater difficulty organizing events in a script (Sirigu et al. 1996). Using similar materials, an fMRI study showed overlapping activations in language-related areas for ordering tasks involving scripts and sentences, as well as partially distinct activations for scripts in bilateral prefrontal and left inferior parietal regions (Crozier et al. 1999). Nonaphasic patients with frontal injury were impaired judging the organizational coherence of 2 successively presented sentences (Ferstl et al. 2002), and left inferior prefrontal activation was seen using similar materials in an fMRI study (Ferstl and von Cramon 2001, 2002). An fMRI study showed that sentences embedded in a coherent narrative recruited medial frontal, temporal-parietal and precuneus regions bilaterally relative to activation for these sentences presented individually (Xu et al. 2005). Frontal activation also has been seen during production of organized narratives (Braun et al. 2001; Horwitz et al. 2003; Troiani et al. 2008). These studies associated organized language materials with

frontal activation, but they did not demonstrate that the materials were organized in a clustered-hierarchical manner rather than in a linear-sequential fashion.

Several recent studies have attempted to establish more precisely the cognitive and neural basis for hierarchically organized processing of complex stimuli, although this work did not use meaningful materials. This is based on an anatomical approach to hierarchical organization suggesting that regions in the frontal lobe, arrayed anatomically in a caudal-rostral fashion, process increasingly complex materials (Fuster 1997, 2004). Consistent with this theory, several studies involving tasks with levels of increasing complexity have demonstrated that relatively simple, sensory-motor associations are mediated by premotor regions, whereas decisions based on higher levels of abstraction recruit more rostral regions of lateral prefrontal cortex (Braver and Bongiolatti 2002; Badre and Wagner 2004; Ramnani and Owen 2004; Koechlin and Jubault 2006; Badre and D'Esposito 2007). The stimuli used in this work are carefully controlled but involved colored geometric shapes that do not reflect important constraints that are an integral part of meaningful, real-world activities.

In the present study, we used a novel, well-controlled method that directly compares linear-sequential and clustered-hierarchical approaches to processing meaningful scripts. We developed scripts about familiar activities such as "making a sandwich" or "going grocery shopping" that contain 6 events and identified clusters of associated events empirically within each script. If scripts are organized hierarchically, then some events within a script should form clusters of closer associations, an organizational substructure that is not apparent in linear-sequential forms of script organization. To test the distinction between clustered-hierarchical and linear-sequential forms of organization directly, participants were asked to evaluate consecutive events in a script that had a special status because they were taken from the same event cluster (Within-Hierarchy), and these were compared with events from different but adjacent clusters (Different-Hierarchy). We monitored regional brain activity with fMRI in healthy young adults while judging linear-sequential and clustered-hierarchical characteristics of scripts. If clustered-hierarchical organization confers a special status on certain events within a script, then judgments of Within-Hierarchy pairs of events should be associated with greater activation of frontal regions than Between-Hierarchy pairs of events in healthy adults.

We sought converging evidence to assess the hierarchical organization of scripts with these materials from a second source. We administered the identical task to individuals with focal neurodegenerative disease due to frontotemporal lobar degeneration (FTLD). This gave us the opportunity to compare fMRI activation and structural MRI evidence of atrophy in patients with difficulty on the same task used in the fMRI study. Patients with progressive nonfluent aphasia (PNFA) have significant difficulty with grammatical organization of sentence-level material during comprehension (Grossman et al. 2005; Murray et al. 2007; Peelle, Cooke et al. 2008; Peelle, Troiani et al. 2008) and expression (Ash et al. 2009). Moreover, atrophy in prefrontal cortex in PNFA correlates with impaired performance on measures of syntactic comprehension (Peelle, Cooke et al. 2008; Peelle, Troiani et al. 2008) and expression (Ash et al. 2009). Despite the absence of aphasia, patients with behavioral variant FTLD (bvFTD) who have a disorder of social comportment and personality are significantly impaired at

expressing narrative in an organized manner (Chapman et al. 2005; Ash et al. 2006). One previous study of script comprehension showed difficulty detecting errors in story event organization in bvFTD (Cosentino et al. 2006). If patients with frontal disease have difficulty with clustered-hierarchical organization, then PNFA and bvFTD patients should differ from control subjects, and they should treat Within-Hierarchy and Between-Hierarchy pairs of events similarly. We related performance to the distribution of cortical atrophy in these patient groups using quantitative structural MRI and expected prominent frontal disease in these patients.

Other patient groups with focal neurodegenerative diseases do not show prominent deficits in planning and organization. Patients with semantic dementia (SemD) and mild Alzheimer's disease (AD) are less impaired on narrative and grammatical measures that may involve hierarchical organization (Waters et al. 1995; Grossman and Rhee 2001; Grossman, Murray, et al. 2007). Likewise, cortical atrophy in these patients is less prominent in prefrontal regions (De Leon et al. 1999; Gorno-Tempini et al. 2004; Grossman et al. 2004; Whitwell et al. 2008). If appreciating the special status of clustered event pairs within a script depends on frontal cortex, then patients with SemD and AD who have less frontal disease should resemble controls and respond more accurately and faster to Within-Hierarchy pairs of events than Between-Hierarchy pairs of events. Quantitative structural MRI should show less frontal atrophy in AD and SemD than in patients with PNFA and bvFTD. Moreover, some of the patients have an aphasia (PNFA and SemD) and others do not (bvFTD and AD). These groups have not been compared previously for the purpose of investigating hierarchical organization of script materials. If the linguistic nature of the material is playing a particularly prominent role in script processing, then PNFA patients and SemD patients should be more impaired than bvFTD patients and AD patients who do not have aphasia. We also examined the extent of cortical atrophy in a frontal region of interest (ROI) defined by the area of fMRI activation seen in healthy adults during performance of the same task. We expected more prominent frontal atrophy in the ROI in impaired patients with PNFA and bvFTD than patients with SemD and AD who resemble controls.

## Materials and Methods

### Participants

In the fMRI imaging study, we assessed 14 healthy young adults from the University of Pennsylvania community. Participants ranged in age from 22 to 26 years ( $M = 24.7$ ,  $SD = 1.3$ ) and had an average of 15.5 ( $SD = 1.6$ ) years of education (Table 1). All were right-handed native English speakers, in good health, and none were taking any medication known to affect cognitive function or brain activity. All participants

gave informed consent in a manner approved by the Institutional Review Board at the University of Pennsylvania.

For the patient study, 38 individuals with a neurodegenerative condition were recruited from the outpatient Neurology clinic at the Hospital of the University of Pennsylvania. Initial diagnosis was established by a neurologist experienced in the diagnosis of neurodegenerative conditions (M.G.). Among these patients, 25 were given the diagnosis of FTL. These patients were further divided into 3 subgroups using modifications of published criteria (McKhann et al. 1984, 2001; Neary et al. 1998). Consensus-based clinical assignment involved the review of a full medical history, a detailed neurological examination, and a complete mental status evaluation by 2 independent examiners. The nonaphasic subgroup of FTL patients, bvFTD patients ( $n = 10$ ), presented with social and behavioral difficulties as well as limited executive functioning. Of the aphasic FTL patients, those with PNFA ( $n = 9$ ) had effortful, nonfluent speech that was grammatically impoverished. The third FTL subgroup included patients with SemD ( $n = 6$ ). These patients had fluent, circumlocutory speech with naming difficulty as well as impaired comprehension of single words and objects. Finally, patients with the diagnosis of AD ( $n = 13$ ) had impaired episodic memory as well as fluent speech with word-finding pauses and circumlocutions.

Exclusion criteria included treatment with a sedating medication or the existence of another condition that could interfere with cognition such as primary psychiatric illness, head trauma, hydrocephalus, or cerebrovascular disease. Some patients were taking a fixed dosage of a cholinesterase inhibitor chronically, and some patients may have been medicated with a low dosage of a nonsedating antidepressant (e.g., serotonin-specific reuptake inhibitors) or an atypical neuroleptic agent as indicated clinically, but none of the patients demonstrated any evidence of sedation suggesting overmedication. Only subjects who satisfied criteria for mild to moderate dementia were included, as defined by a score of 10 or greater on the Mini Mental State Examination (MMSE) (Folstein et al. 1975). All patients were alert and displayed no evidence of visual-perceptual difficulty that could interfere with performance of the task.

Healthy seniors ( $n = 15$ ) were recruited from among spouses of the patients as well as from the community through local advertisements. These older controls were neurologically intact, right-handed, native English speakers. Age- and education-matched elderly controls had higher MMSE scores than the patient groups ( $F(1,51) = 17.32$ ;  $P < 0.001$ ). However, there was no statistical difference in MMSE scores between the patient groups ( $F(3,37) = 1.61$ ;  $P > 0.20$ ) (Table 1).

To ensure that test results were sensitive to clinically relevant impairments, we examined participant performance on 3 different measures of executive functioning. These included Trail Making Test, part B (Reitan 1992), Stroop Interference (Golden 1978), and Letter-guided Category Naming Fluency (FAS) (Spreen et al. 1998). Using age- and education-matched normative data from 25 healthy controls, raw scores of patients were converted to  $z$ -scores. In order to obtain a single representative measure of executive control, a mean executive  $z$ -score was computed by averaging across the 3 tasks for each participant. Because we were interested in studying the role of executive difficulties in impaired processing of script organization, 3 patients with very mild dementia and a positive average executive  $z$ -score were excluded.

### Materials

We developed 22 scripts of familiar activities for this study, each containing 6 routine events. The 22 scripts were adaptations of stimuli used in a prior study of script processing (Cosentino et al. 2006). Cosentino's original scripts contained 4 events each, and we expanded each script at chronologically random points through the addition of 2 events per script. All script stimuli are provided in Appendix A. To establish the organization of these scripts, each event of a script was typed and centered in black Times New Roman font at 14-point size on a 5" × 8" index card, and the events of a script were presented to pilot subjects ( $n = 10$ ). These subjects were asked first to place the script events in order chronologically. The events of all scripts were ordered correctly and identically by all pilot subjects.

**Table 1**

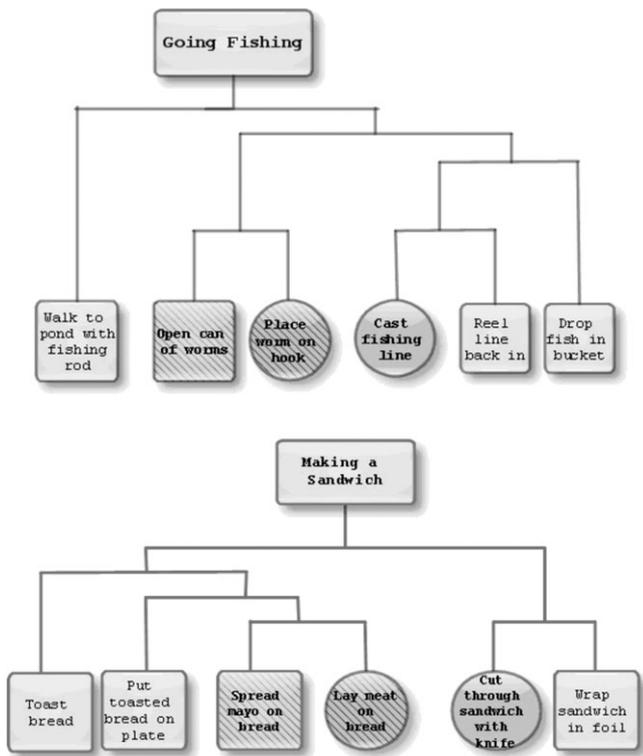
Mean ( $\pm$ SD) demographic and clinical characteristics of patients and healthy subjects<sup>a</sup>

Group ( $n$ )	Age (years)	Education (years)	MMSE (max = 30)
Young adults (14)	24.7 ( $\pm$ 1.3)	15.5 ( $\pm$ 1.6)	—
Healthy seniors (13)	68.9 ( $\pm$ 9.4)	15.1 ( $\pm$ 2.7)	28.2 ( $\pm$ 0.9)
PNFA (9)	66.4 ( $\pm$ 11.0)	14.8 ( $\pm$ 2.4)	24.3 ( $\pm$ 4.7)
bvFTD (10)	69.8 ( $\pm$ 9.6)	17.0 ( $\pm$ 3.4)	25.2 ( $\pm$ 3.4)
SemD (6)	59.7 ( $\pm$ 15.0)	14.3 ( $\pm$ 2.9)	23.5 ( $\pm$ 4.5)
AD (13)	74.2 ( $\pm$ 10.2)	15.1 ( $\pm$ 3.5)	21.1 ( $\pm$ 5.7)

<sup>a</sup>We did not collect MMSE in young adults.

Next, these pilot subjects were asked to cluster the events of each script into as many groups deemed necessary, such that events within the script that seemed most closely associated would be clustered together. Subjects were instructed to cluster each event only once. These pilot data were used to quantify the associativity strength of the 6 events within each of 22 scripts by adding up coclustered events and then generating hierarchical tree structures for each script based on the co-occurrence frequencies. Figure 1 illustrates examples of hierarchical tree structures for 2 scripts, and the tree structures of the remaining scripts are available in Appendix A. We then identified event triplets such that one consecutive pair of events from the triplet came from the same hierarchical cluster (Within-Hierarchy) and a second consecutive pair came from 2 different hierarchical clusters (Different-Hierarchy). These pairs thus shared an event. We minimized the risk of biasing toward a linear, scanning approach to script processing cued by the initial or terminal event by excluding these events from judged pairs within a script (Franklin et al. 2007). Figure 1 illustrates examples of Within-Hierarchy and Different-Hierarchy pairs.

These materials were used to identify event triplets from which 4 types of stimuli were used for the experiment: Correctly ordered pairs of Within-Hierarchy events; incorrectly ordered pairs of Within-Hierarchy events; and correctly ordered pairs of Different-Hierarchy events; incorrectly ordered pairs of Different-Hierarchy events. In the patient study, one instance of these 4 types of stimuli was taken from each of the 22 scripts, resulting in 88 stimuli. We also presented filler material composed of pairs of events from the same narratives. These included 44 correctly ordered pairs of Nonadjacent Different-Hierarchy events and incorrectly ordered pairs of Nonadjacent Different-Hierarchy events from these triplets. Additional filler stimuli included 66 pairs of events containing the first or last event of a script along with an adjacent event, resulting in a total of 198 stimuli. Half of all stimuli were in the correct order and half in the incorrect order. These stimuli were randomly distributed over 6 runs, resulting in a total of 33 items per run, with each different type of stimulus presented from 2 to 5 times per run.



**Figure 1.** Examples of hierarchical tree structures for scripts. Events with diagonal stripes are "Within-Hierarchy"; events in circles are "Different-Hierarchy."

For the fMRI study, 5 of 22 scripts used for the patient study ("Doing the Laundry," "Going to the Movies," "Sunbathing," "Wrapping a Gift," and "Making a Necklace") were removed due to time constraints. One instance of the 4 types of stimuli was taken from each of the remaining 17 scripts, resulting in 68 stimuli. Half of the 68 stimuli were in the correct order and half were in the incorrect order. The fMRI study had fewer filler items than the patient study, including 17 correctly ordered pairs of Nonadjacent Different-Hierarchy events and 41 pairs of events containing the first or last event of a script along with an adjacent event. All of the incorrectly ordered pairs of Nonadjacent Different-Hierarchy events were removed from the fMRI study, so there were 24 more correctly ordered filler items than incorrectly ordered filler items. The fMRI stimuli, totaling 127, were randomly distributed over 6 runs, with 19 to 22 items per run and each different type of stimulus presented anywhere from 1 to 5 times per run. For both the patient study and the fMRI study, stimulus types were presented in a pseudorandom order within each run, ensuring that no type of stimulus occurred in consecutive order more than twice. Although some stimuli from one script occurred twice in a run, these were never presented consecutively. The filler stimuli were eliminated from further analysis.

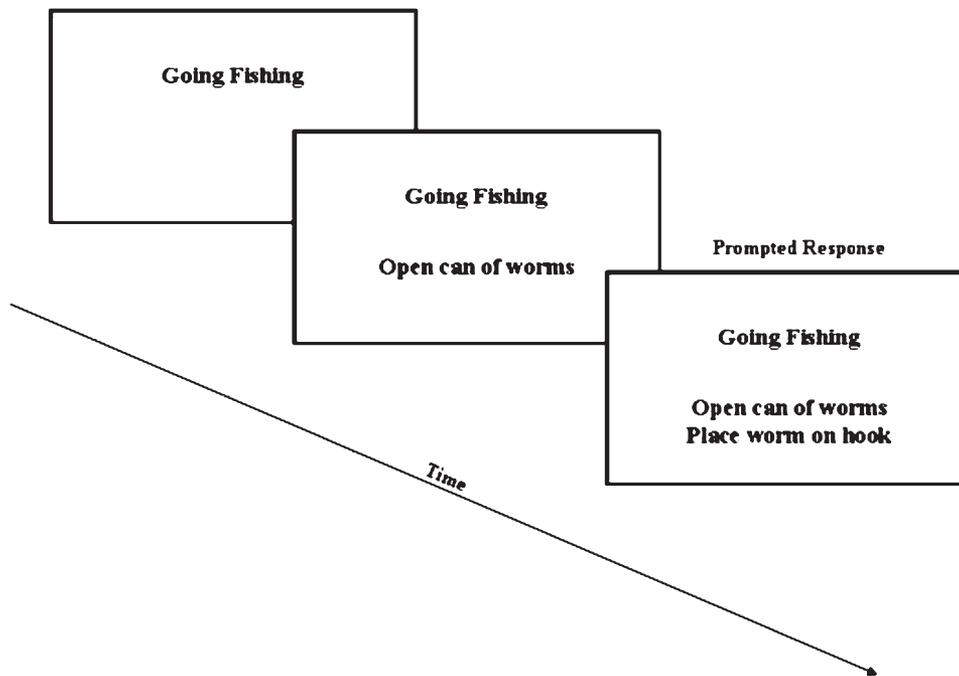
### Procedure

All stimuli were displayed using a Dell Inspiron 1100 laptop. During the fMRI study, the stimuli were projected onto a screen in the participant's view using an Epson projector and an angled mirror. E-Prime v1.4.1 presentation software recorded response accuracy and latency. Participants were presented with a script title and 2 brief written events from the script, and these were arrayed vertically beneath the script title. In the fMRI study, each trial began with a simple fixation asterisk (\*) presented for 750 ms followed by a blank screen for 100 ms. The script title was then presented at the top of the screen for 2150 ms and was followed by blank screen for 100 ms. Then, the previously displayed script title was presented along with a script event for 2900 ms. This was followed by a blank screen for 100 ms. Finally, the script title and event were presented along with a second script event. Figure 2 illustrates stimulus presentation. Participants were given a jittered amount of time to determine the accuracy in vertical ordering of events for the named script title. These events were equally divided across 3-, 6-, 9-, and 12-s events for each type of stimulus and randomly ordered within a run. Responses were recorded by pressing 1 of 2 buttons on a button response box in the MRI scanner.

In the patient study, the script header and pair of events were in black Arial font at 18-point size and displayed on a computer screen. First, the script title was presented at the top of the screen for 3000 ms and was followed by blank screen for 200 ms. Next, the previously displayed script title was presented along with a script event for 4000 ms and was followed by a blank screen for 200 ms. Finally, the previously displayed script title and event were presented along with a second script event. At this point, participants were given as much time as needed to determine the accuracy in vertical ordering of events for the named script title. Responses were recorded by pressing 1 of 2 buttons on the computer keyboard.

Prior to the experiment, participants were given one practice run that included 6 practice judgments. During the practice trials, incorrect answers were corrected and explained by the experimenter, in order to ensure comprehension of task instructions and requirements. Instructions were as follows: "In this test, you will first see the heading of the story/routine. Then you will see 2 phrases, both of which are actions in the routine. Read both statements and decide if they are in the correct order or not. If they are in the correct order as written on the screen, press the 'yes' button. If they are not in the correct order, press the 'no' button. Work as quickly and accurately as you can."

We report response accuracy and latencies for accurate responses. Response times for accurate responses were evaluated after eliminating outliers that were too short or too long for young adults during the fMRI experiment (<500 or >4500 ms) or the patient experiment (<500 or >14,000 ms). Subsequently, an individualized 2.5 standard deviation (SD) filter for latencies was used to normalize responses based on each participant's own distribution of reaction times. In each



**Figure 2.** Illustration of stimulus presentation on successive screens. See text for timing details for the fMRI study and the patient study.

participant, 2.2% of responses were excluded on average during the fMRI experiment, and 4.6% of responses were excluded on average in the patient experiment.

#### **Functional Imaging Procedure and Analysis**

The experiment was carried out at 3 T on a Siemens Treo scanner (Siemens Medical Systems, Erlangen, Germany). Each imaging study began with a 3D magnetization-prepared rapid gradient echo (MPRAGE) protocol (time repetition [TR] = 1620 ms, time echo [TE] = 30 ms,  $192 \times 256$  matrix), acquiring 1-mm isotropic voxels to determine regional anatomy. Blood oxygen level-dependent (BOLD) fMRI images were then acquired to detect alterations in blood oxygenation accompanying increased mental activity. All images were acquired with fat saturation, 3-mm isotropic voxels, flip angle of  $15^\circ$ , TR = 3000 ms,  $TE_{\text{eff}} = 30$  m, and a  $64 \times 64$  matrix, acquiring 42 contiguous axial slices through the entire brain every 3 s.

Individual subject data were then prepared for analysis using SPM5, developed by the Wellcome Trust Centre for Neuroimaging (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>). The images in each subject's time series were registered to the initial image in the series. The images were then aligned to a standard coordinate system using the Montreal Neurological Institute (MNI)152 average brain template. The data were spatially smoothed with an 8-mm full-width half-maximum (FWHM) isotropic Gaussian kernel to facilitate statistical analyses and to account for local variations in activation and sulcal anatomy across participants. Low-pass temporal filtering was implemented by controlling autocorrelation with a first-order autoregressive method.

After eliminating judgment errors (mean  $\pm$  SD accuracy =  $98.3\% \pm 2.5\%$  correct), a random-effects model was used to analyze neural activation for Different-Hierarchy and Within-Hierarchy stimuli presented in the correct order. An event onset was considered the point at which the second event pair appeared on the screen. Event onset times were convolved with a canonical hemodynamic response function to estimate their potential contribution to the fMRI data. We then contrasted the main effects associated with the 2 hierarchy stimuli with each other. A general linear model approach was used to calculate parameter estimates for each type of stimulus pair for each subject and linear contrasts for comparisons of interest. These estimates were then entered into second-level random-effects analyses to allow us to make inferences across participants. Although all stimulus types were

modeled, we focus only on the differences between correctly presented stimuli for Different-Hierarchy compared with Within-Hierarchy pairs. We used a voxelwise threshold of  $P < 0.001$ . To control for false positives, we required the peak voxel in a cluster to pass a threshold of  $P < 0.05$  with a false discovery rate correction for multiple comparisons. Using this procedure, all clusters also had a cluster-level significance of  $P < 0.001$ .

#### **Structural Imaging Procedure and Analysis**

High-resolution structural MRI scans were available for a subset of 20 patients (bvFTD = 7, PNFA = 6, SemD = 2, and AD = 5) to establish cortical atrophy using a modulated version of voxel-based morphometry. Images were acquired by a SIEMENS Trio 3-T MRI scanner. First, a symmetric diffeomorphism procedure was used to normalize high-resolution T1-weighted MR images for shape and intensity (Avants and Gee 2004) using a local template consisting of 16 healthy seniors and 16 patients. We used high dimensional normalization and template-based cortical segmentation to quantify gray matter changes. The brain image was modeled as a dense continuum, sampled at individual voxels, and accompanied by a transformation model that preserved neighborhood relationships among voxels even under very large deformations. A bidirectional technique created unbiased, symmetric diffeomorphisms in order to optimize normalization. Reduced variance in the estimated location of the neuroanatomy achieved by a symmetric diffeomorphic approach reduces the amount of smoothing required in the final statistical treatments of these data (Avants, Anderson, et al. 2008; Avants, Epstein, et al. 2008; Avants and Gee 2004). The resulting images were then segmented using FAST (Zhang et al. 2000). Gray matter images were subsampled to  $2\text{-mm} \times 2\text{-mm}$  voxel sizes, and then warped into MNI space. Images were smoothed with a 4-mm FWHM Gaussian filter and contrasted with a cohort of 39 age-matched controls using an independent samples *t*-test, as described elsewhere (Grossman, Libon et al. 2007). The analysis included all voxels containing any gray matter in the volume. Images were implicitly masked and global calculation was omitted. Because of the small number of participants with imaging studies and the similar patterns of performance (see below), we combined bvFTD and PNFA patients into a single group because of their similar cognitive performance and because these conditions are associated with frontal disease. We also combined AD and SemD patients into a brain-damaged control group because of their similar

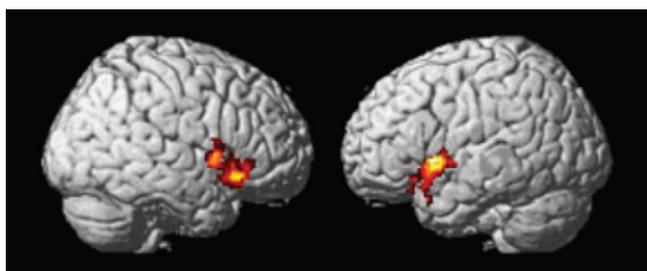
performance and their minimal frontal disease (see below). We set a statistical threshold for identifying significant gray matter atrophy in these groups relative to age-matched controls at a  $P < 0.01$  level.

## Results

### fMRI Results in Healthy Adults

During administration of the protocol to healthy young adults while in the scanner, we observed significantly greater frontal activation for judgments of Within-Hierarchy pairs of events relative to Different-Hierarchy event pairs. Accuracy and latency data were not available in 1 subject, and another subject had latency data from half of the runs, due to computer error. Overall order judgment accuracy was close to ceiling at 97.8% correct. For correctly ordered stimuli, accuracy for Within-Hierarchy pairs was 99.1% correct and for Different-Hierarchy pairs was 98.6% correct. Performance accuracy did not differ between conditions. We analyzed the response latencies of these subjects for Within-Hierarchy and Different-Hierarchy pairs of stimuli with correct responses. Subjects were on average slower for Different-Hierarchy ( $M = 2192$ ,  $SD = 414$  ms) compared with Within-Hierarchy ( $M = 2109$ ,  $SD = 372$  ms) stimuli, a difference that approached significance ( $t(12) = 1.95$ ;  $P = 0.078$ ). This pattern was seen in 10 (76.9%) of 13 individual subjects.

The imaging findings are illustrated in Figure 3, and Table 2 summarizes the location of the peak voxels in the activated clusters. We observed significantly greater activation in bilateral inferior frontal regions during judgments of Within-Hierarchy pairs of events compared with Different-Hierarchy event pairs. These activations extended into anterior-superior temporal cortex. There were no greater activations in the Different-Hierarchy condition compared with the Within-Hierarchy condition. These findings are consistent with the hypothesis that inferior frontal cortex contributes to the processing of hierarchically organized scripts and the specialized processing of closely associated events that fall within a cluster.



**Figure 3.** Significant cortical activation for the contrast of Within-Hierarchy > Different-Hierarchy.

**Table 2**  
fMRI activation in healthy young adults

Cluster locus (Brodmann area)	Coordinates of peak voxel <sup>a</sup>			Z score
	X	Y	Z	
Within-Hierarchy > Different-Hierarchy				
Left inferior frontal (47)	-52	12	-2	4.25
Right inferior frontal (47)	54	30	-4	4.14
Different-Hierarchy > Within-Hierarchy				
No significant activations				

<sup>a</sup>These coordinates are from the Talairach reference system.

### Behavioral Results in Patients with Neurodegenerative Disease

Healthy seniors and patients with less frontal disease distinguished between Within-Hierarchy pairs and Different-Hierarchy pairs, but patients known to have significant frontal atrophy failed to distinguish between these event pairs. Analysis of variance for accuracy and latency were performed with a group (3—controls, patients with significant frontal disease, patients with less frontal disease)  $\times$  hierarchy (2—Within-Hierarchy, Between-Hierarchy) design. This revealed significant main effects for group (accuracy:  $F(2,50) = 4.09$ ;  $P = 0.02$ ; latency:  $F(2,49) = 9.14$ ;  $P < 0.001$ ) and hierarchy (accuracy:  $F(1,50) = 26.22$ ;  $P < 0.001$ ; latency:  $F(1,49) = 8.26$ ;  $P = 0.006$ ), and a significant group  $\times$  hierarchy interaction (accuracy:  $F(2,50) = 3.39$ ;  $P = 0.04$ ; latency:  $F(2,49) = 4.24$ ;  $P = 0.02$ ).

Healthy seniors were significantly more accurate ( $t(13) = 4.17$ ;  $P = 0.001$ ) when judging Within-Hierarchy stimuli compared with Different-Hierarchy stimuli, as summarized in Table 3. Table 4 shows that healthy seniors also were faster ( $t(13) = 4.58$ ;  $P = 0.001$ ) when judging Within-Hierarchy stimuli compared with Different-Hierarchy stimuli.

Consider patients' performance in this context. Table 3 shows that patients with PNFA ( $t(21) = 3.21$ ;  $P < 0.005$ ) or bvFTD ( $t(23) = 2.21$ ;  $P < 0.05$ ) were less accurate at judging the sequencing of script events than controls. Table 4 shows that PNFA patients ( $t(21) = 4.05$ ;  $P = 0.001$ ) and bvFTD patients ( $t(23) = 3.25$ ;  $P < 0.005$ ) also were significantly slower than controls even when they correctly judged event order. Moreover, within-patient comparisons revealed that this was due to the impoverished representation of the special status associated with highly associated pairs of events. Responses to Within-Hierarchy event pairs and Different-Hierarchy event pairs in PNFA patients thus were equally inaccurate ( $t(8) = 0.44$ ;  $P = 0.7$ ) and did not differ in their judgment latencies ( $t(8) = 0.49$ ;  $P = 0.6$ ). Likewise, bvFTD patients did not distinguish between Within-Hierarchy event pairs and Different-Hierarchy event

**Table 3**  
Mean ( $\pm$ SD) percent accuracy judging event order<sup>a</sup>

Group	Overall	Within-hierarchy accuracy	Different-hierarchy accuracy	Difference score (within-hierarchy – different-hierarchy)
Healthy seniors	0.94 ( $\pm$ 0.1)	0.99 ( $\pm$ 0.0)	0.90 ( $\pm$ 0.1)	0.09 ( $\pm$ 0.1)*
PNFA	0.84 ( $\pm$ 0.1)	0.85 ( $\pm$ 0.1)	0.83 ( $\pm$ 0.1)	0.02 ( $\pm$ 0.1)
bvFTD	0.86 ( $\pm$ 0.1)	0.87 ( $\pm$ 0.1)	0.85 ( $\pm$ 0.2)	0.02 ( $\pm$ 0.1)
SemD	0.81 ( $\pm$ 0.1)	0.86 ( $\pm$ 0.1)	0.77 ( $\pm$ 0.1)	0.09 ( $\pm$ 0.1)*
AD	0.88 ( $\pm$ 0.1)	0.92 ( $\pm$ 0.1)	0.84 ( $\pm$ 0.1)	0.08 ( $\pm$ 0.1)*

<sup>a</sup>Significant at the  $P < 0.05$  level.

**Table 4**  
Mean ( $\pm$ SD) latency (ms) responding to correctly judged event order

Group	Overall	Within-hierarchy latency	Different-hierarchy latency	Difference score (within-hierarchy – different-hierarchy)
Healthy seniors	3433 ( $\pm$ 994)	3311 ( $\pm$ 972)	3555 ( $\pm$ 1026)	244 ( $\pm$ 199) <sup>a</sup>
PNFA	6335 ( $\pm$ 2404)	6397 ( $\pm$ 2660)	6273 ( $\pm$ 2186)	124 ( $\pm$ 766)
bvFTD	5792 ( $\pm$ 2483)	5748 ( $\pm$ 2921)	5835 ( $\pm$ 2144)	86 ( $\pm$ 1267)
SemD	7464 ( $\pm$ 3275)	6977 ( $\pm$ 3113)	7950 ( $\pm$ 3507)	973 ( $\pm$ 1046) <sup>b</sup>
AD	6145 ( $\pm$ 2126)	5814 ( $\pm$ 1965)	6475 ( $\pm$ 2336)	661 ( $\pm$ 749) <sup>a</sup>

<sup>a</sup>Significant at the  $P < 0.05$  level.

<sup>b</sup>SemD patients' difference score approached significance ( $P = 0.07$ ).

pairs in their accuracy scores ( $t(10) = 0.58$ ;  $P = 0.6$ ) and latency scores ( $t(10) = 0.23$ ;  $P = 0.8$ ).

Patients with little frontal disease were sensitive to hierarchical structure. Table 3 shows that SemD patients' overall order judgment accuracy was significantly less than healthy seniors' accuracy ( $t(18) = 4.46$ ;  $P < 0.001$ ), and Table 4 shows that their overall latency to respond to correctly judged event pairs was significantly slower than healthy seniors' latency ( $t(18) = 4.30$ ;  $P < 0.001$ ). Nevertheless, like controls, SemD patients showed some sensitivity to hierarchical structure. They were significantly more accurate judging Within-Hierarchy event pairs compared with Different-Hierarchy event pairs ( $t(5) = 3.89$ ;  $P = 0.01$ ). SemD patients also were faster when judging Within-Hierarchy compared with Different-Hierarchy event pairs ( $t(5) = 2.28$ ;  $P = 0.07$ ). AD patients were significantly less accurate ( $t(25) = 1.86$ ;  $P < 0.01$ ) and significantly slower than healthy seniors ( $t(24) = 4.27$ ;  $P < 0.001$ ). Yet, AD patients were more accurate ( $t(12) = 5.20$ ;  $P < 0.001$ ) and faster ( $t(11) = 3.06$ ;  $P = 0.01$ ) responding to Within-Hierarchy compared with Different-Hierarchy event pairs, showing relatively good sensitivity to hierarchical structure.

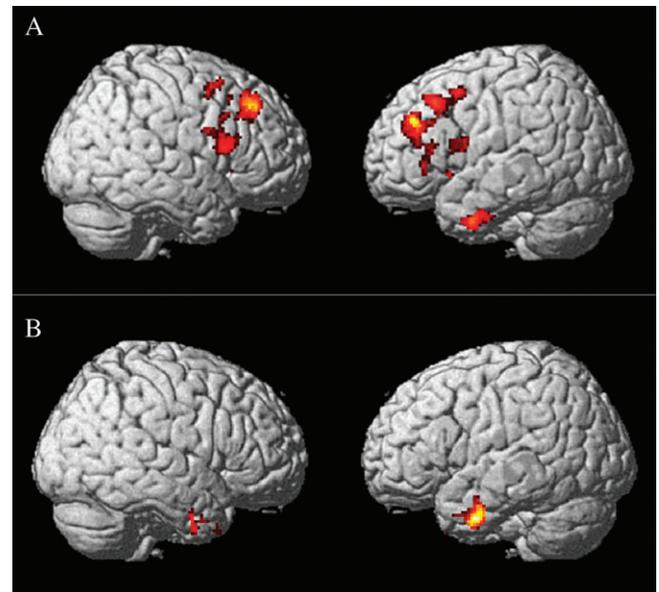
### Structural MRI Results in Patients

Patients with difficulty clustering highly associated events also had significant frontal disease. Figure 4 shows cortical atrophy in the patients we assessed who also had structural MRI studies. The anatomic localization of the clusters and the coordinates of the peaks in each cluster are summarized in Table 5. In PNFA and bvFTD patients who were relatively insensitive to hierarchical organization and had relative difficulty judging Within-Hierarchy pairs, we found significant cortical atrophy in inferior and dorsolateral frontal regions bilaterally, as well as left anterolateral temporal cortex. In SemD and AD patients who were relatively sensitive to hierarchical organization and appreciated the special status of events tightly clustered within a script, we did not find significant frontal atrophy. However, we saw bilateral temporal atrophy.

Inspection of Figures 3 and 4 suggests that fMRI activation in healthy young adults and cortical atrophy in impaired patients are adjacent to each other and partially overlap. We used SPM5 to count the number of atrophic voxels in the patient imaging studies that correspond to the area significantly activated in the fMRI study of healthy adults. The ROI was defined by the left inferior frontal area of activation seen in the fMRI study of healthy adults. This ROI was then applied as a binary image to each patient's gray matter image within a normalized space. We extracted gray matter density within this ROI for each subject by summing values from the segmented image over all voxels contained within the ROI. An independent sample  $t$ -test showed that PNFA and bvFTD patients have significantly more prominent atrophy in the ROI compared with healthy seniors ( $t(50) = 2.03$ ;  $P < 0.05$ ), but the group of AD and SemD patients did not differ from healthy seniors ( $t(44) = 1.28$ ;  $P > 0.2$ ).

### Discussion

Converging evidence from an fMRI study of young adults and a study of patients with focal neurodegenerative disease is consistent with the hypothesis that scripts are organized in a clustered-hierarchical manner rather than a linear-sequential manner, and that clustered-hierarchical script processing depends in part on frontal cortex. Specifically, young adults



**Figure 4.** Significant cortical atrophy in patients relative to healthy seniors. (A) PNFA and bvFTD; (B) SemD and AD.

**Table 5**

Distribution of significant cortical atrophy in patients relative to healthy seniors

Cluster locus (Brodmann area)	Coordinates of peak voxel <sup>a</sup>			Z-score
	X	Y	Z	
PNFA + bvFTD < controls				
Left dorsolateral prefrontal (46)	-26	30	24	4.45
Left inferior frontal (44)	-36	10	16	3.75
Left dorsolateral prefrontal (9)	-26	30	24	4.45
Left anterolateral temporal (20)	-46	0	-38	3.72
Left medial parietal (7)	-10	-50	52	3.60
Right inferior frontal (47)	42	46	-12	3.81
Right superior frontal (8)	30	34	40	4.31
SemD + AD < controls				
Left medial temporal	-30	-2	-16	4.98
Left lateral temporal (20)	-48	-2	-34	3.48
Left fusiform (36)	-26	-38	-14	3.67
Right medial temporal	18	-6	-14	4.07

<sup>a</sup>These coordinates are from the Talairach reference system.

activated inferior frontal cortex bilaterally during judgments of consecutive event pairs that are highly associated and from the same cluster, relative to judgments of consecutive event pairs from different clusters within a script. Because all event pairs consist of consecutively ordered events, it is unlikely that this pattern can be attributed to linear-sequential processing. Healthy seniors perceived the special status of highly associated events, consistent with clustered-hierarchical processing, because they showed faster responses during judgments of Within-Hierarchy relative to Different-Hierarchy event pairs. However, patients with PNFA and bvFTD were relatively insensitive to the clustered-hierarchical organization of events in a script. These patients treated Within-Hierarchy pairs and Different-Hierarchy pairs in a statistically identical manner. Insensitivity to the associativity strength that distinguishes between these pairs of events was related to frontal cortical atrophy. The areas of significant cortical atrophy in PNFA and bvFTD were adjacent to and partially overlapped with the fMRI activation seen in healthy young adults, although areas of cortical atrophy in patients and fMRI activations in young adults

were not identical and these results should be interpreted cautiously. Moreover, PNFA and bvFTD patients showed significantly greater cortical atrophy in an ROI corresponding to the inferior frontal activation seen in the fMRI study than healthy seniors. To evaluate whether insensitivity to hierarchical organization is a general consequence of neurodegenerative disease, we also examined patients with AD and SemD. These patients, like healthy seniors, were significantly more accurate and faster in their judgments of Within-Hierarchy pairs than Different-Hierarchy pairs. AD and SemD patients did not have significant frontal atrophy, and they did not differ from healthy seniors in the frontal ROI corresponding to the fMRI activation study.

Our findings are consistent with the hypothesis that comprehending the events in a script depends in part on clustered-hierarchical organization rather than linear-sequential processing (Miller and Cohen 2001; Fiebach and Schubotz 2006; Tettamanti and Weniger 2006; van Schie et al. 2006). Previous experimental evidence directly comparing these approaches is sparse. One previous study of patients with frontal insult reported difficulty judging the boundary of “large events” in a script compared with “small events” (Zalla et al. 2003). Defining a large event may involve perceiving the relationship between multiple events, but patients were not constrained experimentally on the nature of the process implicated in judging large events, large events contained more components and thus were more susceptible to working memory limitations, and judging small events was not clearly sequential. A second study used fMRI to show left inferior frontal activation during coherence judgments of incoherent sentence pairs where lexical information shared by sentences falsely suggested sentence coherence (Ferstl and von Cramon 2001, 2002). However, there is no empirical evidence that the lexical content shared by the sentence pairs is necessarily linking sentences in a linear-sequential manner, and the incoherent nature of these sentence pairs raises questions about the generalizability of error detection to the real-world processing that ordinarily underlies coherent scripts.

Prior work suggests clustered-hierarchical processing in other cognitive domains. For example, words and phrases in a sentence that are not adjacent to each other must be linked in a flexible manner that allows the sentence to be interpreted. Because our materials were presented linguistically, it is possible that sentence-level hierarchical organization mediated processing scripts in the present study, and this may have been related to left inferior frontal cortex. Patients with PNFA have sentence comprehension difficulty that appears to be due in part to syntactic limitations (Grossman and Moore 2005; Grossman et al. 2005; Murray et al. 2007; Peelle, Cooke et al. 2008; Peelle, Troiani et al. 2008), and direct correlations of impaired grammatical processing with cortical atrophy in PNFA implicate left inferior frontal cortex (Peelle, Cooke et al. 2008; Peelle, Troiani et al. 2008). We think it is unlikely that the findings of the present study can be explained by the role that left inferior frontal cortex plays in syntactic processing. All stimulus events were grammatically simple phrases, and all pairs of events were consecutive, reducing the likelihood that the phrases required linkage by long-distance syntactic relations. This differs from the sentence materials used by Sirigu et al. (1996) and Crozier et al. (1999) that had grammatical markers. Moreover, we directly contrasted pairs of events, and any syntactic-like mediation required for the

integration of event pairs should have been equally present in both pairs and thus should have been subtracted out of the activations.

A narrow linguistic account also would not fully explain the deficit of nonaphasic patients with a bvFTD profile who were as impaired as PNFA patients on this task. These patients are significantly impaired clinically in their narrative expression. Detailed analyses of the narratives of bvFTD patients and correlations with the performance on measures of executive control suggested that this is due in part to the poor organization of their extended speech (Chapman et al. 2005; Ash et al. 2006). These patients have significant bilateral frontal atrophy that is most apparent in the right hemisphere (Rosen et al. 2005), and impoverished organization of narrative expression in these nonaphasic patients is directly related to right frontal cortical atrophy (Ash et al. 2006). The limited hierarchical processing of scripts does not mean that bvFTD patients have no comprehension of the scripts. Instead, they may be able to engage linear-sequential processing, and this presumably allows these patients to recover at least a partial representation of script meaning, albeit one that is likely to be relatively inflexible.

We also found right inferior frontal activation in the fMRI study during judgments of Within-Hierarchy events compared with Different-Hierarchy events. Right inferior frontal cortex is implicated in the comprehension of narratives in other work (Nichelli et al. 1995; Caplan and Dapretto 2001; Ferstl et al. 2005; Xu et al. 2005). A meta-analysis of 23 imaging studies using a variety of techniques to study processes for integrating multiple sentences also emphasized bilateral frontal activation (Ferstl et al. 2008). fMRI studies of narrative speech show right frontal activation during expression of narrative (Braun et al. 2001; Troiani et al. 2008). However, previous work did not empirically constrain materials or performance sufficiently to establish the linear-sequential or clustered-hierarchical basis for script processing with confidence, and different materials often were used in tasks comparing sentences and scripts (Nichelli et al. 1995; Partiot et al. 1995; Sirigu et al. 1996; Crozier et al. 1999; Caplan and Dapretto 2001; Ferstl and von Cramon 2001, 2002; Ferstl et al. 2002, 2005; Zalla et al. 2003; Knutson et al. 2004; Xu et al. 2005). Future studies should confirm the inferior frontal distribution of hierarchical processing for scripts with picture materials.

The distinction between Within-Hierarchy and Different-Hierarchy pairs of events is not easily attributed to poor comprehension of script content. Patients with AD and SemD appeared to have some difficulty understanding these scripts. Thus, they were less accurate overall and slower in their judgments than controls. One previous study found that script performance is compromised primarily by degraded semantic knowledge in patients with AD (Grafman et al. 1991), and our prior work showed a deficit in script comprehension due in part to impoverished semantic knowledge in SemD but not bvFTD (Cosentino et al. 2006). Nevertheless, AD and SemD patients distinguished between Within-Hierarchy and Different-Hierarchy pairs of events. These earlier findings may differ from the present results in that the hierarchical organization of the scripts was not clearly specified, and initial and terminal events were probed despite the special status of these components of a script (Franklin et al. 2007). Also, one imaging study showed different activation patterns for narrative and semantic aspects of scripts (Nichelli et al. 1995). Although compromised word meaning may

interfere with script comprehension, some evidence in fact suggests that scripts provide a context that is enriched enough to supplement residual comprehension in SemD (Funnell 2001). This may allow patients with SemD and AD to demonstrate their sensitivity to the hierarchical organization of scripts. This is consistent with the relatively modest frontal disease in these patient groups: SemD patients have primarily anterior temporal atrophy (Mummery et al. 2000; Avants, Anderson, et al. 2008; Avants, Epstein, et al. 2008; Bonner et al. 2010), and AD patients have atrophy of medial temporal and temporal-parietal regions (Baron et al. 2001; Schuff et al. 2009).

The fMRI study of healthy adults and the structural MRI studies of patients also implicated anterior-superior temporal neocortex. The precise contribution of anterior temporal cortex to language processing is a matter of some debate. Although this area may play a role in the conversion of speech sounds to a meaningful representation of words (Dehaene-Lambertz et al. 2005; Liebenthal et al. 2005), others suggest a crucial role for anterior temporal cortex in amodal semantic representations that underlie word meaning (Patterson et al. 2007). Indeed, observations in the current study emphasize that there are at least 2 anterior temporal foci that may contribute to the processing of narrative. One of these is in the middle and inferior temporal gyri anteriorly. The presence of this atrophy in SemD and AD is associated with the semantic representations that are difficult for these patients, and dissociates this area from their relatively preserved hierarchical organization. The second anterior temporal locus is in the superior temporal gyrus. This area emerged in a meta-analysis assessing comprehension of a wide variety of texts (e.g., single sentences, sentence pairs, metaphors, and extended narratives) relative to various kinds of baselines (e.g., resting, perceptual, and incoherent texts) (Ferstl et al. 2008). The present study used a very closely matched baseline to demonstrate inferior frontal activation, and this frontal activation extended into the superior temporal lobe. Additional work is needed to define more carefully the apparent contribution of this anterior-superior temporal region to language comprehension.

Patients with PNFA and bvFTD have working memory limitations (Kramer et al. 2003; Libon et al. 2007, 2008). There is also extensive evidence that left inferior frontal cortex supports verbal working memory (Smith and Jonides 1999; Smith et al. 2002). The findings of our study may implicate working memory in processing pairs of events because one event must be maintained in an active mental state until the second event can be processed. We think this explanation is unlikely because the events being judged are both available during stimulus presentation. Moreover, fMRI activation associated with working memory is subtracted out of the contrast involving pairs of events. Some investigators have related prefrontal activation specifically to the level of abstraction of working memory representations (Ramnani and Owen 2004), and it is possible that there is greater working memory demands for Different-Hierarchy pairs because these are not as closely associated as Within-Hierarchy pairs. Even if true, such a role for verbal working memory would not clearly explain the findings implicating right inferior frontal cortex in this verbally mediated task.

The findings of the present study are consistent with a wider body of work suggesting a crucial role for frontal cortex in multiple types of hierarchically organized material (Botvinick and Plaut 2006a; Cooper and Shallice 2006). Our findings are not easily attributed to an organization involving the linear-

sequential ordering of events occurring chronologically in time (Hue and Erickson 1991; van der Meer et al. 2002; Botvinick and Watanabe 2007). The present study thus is consistent with the possibility suggested by Lashley (1951) that a modality- and material-neutral mechanism contributes to a variety of complex behaviors that are organized hierarchically.

### Supplementary Material

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

### Funding

National Institutes of Health (NS53488, AG15116, AG17586, and NS44266).

### Notes

Portions of this work were presented at the Society for Neuroscience Annual Meeting, San Diego, 2007, and the International Conference on Frontotemporal Dementias, Rotterdam, 2008. M.G. is a consultant for Allon Pharmaceuticals. *Conflict of Interest:* None declared.

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