

## **Brain plasticity revealed by functional MRI of script processing**

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**Abstract**

Praxis (procedural memory) can be defined as a script of steps necessary to execute a routine; apraxia is an early finding in Alzheimer's disease and frontal lobe dementias. Functional MRI was used to detect active areas of cerebral cortex during a script processing task. Over four consecutive sessions, eight right-handed subjects read five-item descriptions of common behavioral scripts (e.g., dining at a restaurant) and judged whether they were in proper semantic order (experimental condition) or in alphabetic order (control condition). Subjects were highly accurate across sessions, and improved response times following the first session. Initially, script processing preferentially activated left frontal, left temporal, and right cerebellar regions. During subsequent sessions, activations spread to additional frontal, temporal, and occipital regions, with most diffuse activation during the third session. During the last session, activations became localized to left temporal and midline cerebellar regions. These sequential changes form a pattern associated with progressive improvement in the task, consistent with plasticity expected to accompany learning. The pattern of changes fits a model whereby discrete regions reorganize to optimally handle script processing. These findings may serve as a basis for early detection of Alzheimer's and related disorders, where a discriminating pattern would potentially emerge.

## Introduction

A major question in cognitive neuroscience is how higher order information is represented in the brain. One particular framework, derived from work in artificial intelligence, is the notion of a script. Scripts are mental constructs referring to the ways in which individuals interpret and interact with their environments. The execution of a script leads to the realization of a goal; thus, scripts encapsulate goal-oriented behaviors <sup>1</sup>. Scripts are typically expressed as a linear sequence of steps, each of which must be completed before proceeding to the next. For example, a script for grocery shopping might include driving to the store, getting a cart, selecting groceries, paying for groceries, and loading the bags in the car. As types of procedural memories, akin to praxis, scripts are involved in everyday planning and execution of behavioral routines. These higher-order cognitive functions appear to be associated with executive system abilities <sup>1,2</sup>.

Identification of brain regions associated with script processing is important not only from a basic science perspective, but also from the perspective of eventual application to diagnosis and treatment of neurological dysfunction. Basic research on script processing contributes to brain mapping efforts; such research may ultimately lead to improved understanding of apraxia and executive disorders, which involve the frontal lobes and often appear as early signs of dementia such as Alzheimer's disease <sup>3</sup>.

Lesion studies indicate that script processing is at least partially subserved by frontal lobe regions. Sirigu et al. found that patients with frontal lobe lesions, when given written script components (steps) in random order, were unable to create behavioral scripts without making sequencing errors (in which the scripts were not appropriately ordered), and boundary errors (in which there was mixing of conceptual steps between script domains) <sup>2</sup>. Even when given an

opportunity to correct their scripts, they did not correct their sequencing errors and continued to include inappropriate steps in their scripts.

Functional neuroimaging has confirmed that the frontal lobes are involved in script processing, along with the temporal lobes. In the only previously published functional neuroimaging study of script processing, Partiot et al. used positron emission tomography (PET) to identify the right frontal lobe, left superior temporal gyrus, and bilateral middle temporal gyrus as regions subserving the sequential ordering of script components<sup>1</sup>. When various conditions were subtracted from the script ordering condition, results suggested that the temporal lobe activations were related to semantic processing.

Our goal was to isolate the cognitive activity associated with the sequential ordering of scripts by making the experimental and control conditions as similar as possible with the exception of the semantic ordering component. The current study compared brain activity during a semantic verification task (experimental condition), in which subjects were asked if a series of five script events was in the correct sequential order, and an alphabetical verification task (control condition), in which subjects were asked if the events were in the correct alphabetical order. Thus, the control condition is virtually identical to the experimental condition in that it demands basic lexical processing, basic sequencing, visual scanning, and a motor response to indicate an answer. By subtracting the sequencing involved in the alphabetizing task from the sequencing involved in the semantic task, we expected to identify only brain regions involved in a) procedural memory or praxis, and b) semantic sequencing of script events.

The current study focuses on the effect of semantic ordering of script events in discrete domains, thereby avoiding the potential confound of boundary errors. The script ordering task used in the current study differs from the one used by Partiot and colleagues in that it presents

five script steps simultaneously, rather than one at a time<sup>1</sup>. Thus, we expected our semantic task to reflect a unitary cognitive operation and to reduce the working memory requirements of the task. Generation of scripts was also avoided because a left dorsolateral prefrontal activation would probably appear, as has been seen in several imaging studies involving a generation condition<sup>4</sup>. The current study replicates and extends previous literature using functional MRI, which has the advantage of higher spatial and temporal resolution than PET, and the ability to carry out more repetitions without fear of accumulating radiation dose.

Based on previous research we expected a) that the procedural memory demands of the task would activate the left superior temporal gyrus and bilateral middle temporal gyrus, and b) that frontal gyri would be involved due to the task's requirement for semantic sequencing<sup>1</sup>. Recent research has suggested the left superior frontal gyrus also subserves sequencing of verbal items<sup>5</sup>. We anticipated that prefrontal activations, if found, would reflect the act of determination of logical sequence, rather than verbal working memory, as seen in left frontal cortex in accordance with previous findings<sup>6,7</sup>.

It stands to reason that some degree of mental imagery is involved in the determination of semantic order. Indeed, our pilot subjects indicated that they imagined themselves executing the scripts. Evoking imagery has been associated with precuneate and extrastriate activation<sup>1,8</sup>.

Recent research has identified the cerebellum as an important structure in mental imagery, shifting attention, planning, and other executive functions<sup>9</sup>. Because the semantic condition was believed to differentially recruit these functions, we anticipated cerebellar activation. Neuroscience research over the past decade has revealed afferent and efferent connections between frontal regions and contralateral cerebellar regions<sup>9,10</sup>. Previous functional neuroimaging studies have confirmed that frontal lobe activity correlates with contralateral

cerebellar activity<sup>9</sup>. As the semantic task is a verbal task, we expected to identify left frontal and right cerebellar activations during this task.

Up to now we have discussed only the static representation of scripts in the brain. To extend this work into the arena of learning and to explore the interaction of script memory with the acquisition of the semantic task, we exposed naïve subjects to four consecutive sessions in order to assess practice-related changes over time.

To summarize, we have hypothesized that (a) the semantic verification condition would result in bilateral temporal, left frontal, and contralateral cerebellar activation, (b) a non-semantic ordering condition such as determination of alphabetic order would not result in such activations, as there is sufficient “cognitive distance” between the two conditions, (c) activation seen when subjects are naïve to the task should change with subsequent repetition, in accordance with findings in the brain plasticity and learning literature<sup>11-13</sup>.

## **Methods**

### *Subjects*

Subjects were eight healthy adults (6 women, 2 men), averaging 26 years of age (range 19-33) and 16.9 years of education (range 13-20), who volunteered for the study and produced useable data. Subjects were all strongly right-handed, with an average Edinburgh Handedness Inventory<sup>14</sup> score of 95.4 (range 84.6-100). Subjects were excluded if they had any history of neurological or psychiatric dysfunction, illicit drug use, or heavy alcohol use. Additional exclusion criteria included current use of psychotropic medication, tobacco, or high levels of caffeine within one week of the study. All subjects gave written informed consent, and were paid a modest hourly

stipend. The current study was approved by the Institutional Review Board for Human Subject Research at Barrow Neurological Institute.

The Beck Depression Inventory was used to confirm that subjects were not currently depressed; no subject had a score greater than 4. WAIS-R (The Psychological Corporation, San Antonio) Vocabulary and Picture Arrangement scores were used to confirm normal cognitive performance, with mean scores of 12 on both subtests and no scores lower than 10.

### *Apparatus and Scanning Procedure*

All scans took place on the same imager, a General Electric Signa 1.5T with EchoSpeed Echo-Planar Imaging upgrade (GE Medical Systems, Milwaukee). The series of scans obtained comprised a sagittal T1-weighted localizer upon which slices were planned for subsequent axial acquisitions; a 3D volumetric spoiled-gradient-echo sequence (effective T1-weighting) anatomic image; and four subsequent sets of functional MRI, which were acquired using a 2D spiral EPI pulse sequence. A frame of 15 slices with 7 mm spacing (0 mm skip) were acquired every 3 s with a flip angle of 60°, 20 cm field of view, and displayed on a 128 x 128 matrix, giving voxels of 1.56 mm x 1.56 mm x 7 mm in size.

The scanning session began with placing the subject in the scanner with the head secured by tape and foam padding to minimize range of motion. Earplugs minimized subject discomfort. Subjects were given thumb-triggers built into bicycle grips which were to be depressed with the left or right thumb for YES and NO; assignment of YES or NO responses to the right or left thumb triggers was counterbalanced across subjects. Subjects were naïve to the tasks but were given verbal instruction prior to the experiment regarding what to expect and which thumb-triggers to use to respond YES and NO.

A session consisted of 72 frames and lasted 216 s. During each session, subjects were exposed to alternating experimental and control conditions via a back-projection screen illuminated by an 800 lumen Epson projector (Epson America, Torrance, CA) which was in the control room and not the magnet chamber to avoid RF interference. An Intel-based computer drove the projector using CNS Presenter (Xenoscience, Phoenix), a stimulus presentation system. The Signa has an RF-unblank TTL line, which was connected to the computer via a custom joystick port, in order to synchronize the start of tasks with the initiation of a set by the MRI technologist.

### *Image Analysis*

Images were obtained in raw format from the scanner and transferred electronically to a Sun SparcStation (Sun Microsystems, Inc., Mountain View). There they were reconstructed into individual files corresponding to frames, which were in a format suitable for Statistical Parametric Mapping (SPM) for Windows 1.01<sup>15</sup>. This version of SPM has been deemed statistically identical to SPM 96 with regard to results<sup>16</sup>.

Within each of the four consecutive sessions all eight subjects were realigned together using the SPM package, and then averaged<sup>17</sup>. This produced a single set of realigned images, corrected for head motion using a 6-parameter affine transformation. The averaged set of images was then normalized into the stereotaxic space of Talarach and Tournoux<sup>18</sup>, permitting reporting of statistical activation in a standardized coordinate system. Once normalized, the images were then smoothed with an 8 mm Gaussian kernel, which enhanced comparability and minimized anatomic variation.

Statistical analysis for fMRI was performed using the module in SPM for Windows, examining one-tailed differences in the experimental condition contrasted with the control condition. The threshold of expected peaks ( $u$ ) was set at 0.001 ( $Z \geq 3.09$ ). Clusters were accepted if they exceeded 5 voxels in size ( $k \geq 5$ ). These clusters are deemed activations in the following discussion.

## **Results**

### *Behavioral Data*

An accuracy score of 90% across experimental and control condition sessions was required for inclusion in subsequent behavioral and fMRI analyses. Six of the eight subjects had complete behavioral data, but the data of two subjects could not be analyzed due to technical difficulties with our recording equipment. The data of these two subjects, while not included in subsequent analyses, did indicate that the subjects were accurately completing the experimental and control tasks. Thus, their imaging data were included in SPM analyses.

Behavioral data were analyzed in terms of reaction time (RT) and accuracy. Subjects differed in their RTs ( $F=7.85$ ,  $p<0.01$ ), but did not differ in their accuracy of responding ( $F=1.22$ , ns). Reaction times decreased significantly following the first session, such that Session 1 RTs were longer than those of Session 2, Session 3, and Session 4 (Tukey HSD  $p<0.001$ ). Overall subject accuracy rates ranged from 91% to 99% across conditions. Accuracy rates remained stable across task sessions ( $F=1.44$ , ns).

As expected, subject RTs were significantly shorter during the control task, requiring them to judge the alphabetical order of the stimulus items, than during the experimental task, requiring them to judge the semantic order of the items ( $M=2586$  ms and 3592 ms, respectively;

$F=48.80$ ,  $p<0.005$ ). Subjects were highly accurate during the experimental and control tasks (mean accuracy was 95% for the experimental task and 97% for the control task;  $F=0.15$ , ns).

There was significant subject variability in RTs across tasks (the task by subject interaction was significant,  $F=11.18$ ,  $p<0.001$ ) and across sessions (the session by subject interaction was significant,  $F=3.54$ ,  $p<0.05$ ). There was also significant subject variability in accuracy across tasks and sessions (the session by task by subject interaction was significant,  $F=4.33$ ,  $p<0.001$ ).

### *Functional MRI*

Activations in the experimental (semantic) condition initially engaged left frontal area BA 6, left temporal regions BA 20 and 37, as well as right posterior cerebellum. Activations for this first session were modest in size with a total activation of 76 voxels. This compares with a total activation of 73 voxels in the control (alphabetical) condition where activations were primarily frontal and parietal, and also lateralized to the left hemisphere.

Session two showed an increase in total activation in the experimental condition (198 voxels) while the total number of active voxels in the control condition decreased (27 voxels). Increased experimental condition activation during this second session was due to a continuation of the frontal (BA 6) and temporal (BA 20, 37) activations, with the addition of an occipital activation in area BA 19. Cerebellar activation shifted toward the midline but remained posterior. Cortical activations in the experimental and control conditions dissociated hemispheres in session two with all experimental activations lateralizing to the left hemisphere while control activations now lateralized to the right hemisphere. Control activations consisted of modest parietal lobe activity.

A definite increase in activation occurred in both experimental and control conditions in session three. This session was characterized by an increase in the total number of activated voxels per task (378 voxels for the experimental condition and 163 for the control condition), and an increase in the number of areas activated by the tasks. In the experimental task left frontal activation shifted rostral and ventral in the frontal lobe from BA 6 to BAs 9 and 47. This frontal activation also grew in size from 75 voxels to 200 voxels. Left temporal activations in BA 37 persisted into this third session. A dichotomy of activations within both the experimental and control conditions occurred in this session with activations lateralizing to both hemispheres. Experimental condition activations moved into the right cerebrum with occipital activations localized to Brodmann Areas 18 and 19. Cerebellar activations for this condition were strongly lateralized to the posterior region of the right cerebellar hemisphere. Control condition activations become bilateral in the frontal lobe and exclusively left hemispheric in the parietal lobe.

Session four was characterized by a distinct decrease in activation in the experimental condition (192 active voxels) but an increase in the control condition. Experimental condition succinctly activated BAs 21 and 38 in the left temporal lobe, and bilateral anterior cerebellum. Control condition activations were primarily right frontal and parietal with some left temporal lobe and left cerebellar activations.

## **Discussion**

In the 1890s William James observed that habit diminishes the conscious attention with which acts are performed. Indeed, the observation that familiarity and learning alter the performance of actions is not a recent revelation. However, the ability to quantify how these

changes in performance are reflected in human cognition has only recently been addressed with the advent of functional imaging. Previous studies of higher-order cognitive processing have documented changes in activations across time as subjects become increasingly familiar with the task. A common observation involves increased neural activation while performing novel tasks. Haier et al used FDG-PET to determine that a decrease occurs in regional glucose metabolic rate when subjects perform a complex visuospatial/ motor task after weeks of daily practice on this task<sup>19</sup>. The cognitive activations altered most dramatically with practice were associated with the greatest improvements in performance, suggesting that learning may result in a more efficient cognitive strategy that recruits fewer metabolic resources.

Practice in the form of priming also produces a reduction in activation. Buckner reported that comparing the activation of a primed task to the activations during naïve or unprimed task exposes an overall reduction in neural activation with priming<sup>20</sup>. In Raichle et al's 1994 study the neural circuitry associated with a verbal response selection task was transformed by brief practice such that the neural circuitry associated with this task became indistinguishable from the circuitry activated by word repetition<sup>13</sup>. Evidence is mounting to suggest an economy of neural activation whereby exposure to a task is associated with increased neural efficiency as measured by decreased activation.

Neural activation during the first session of the current task (when subjects were naïve to the tasks) highlighted activation in left frontal lobe, left temporal lobe, and right cerebellum. Raichle and colleagues discovered a similar pattern of frontal and temporal activation during naïve performance of a verbal response selection task<sup>13</sup>. The current study replicates this pattern of activation in the naïve condition, as the pattern does not persist beyond the first session. Andreasen et al. also demonstrated increased frontal activation with performance on a

novel task<sup>11,12</sup>. This heightened frontal activation may be attributed to encoding of a novel stimulus or navigating a new situation.

Frontal activation is related to the implementation of cognitive planning and strategy. Studies of individuals with frontal lobe damage illustrate the importance of frontal lobe function in higher order cognitive tasks. Patients with frontal lobe dysfunction exhibit difficulty on executive function tasks such as the Tower of Hanoi and the Tower of London<sup>21,22</sup>. Although the source of these frontal lobe associated difficulties has not been firmly established it is suspected that these patients are unable to efficiently assemble events or actions into a coherent plan<sup>23</sup>.

In the current study frontal activation was consistently elicited in the first three sessions of the semantic condition when subjects were asked to determine whether or not a series of events was arranged in a logical sequence. Frontal activation was not seen in the fourth session, presumably because subjects were sufficiently familiar with the task and the items from the 24 script domains that the task incorporated less executive function involvement in this final session.

In contrast to the findings of Partiot et al these frontal lobe activations associated with the semantic condition lateralized exclusively to the left, as opposed to the right, hemisphere. This may be attributed to a difference in methodology. The Partiot study presented script components one at a time, thus increasing the retrieval demands of the task, while the current study presented all script components to the subject in a single screen. Indeed, right frontal activations are a consistent finding in retrieval tasks involving sequential presentation of lists, and this retrieval scenario was not implemented in the methodology of the current study<sup>4</sup>.

Executive processing difficulties are also seen in patients with cerebellar damage. Grafman et al. found that patients with cerebellar atrophy exhibited increased time in planning the initial move on the Tower of Hanoi task<sup>24</sup>. Motor deficit, verbal memory demands or a specific population characteristic could not explain this cognitive planning deficit. Appollonio et al. discovered that patients with cerebellar atrophy were significantly impaired only on tests of executive function when faced with a neuropsychological battery including tests of intellectual ability, memory, speed of processing and verbal fluency<sup>10</sup>.

Cerebellar activation is implicated in both executive processes and practice related learning. The crucial role of cerebellar activation in practice related learning has been demonstrated through studies of normals and of patients with cerebellar pathology<sup>13,25,26</sup>. Specifically, executive functions appear to activate the posterior cerebellum while motor activity translates into activation of the anterior cerebellum<sup>9,27</sup>. Cerebellar activations in the current paradigm shifted from their initial location in the posterior cerebellum in session one to a more anterior location by the fourth session. This finding is consistent with posterior cerebellar recruitment of executive functions during novel stimulus presentation.

It is interesting to note that evolutionary expansion of the neocerebellum has paralleled expansion of the frontal lobe. Coactivation of the left frontal lobe and the right cerebellar hemisphere is well documented in previous functional imaging literature of higher order cognitive tasks<sup>4,13,28</sup>. These patterns of frontocerebellar coactivation show a tendency for parallel increases or decreases in activation in these areas, and suggest that concurrent frontal and cerebellar activation plays a role in verbal working memory tasks with increased working memory demands<sup>28</sup>. The current study replicates this frontocerebellar coactivation in the early

sessions of a semantic task where subjects responded to both working memory and planning demands.

Functional imaging studies have demonstrated temporal lobe activity in both the encoding and retrieval of memories<sup>29</sup>. Similar activations have been attributed to praxis<sup>1</sup>. The semantic task of the current paradigm engaged regions of the left temporal lobe throughout all four sessions, culminating in a final session that is characterized solely by temporal and cerebellar activity. This may reflect the procedural and working memory demands of the semantic condition, as temporal activation was not reliably elicited during the alphabetical condition where subjects were asked process the script items according to lexical order.

Medial and superior temporal gyri in the left hemisphere were consistently activated during this script processing task. The medial and superior aspects of the temporal lobe in the left cerebral hemisphere appear to have a role in the retrieval of episodic memories<sup>30,31</sup>. Subjects may be representing the individual scripts in the current study as episodic memories, thus contributing to medial and superior temporal activations lateralized to the left hemisphere. Such activation is most notable in the final session where subjects may be sufficiently familiar with the 24 scripts that they are essentially retrieving the script items as episodic memories.

The addition of occipital lobe activation in the second and third sessions of the current study suggests that the semantic condition involved comparatively more reading than the alphabetizing condition. Indeed, occipital lobe activation is associated with reading<sup>32</sup>. Following the initial session subjects may have switched strategies to scan only the first letter in the alphabetizing condition rather than read the entire item as was necessary in the semantic condition. The lack of occipital lobe activation in the final session suggests that subjects were recruiting fewer neural resources to complete both the semantic and the alphabetizing tasks, thus

no differential occipital activation was observed. Another possible explanation attributes this extrastriate occipital activation to subjects invoking mental imagery during the intermediate sessions of the semantic condition <sup>8</sup>.

Overall, the semantic verification condition resulted in the hypothesized temporal, frontal, and cerebellar activations. Extrastriate activation in the occipital lobe was realized in two of the four sessions, possibly due to subjects invoking mental imagery or due to the differential reading involved in sessions two and three of the semantic task. The alphabetizing condition resulted in predominately parietal and frontal activations, presumably because sufficient “cognitive distance” exists between the two conditions. Neural regions activated by the semantic and alphabetical tasks changed throughout the progressing sessions in accordance with the literature on brain plasticity and learning <sup>11-13</sup>.

These changes in cerebral activations over four experimental sessions appear to reflect increased cognitive efficiency with learning. The pattern of activation over time suggests a model of cognitive processing whereby distinct brain regions reorganize to optimally execute the semantic task. This model is consistent with the economy of activation believed to occur with brain plasticity. Economizing neural activations allows for a reduction in total activation over time so that fewer active clusters are necessary to perform a familiar task. This reduction in neural activation may be advantageous in minimizing the number of synapses (connections) necessary to complete an action, thus reducing the possibility of adverse events occurring in the neural cascade leading to action.

Such economy of activation is presumed to break down in dementia. Functional imaging studies of patients with Alzheimer’s Disease compared to normals have shown that these patients

recruit additional areas while performing the same tasks. This pattern of activation has been documented in both visuoperceptual and verbal working memory paradigms<sup>33,34</sup>.

It would be worthwhile to use fMRI to investigate learning in a variety of modalities. Time-series analysis of functional images appears to demonstrate changes in activations over time, reflecting changes in the underlying neural networks that comprise the cortex. Further work will be necessary to clarify the nature of these network interactions and how clusters of activated cell columns cooperate to represent acquired knowledge in the task domain.

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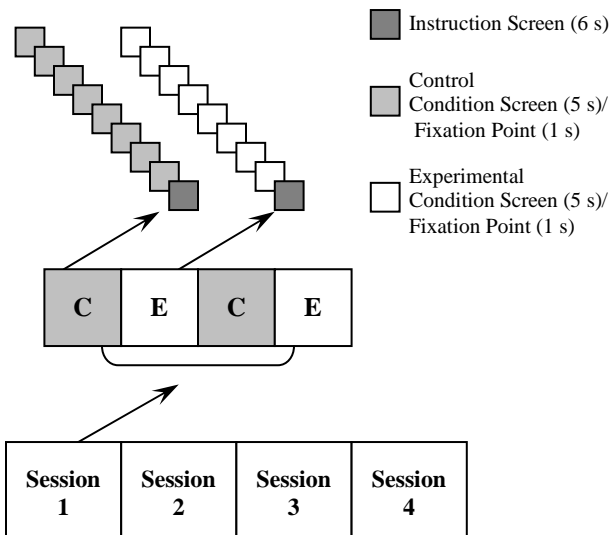
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**Are these items in the  
proper sequential order?**

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**Drive to ballpark**  
**Find seats**  
**Park the car**  
**Watch the game**  
**Leave the stadium**  
-----

+

**Are these items in  
alphabetical order?**

-----  
**Bake in oven**

**Eat cookies**

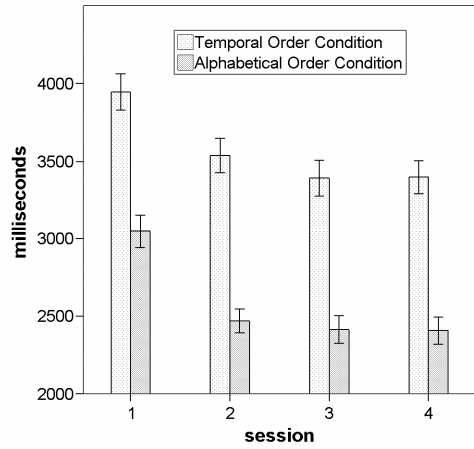
**Form cookies**

**Mix ingredients**

**Select recipe**  
-----

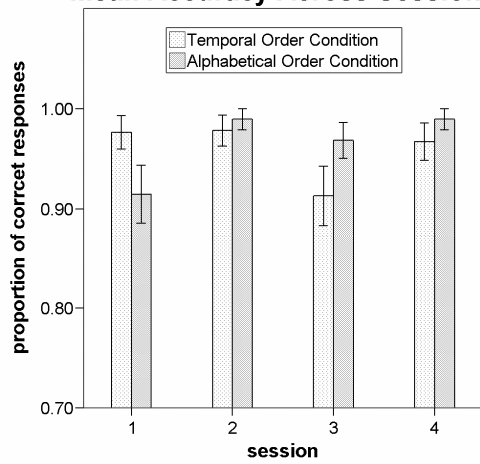
+

### Mean Reaction Time Across Sessions



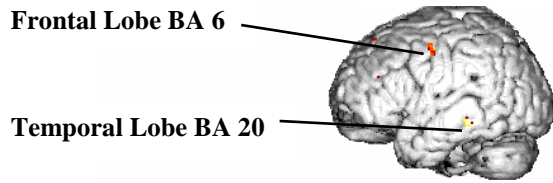
Error Bars show Mean +/- 1.0 SE

### Mean Accuracy Across Sessions

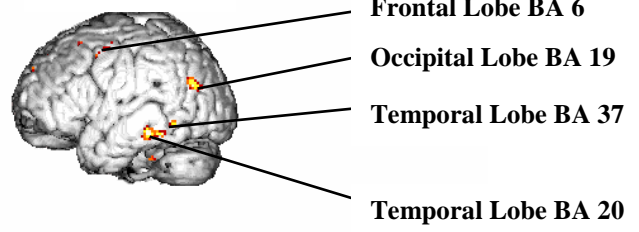


Error Bars show Mean +/- 1.0 SE

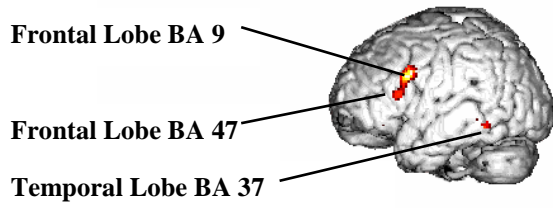
**Session One**



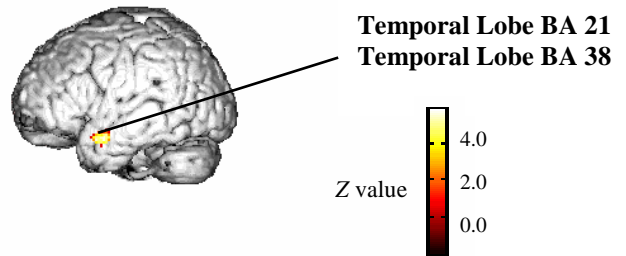
**Session Two**



**Session Three**



**Session Four**



### **Figure 1 Experimental Design**

Schematic representation of the experimental paradigm. The design consisted of four consecutive sessions presented to each subject (Session 1 through Session 4). Each session consisted of four sets; two of these four sets were comprised of control condition items ( C ) and two were comprised of experimental condition items ( E ). Control condition sets alternated with experimental condition sets in each session; a control set was always presented first in the series.

Each set included one instruction screen followed by eight trials. The first screen in each set was an instruction screen presented for 6 s informing subjects to perform either the control condition task or the experimental task during the proceeding eight trials. Each trial consisted of five script items arranged top to bottom on the screen for 5 s, during which the subject was to respond with the YES or NO button regarding whether the steps were in proper semantic order for that particular script (experimental condition) or in alphabetical order (control condition). After the 5 s, a 1 s fixation cross was displayed, acting as visual punctuation before the next trial.

Half of the displayed scripts were in proper semantic or alphabetical order; half were in a randomized, non-semantic or non-alphabetical order. No script items were interchanged between scripts. There were 24 scripts total, which were selected from a larger set of 30 by extensive pilot testing. Scripts were corrected subtending a similar visual angle in the displayed font (Times New Roman, 32-point bold). CNS Presenter randomized selection of script domains.

### **Figure 2a Experimental Condition**

An example instruction screen and a single experimental condition trial for items belonging to the “ballgame” domain. After the instruction screen is displayed for 6 s (top of diagram) eight

consecutive trials of script items are displayed for 5 s each (middle of diagram). For 1 s following each trial a fixation cross is displayed (bottom of diagram) acting as visual punctuation before the next trial.

### **Figure 2b Control Condition**

An example instruction screen and a single control condition trial for items belonging to the “baking cookies” domain. This condition also consisted of an instruction screen followed by eight trials. Trials were similar to the experimental condition in every way, except that the subject was to respond with the YES or NO button regarding whether the steps were in alphabetical order.

### **Figure 3 Subject Accuracy Across Sessions**

Subjects were highly accurate during the experimental condition and control condition tasks (mean accuracy was 95% for the experimental task and 97% for the control task;  $F=.15$ , n.s.). Overall subject accuracy rates ranged from 91% to 99% across conditions. Accuracy rates remained stable across task sessions ( $F=1.44$ , n.s.).

### **Figure 4 Subject Reaction Time Across Sessions**

Behavioral data was analyzed in terms of reaction time (RT). Subjects’ reaction times decreased significantly following the first session, such that Session One RTs were longer than those of Session Two, Session Three, and Session Four (Tukey HSD  $p<.001$ ). As expected, subject RTs were significantly shorter during the control task, requiring them to judge the alphabetical order

of the stimulus items, than during the experimental task, requiring them to judge the semantic order of the items ( $M=2586$  ms and  $3592$  ms, respectively;  $F=48.80$ ,  $p<.005$ ).

### **Figure 5 Plasticity Across Sessions**

Rendered images showing the brain areas activated by the semantic order condition versus the alphabetical order condition. Active areas are indicated by a hot metal palette color scheme (corresponding  $Z$  values indicated by color bar). Activations are illustrated across sessions as subjects subsequently learn the semantic order and the alphabetical order tasks. Activity throughout the progressing sessions was primarily confined to the left cerebral hemisphere with bilateral activation in the cerebellum. In session one subjects are naïve to the paradigm with activations of 30 voxels or less in size distributed in the frontal and temporal lobes. Activations continue to change in sessions two and three as subjects learn the tasks. By the final session activations are no longer distributed across lobes but consolidated to BA 21 and BA 38 in the temporal lobe.