

Dissociating Neural Mechanisms of Temporal Sequencing and Processing Phonemes

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Summary

Using fMRI, we sought to determine whether the posterior, superior portion of Broca's area performs operations on phoneme segments specifically or implements processes general to sequencing discrete units. Twelve healthy volunteers performed two sequence manipulation tasks and one matching task, using strings of syllables and hummed notes. The posterior portion of Broca's area responded specifically to the sequence manipulation tasks, independent of whether the stimuli were composed of phonemes or hummed notes. In contrast, the left supramarginal gyrus was somewhat more specific to sequencing phoneme segments. These results suggest a functional dissociation of the canonical left hemisphere language regions encompassing the "phonological loop," with the left posterior inferior frontal gyrus responding not to the sound structure of language but rather to sequential operations that may underlie the ability to form words out of dissociable elements.

Introduction

Understanding how the brain processes the distinctive sound elements of language and integrates those sounds into meaningful linguistic sequences is fundamental to dissociating the components of language processing. Traditionally, Broca's area is thought to mediate the sequential integration and production of linguistic units. Recent neuroimaging studies have identified a subregion within Broca's area, the posterior, superior portion of the inferior frontal gyrus (IFG), that appears to play a specific role in phonological processing (Bookheimer, 2002). However, several recent accounts have suggested that this region is not only specialized for such distinctive operations on phonologic content but also for specific acoustic and motor processes that may give rise to language. Using fMRI, we sought to determine whether there are neural mechanisms specific to the sequencing of language content or whether the process of sequencing is a more general cognitive mechanism underlying the function of this region, by requiring subjects to perform sequencing operations on human vocal stimuli that did or did not contain phonemes.

It is unclear whether the same brain regions mediate the identification of discrete phoneme segments and the process of sequencing those segments. Recent neuroimaging studies have confirmed the role of a portion of Broca's area, the left posterior, superior inferior frontal

gyrus, in identifying the individual sound units of language within a word (Burton et al., 2000; Demonet et al., 1992, 1994; Zatorre et al., 1992, 1996; Thierry et al., 1999; Paulesu et al., 1997). However, neuropsychological studies have found verbal sequencing deficits in patients with various types of aphasia. These include deficits in repetition of individual words and word lists (Canter et al., 1985; Monoi et al., 1983; Tzortis and Albert, 1974; Shallice and Warrington, 1977), in spontaneous speech (Tanji et al., 2001), and in pointing to visual representations of a series of heard words (Albert, 1972; Kim, 1976; Kim et al., 1980). On the other hand, ordering of visuospatial materials does not seem impaired in aphasics (Kim et al., 1980).




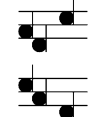


Other behavioral and neuropsychological studies have suggested that the process of sequencing, whether involved in the ordering of combined visual and auditory patterns (Carmon and Nachshon, 1971) or in the execution of motor movements (Lomas and Kimura, 1976; Kimura and Archibald, 1974), may be a basic specialization of the left hemisphere. Further psychological and electrophysiological studies have argued that organizing individual finger (Martin et al., 1994) or orofacial (Ojemann and Mateer, 1979) movements into a sequence may share common neural mechanisms with language processes, particularly those involving the frontal cortex. In the primate literature, Rizzolatti and Arbib (1998) have noted that F5, the monkey homolog to Broca's area, is capable of linking the observation and execution of a series of motor movements. These authors have suggested that the human ability to combine limited phonemes to form infinite words might have arisen from the ability of the left IFG to link a sequence of observed manual movements into a sequence of executed manual movements. Together, these studies support the possibility that neural mechanisms of sequencing are not specific to language and that the sequencing of other human-produced sounds may also engage Broca's area.

Recent neuroimaging studies have provided evidence that Broca's area mediates other processes that may underlie language but are not specific to it. One such process is the integration of rapid acoustic transitions, occurring in comprehensible speech (Poldrack et al., 2001; Fiez et al., 1995) and in certain nonspeech stimuli (Fiez et al., 1995; Benson et al., 2001). Overt and covert motor imitation also appears to engage Broca's area (Iacoboni et al., 1999; Bookheimer, 2002) and may share neural resources with language processes (Iacoboni et al., 1999). These models hold that Broca's area does not function exclusively in the domain of language; rather, its role in certain language processes may result from the integration of several underlying cognitive mechanisms.

The human voice represents a general ecological sound category and can be subdivided into speech and nonspeech components. Neuroimaging (Perry et al., 1999; Riecker et al., 2000; Scott et al., 2000) and intracarotid amobarbital (Bogen and Gordon, 1971; Gordon and Bogen, 1974) studies have generally localized perception and production of vocal pitch and melody to the

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Table 1. Examples of Stimuli and Response Characteristics for Sequencing Tasks

Task	Response		Task	Response	
	Yes	No		Yes	No
Match syllables	ruk-dup-nid ruk-dup-nid	ruk-dup-nid ruk-nid-dup	Match Hums		
Reverse syllables	mip-saf-vam vam-saf-mip	mip-saf-vam vam-mip-saf	Reverse Hums		
Delete syllables	kiv-zot-fif kiv-fif	kiv-zot-fif zot-fif	Delete Hums		

right hemisphere. One fMRI study has directly examined differences between speech and other orally produced sounds (e.g., sighs and laughs) (Belin et al., 2002), and these authors found specific activity in the left superior temporal lobe for speech sounds and in the right superior temporal lobe for other vocal sounds. However, melodies and other human vocal sounds are generally produced as an intact whole and are not composed of dissociable units such as phonemes and syllables. It is thus unclear if manipulating vocal sounds into discrete units and requiring subjects to sequence them might also engage left hemisphere mechanisms.

One neuroimaging study (Zatorre et al., 1994) has examined processing of individual nonspeech sounds. Specifically, Zatorre and colleagues required subjects to monitor the temporal order of eight-note tonal melodies and to decide if the last note of the sequence was higher in pitch than the first note. In comparison to passive listening, a distributed network involving the right inferior frontal cortex and right superior temporal gyrus was activated, with a smaller peak in the left inferior frontal gyrus. Although these results suggest that directed attention to sequential aspects of musical stimuli still engages right hemisphere mechanisms, the sequencing demands in this study were minimal, since subjects were only monitoring for order instead of actively manipulating it. Moreover, as the authors themselves have discussed (Zatorre et al., 1996), passive listening is not an attentionally constrained control task, and it is not clear how sequential processing differs from other demands associated with performing a musical task. Further, instrument-produced complex tones do not have the ecological salience or acoustical complexity of the human voice.

In the present study, we sought to distinguish the ability to recognize a vocal percept from the ability to manipulate the temporal order of a sequence, independent of articulatory/production requirements, using fMRI to measure blood oxygenation-level dependent (BOLD) changes in signal intensity which correlate with relative increases in cerebral blood flow (CBF). To this end, we used two types of human vocal stimuli, sequences of hummed notes and of syllables, and employed two sequential manipulation tasks and one sequence recognition task (see Table 1). In a sequence

reversing task, subjects rearranged the order of a sequence of syllables or hummed notes, while in a sequence deletion task, they removed and reintegrated elements of the sequence. The first task was adapted from the Digits Backward test (Wechsler, 1974), known to involve verbal working memory, while the second was adapted from a phoneme deletion task that is sensitive to phonological processing deficits (Stuart, 1990; Oakhill and Kyle, 2000). In a control pattern-matching task, subjects simply determined if two sequences of syllables or hummed notes matched. Brain regions that implement sequencing generally, regardless of linguistic content, should show fMRI activation in the sequence manipulation tasks. Conversely, brain regions specialized for processing phonemes should show activation for phonemic versus nonphonemic vocal stimuli, regardless of the sequencing demands of the task.

Results

Behavioral Performance

Behavioral data were analyzed using separate repeated-measure two-way analyses of variance (ANOVAs) for accuracy and reaction time, with stimulus type (syllables, hums) and task (match, delete, reverse) as within-subject factors. Behavioral data were available for nine subjects.

The ANOVA on reaction times revealed no significant main effects or interactions. However, the accuracy ANOVA demonstrated a significant main effect of stimulus type [$F(1,8) = 7.210$; $p < 0.03$], indicating that subjects were more accurate with syllables than hums, and also revealed a significant main effect of task [$F(2,8) = 5.458$; $p < 0.02$]. Post-hoc F tests for means confirmed that subjects were significantly less accurate on the reverse task than on the match task ($F = 10.803$; $p < 0.005$) but that the delete task was intermediate in difficulty and thus did not interact significantly with either the match or reverse tasks. The ANOVA also showed a significant stimulus type by task interaction [$F(2,8) = 4.652$; $p < 0.03$], which was due solely to the interaction between delete syllables and delete hums (Delete syllables: M, 98.4%; SD, 4.8; delete hums: M, 77.8%; SD, 16.1; $F = 16.967$; $p < 0.0009$). However, subjects were

Table 2. Brain Activations for Task-Specific Contrasts

Location			Significance		Coordinates			Secondary Coordinates		
Area	H	BA	z test	Voxels	X	Y	Z	X	Y	Z
Task-specific effects										
Match > delete + reverse										
Central sulcus ^a	L	4	5.22	39	-30	-16	32			
Middle cingulate	L	24	3.39	*	-20	-10	42			
Posterior cingulate	M	31	5.08	1008	2	-52	30			
Middle cingulate	M	24/31	3.95	44	2	-22	36	-8	-28	36
Medial frontal gyrus	L	8/32	3.83	35	-18	24	36			
Middle frontal gyrus	L	8/9	3.25	*	-28	24	36			
Caudate nucleus	R	-	3.82	57	14	16	14			
Insula	R	-	3.48	*	22	12	14	34	6	12
Medial frontal gyrus	L	8/32	3.73	18	-12	34	26			
Middle frontal gyrus	L	9	3.53	14	-28	32	34			
Angular gyrus	L	39	3.50	16	-46	-62	26			
Insula	L	-	3.42	17	-32	4	18			
Posterior cingulate	R	31/7	3.20	16	14	-22	42	10	-32	42
Reverse > match										
Precentral gyrus	R	6	4.27	20	48	-4	36			
Precentral gyrus/middle frontal gyrus	L	6/9	3.73	79	-34	2	38			
Inferior frontal sulcus	L	6/9/44	3.60	*	-50	10	36			
Inferior frontal gyrus	L	44/6	3.32	*	-48	8	28			
Thalamus	L	-	3.73	29	-16	-28	8			
Supramarginal gyrus	L	40	3.48	17	-44	-40	40			
Thalamus	L	-	3.45	17	-12	-14	2			
Superior parietal lobule	L	7	3.18	24	-26	-66	38			
Delete > match										
Brainstem ^b	M	-	4.10	44	0	-32	0			
Posterior cingulate	M	23/31	3.43	13	4	-60	12			
Middle frontal gyrus	L	44/9	3.19	31	-36	8	30			
Inferior frontal gyrus	L	44/6	2.96	14	-48	10	30			

Note: Column H indicates left (L) hemisphere, right (R) hemisphere, or (M) medial region. BA, Brodmann's area of peak activation, obtained from atlas of Talairach and Tournoux (1988). Coordinates are in millimeters, reflecting distance from anterior commissure, and express the peak activation of a cluster of voxels in a particular anatomical region, as determined by one-sample t tests. Cluster size reflects the number of activated voxels above the chosen threshold. All reported regions were significant after random effects analysis and survived a threshold of $p < 0.005$ at the voxel level and 13 voxels at the cluster level. For peak activations within 8 mm of each other and situated in both the same Brodmann's region and anatomical region, the peak with the highest z value is reported. The * indicates that a region is part of the cluster listed directly above.

^a Cluster's location is unclear but is likely deep in the central sulcus.

^b Brainstem focus is in or near colliculi.

comparably accurate with both syllables and hums within the match and reverse tasks (match syllables: M, 98.4%; SD, 4.8; match hums: M, 93.6%; SD, 7.5; reverse syllables: M, 82.5%; SD, 17.2; reverse hums: M, 82.5%; SD, 15.6).

Imaging Results

Task-Specific Brain Regions

In order to determine task-related changes in MR signal intensity (which we will refer to as "activation"), we pooled across stimulus types. Table 2 and Figure 1 present significant activations that were specific to the match, reverse, and delete tasks, respectively. Because comparisons between task conditions represent relative changes in MR signal intensity, we cannot clearly differentiate when an active region is due to an increase in the activation task or a decrease in the control task.

In general, MR signal increases during the two tasks involving sequential manipulations (contrasts: reverse versus match, delete versus match) were left lateralized. Both tasks engaged a region in the left posterior, superior IFG, extending superiorly to the junction of the left

inferior frontal and precentral sulci and medially into the left middle frontal gyrus. Additionally, the task requiring subjects to reverse the components of a sequence (contrast: reverse versus match) produced unique MR signal increases in the left inferior parietal lobule and left posterior, superior parietal lobule, with both peaks bordering the inferior parietal sulcus. We also observed a significant right hemisphere peak in the reverse task in the right precentral gyrus, as well as a smaller subcortical response in the left pulvinar thalamus. Activation in the posterior cingulate was particular to the delete task.

Brain regions showing activation in the match task relative to the two sequence manipulation tasks (contrast: match versus delete + reverse) were located bilaterally. Specifically, several separate peaks were observed in the mid to posterior cingulate region, extending toward the precuneus. Additionally, the left medial frontal region was engaged, as well as a more lateral left middle frontal locus. We observed smaller signal increases in several brain regions, including the left angular gyrus, bilateral insula, and right caudate nucleus, during the match task (see Table 2). Generally, the match task engaged the

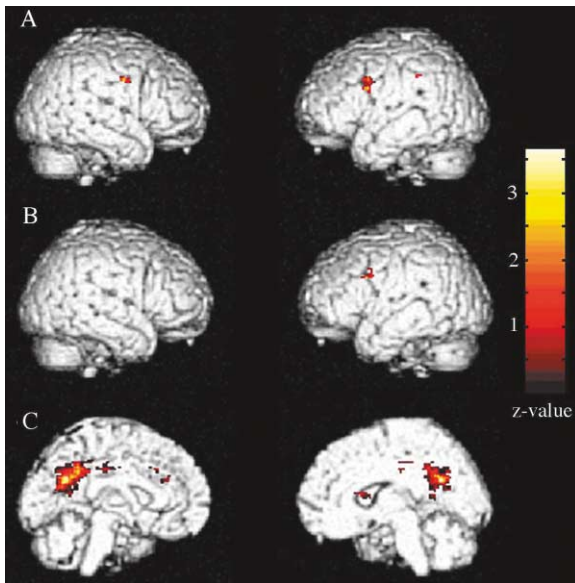


Figure 1. Task-Specific Contrasts

These figures show cortical surface renderings of increases in fMRI signal intensity during specific tasks, pooled across stimulus types (syllables, hummed notes) and averaged across subjects. The reverse and delete tasks are the sequence manipulation tasks, and the match task has no explicit sequential manipulation requirements. (A) A lateral view of activation in the contrast reverse versus match. Note a robust response in posterior, superior Broca's area, extending into the left middle frontal gyrus (MFG), and a second peak in the supramarginal gyrus, observed for reversing both syllables and hummed notes. (B) The delete versus match contrast showed the same increase in Broca's area, again extending into L MFG. (C) Medial view of activation in the contrast match versus delete + reverse. We did not observe a Broca's or supramarginal response in this contrast. However, we found a large cluster of neural activity in the middle to posterior cingulate, for both syllables and hummed notes. In all reported regions, activations were significant at $p < 0.005$ at the voxel level and survived a cluster threshold of 13 voxels. See Table 2 for a complete list of regional activations.

greatest number of distinct anatomical regions and showed the largest spatial extent of activation.

Stimulus-Specific Brain Regions

To determine differences in brain activity due to stimulus type, we compared syllables to hums, independent of task. Relative increases in activation for syllables and hummed notes, respectively, are presented in Table 3.

In contrast to the prominent task-specific MR signal increases, no regions responded more to syllable stimuli than to hummed notes. However, several regions in the right hemisphere showed an additional activation for hums. We observed separate clusters of activation in the right inferior frontal gyrus and the right precentral gyrus. Additionally, we found several temporal lobe regions activating specifically to hums, including the right superior temporal sulcus and the right superior and middle temporal gyri (see Table 3).

Stimulus-Specific Brain Regions within Each Task

To examine task-specific modulation of stimulus processing, we determined differences in brain activity between syllables and hummed notes within each task, as presented in Table 3.

No regions showed a relative increase for syllables compared to hums in the reverse or delete tasks, confirming that subjects relied on similar neural mechanisms to perform sequence manipulations with speech and nonspeech human vocal sounds. Only the match task, which required recognition of stimulus-specific sequences instead of manipulation, revealed brain regions particular to syllable stimuli; these were in the posterior cingulate.

Brain regions showing relative MR signal increases for hummed notes relative to syllable stimuli, within each task, were in the right hemisphere for the match task and the left hemisphere for the delete task (see Table 3). No regions responded specifically to hummed notes in contrast to English syllables during the reverse task. The match Hums task revealed a focus at the border of the right pars opercularis and right premotor cortex, in the same region observed as a main effect of the hums stimuli. Additionally, match hums uniquely engaged the right anterior superior and middle temporal gyri, which were within 4 mm of similar peaks revealed as a main effect of stimulus type. The delete hums task engaged a region in the left hemisphere, which was near the similar left pars opercularis/left premotor cortex response revealed as a main effect of the delete task.

Post-Hoc and Conjunction Analyses

In order to confirm that the posterior, dorsal region of Broca's area showed an increase in activation for both stimulus types during the sequential manipulation tasks (reverse, delete), we performed direct comparisons between each sequential manipulation task and the corresponding match task, for each stimulus type. We then performed a conjunction analysis between the hummed notes and syllable conditions for both the reverse and delete tasks, to confirm activation in the left posterior IFG for both stimulus types in both sequential manipulation tasks. Figure 2 presents the results of the conjunction analysis in posterior, dorsal Broca's area, for both the reverse and delete tasks.

Activation was observed in the posterior, dorsal region of Broca's area for all four comparisons (reverse Hums versus match Hums; delete Hums versus match Hums; reverse Syllables versus match Syllables; delete Syllables versus match Syllables). The peaks of activation revealed by each direct comparison were located in the same region (BA 44/6) and were approximately equivalent in magnitude for both stimulus types in both manipulation tasks (see Table 4). In order to formally confirm left posterior inferior frontal activation for both syllables and hummed notes, we performed a conjunction analysis between syllables and hummed notes for the reverse and delete tasks, respectively. A conjunction analysis computes the joint probability of independently observing activation in a particular region for two discrete comparisons. This analysis confirmed that the left posterior IFG was activated for both syllables and hummed notes in both the reverse and delete tasks (see Table 4). The conjunction analysis showed activation in the same region of the left posterior IFG across stimulus types, and peaks of left posterior IFG activation differed 12 mm in the x dimension across tasks, with no differences across stimuli.

When comparing the reverse to the match task, pooling across stimulus types, we observed activation in

Table 3. Brain Activations for Stimulus-Specific and Interaction Contrasts

Location			Significance		Coordinates			Secondary Coordinates		
			z test	Voxels	X	Y	Z	X	Y	Z
Area	H	BA								
Stimulus-specific effects										
Syllables > hums										
No significant activity										
Hums > syllables										
Inferior frontal gyrus	R	44/6	3.96	38	48	10	28	38	10	30
Precentral gyrus	R	6	3.55	67	52	4	12			
Inferior frontal gyrus	R	44/6	3.12	*	46	8	16	38	14	16
Superior temporal gyrus	R	22	3.20	14	48	-10	2			
Superior temporal sulcus	R	22	3.15	34	46	2	-8			
Middle temporal gyrus	R	21	2.77	*	44	-6	-10			
Interaction effects										
Match										
Syllables > hums										
Posterior cingulate	M	31	3.58	36	-6	-44	34	4	-48	28
Hums > syllables										
Inferior frontal gyrus	R	44/6	4.16	47	52	4	18	48	8	30
Anterior cingulate	L	24/32	3.20	18	-22	14	36			
Middle temporal gyrus	R	21	3.09	20	42	-6	-10			
Superior temporal gyrus	R	22	2.91	*	46	4	-4			
Reverse										
Syllables > hums										
No significant activity										
Hums > syllables										
No significant activity										
Delete										
Syllables > hums										
No significant activity										
Hums > syllables										
Inferior frontal gyrus	L	44/6	3.36	27	-54	10	18			

Note: Abbreviations are identical to those in Table 2. Coordinates are in millimeters, reflecting distance from anterior commissure, and express the peak activation of a cluster of voxels in a particular anatomical region, as determined by one sample t tests. Cluster size reflects the number of activated voxels above the chosen threshold. In all reported regions, $p < 0.005$ at the voxel level and clusters are larger than 13 voxels, following random effects analysis. For peak activations within 8 mm of each other and situated in both the same Brodmann's region and anatomical region, the peak with the highest z value is reported. The * indicates that a region is part of the cluster listed directly above.

the left supramarginal gyrus. In the individual post-hoc comparisons, neither the comparison reverse Hums versus match Hums nor the comparison reverse Syllables versus match Syllables revealed left supramarginal gyrus activation at our original statistical threshold. Activation was subthreshold for both stimulus types, significant at $p < 0.01$ at the voxel level for both comparisons. However, the activation in the left supramarginal gyrus was more robust for the syllable stimuli (center of activation: -40, -38, 40; $z = 3.41$; cluster size = 27 voxels) than the hummed notes (center of activation: -34, -52, 40; $z = 2.58$; cluster size = 7 voxels). The conjunction analysis revealed a common focus of activation for the syllables and hummed notes in the reverse task (center of activation: -44, -42, 40; $z = 4.10$, cluster size = 16 voxels) at $p < 0.001$ uncorrected, which was just subthreshold. Although the left supramarginal gyrus may not be entirely specific to phonemic stimuli, it seems clear that this region is more involved in manipulating stimuli containing phonemes than stimuli containing hummed notes.

Examination of the post-hoc comparison delete Syllables versus match Syllables also revealed a focus in the left supramarginal gyrus, significant at our original threshold (peak activation: -36, -46, 40; $z = 4.18$; cluster size = 25 voxels), further suggesting that the left supramarginal gyrus is more specific to processing phonemes than general to sequencing discrete units.

Discussion

Using fMRI, we examined neural mechanisms underlying the sequencing of phonological and nonlinguistic vocal information (hummed notes). We found a functional dissociation in the left-lateralized regions associated with the "phonological loop" (Baddeley, 1986; Paulesu et al., 1993). Posterior, superior Broca's area showed increased neural activity when subjects manipulated temporal order, independent of whether the stimuli were linguistic in nature. A conjunction between stimuli containing phonemes and hummed notes, for each of the sequence manipulation tasks (reverse and delete), confirmed that the left posterior IFG was equally active for phonological stimuli and hummed notes. The activation in the left posterior, superior IFG extended across the left inferior frontal sulcus and into the left middle frontal gyrus, suggesting that the left middle frontal locus is part of the same functional region. These results suggest that some left hemisphere language regions respond to the sound structure of language, while others implement sequential operations that may underlie the ability to form words out of phoneme segments. In contrast, matching phoneme segments and hummed notes, a task without an explicit sequential manipulation requirement, produced extensive activation in the posterior cingulate, a region associated with familiar and context-dependent recognition (Kim et al., 1999, 2002; Henson

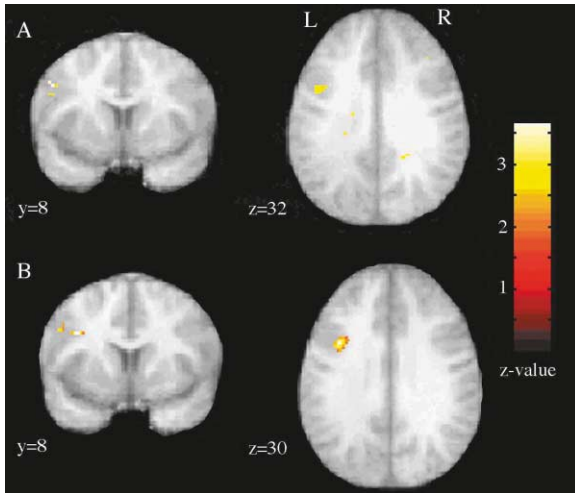


Figure 2. Conjunctions

This figure shows the results of the conjunction analysis revealing common activations of the left posterior inferior frontal gyrus for both syllables and hummed notes in the sequence manipulation tasks (reverse, delete) as compared to the match task. Activations are averaged across subjects and overlaid on coronal (left) and axial (right) slices of an averaged T1-weighted anatomical template (Woods et al., 1999).

(A) Conjunction of syllables and hummed notes for the comparison reverse versus match.

(B) Conjunction of syllables and hummed notes for the comparison delete versus match. Conjunctions are displayed at a significance threshold of $p < 0.001$. See Table 4 for peak locations of left posterior IFG activation in Talairach space.

et al., 1999) and episodic retrieval success (Konishi et al., 2000; von Zerssen et al., 2001).

Our data are partially consistent with earlier models positing that left frontal areas may mediate the sequential processes underlying phonologic organization (e.g., Stuss and Benson, 1986; Alexander et al., 1989). However, our results indicate that sequencing may be a general organizing principle of the left posterior inferior frontal region, not specific to phonemic content. This principle is supported by studies in the motor domain, which have argued that sequencing motor movements may share cognitive resources with language tasks in left frontal regions. For instance, Martin and colleagues

(1994) found that sequential but not repetitive finger tapping interfered with performance on a concurrent phonemic fluency task, suggesting that language and motor tasks may share cognitive resources that mediate the coordination of a sequential response. Likewise, Ojemann and Mateer (1979) found that cortical stimulation in the left inferior frontal cortex disrupted phoneme monitoring and the ability to copy sequential but not individual orofacial movements. Together with these previous studies, our data suggest that sequencing may be a more general function of Broca's area, involved in temporal manipulations of both speech and nonspeech sequences. Others (Rizzolatti and Arbib, 1998; Iacoboni et al., 1999) have argued that motor movements and language processes share neural resources in posterior, superior Broca's area due to an imitation mechanism, which provides an overlapping system for gesture recognition and production and underlies language acquisition in young children (Iacoboni et al., 1999). Although our study did not address these issues directly, this model provides further evidence that Broca's area mediates processes that are not specific to language.

Functional imaging studies using auditory language stimuli have implicated the posterior portion of Broca's area in subvocal articulation (Demonet et al., 1994; Burton et al., 2000; Zatorre et al., 1992, 1996; Fiez et al., 1995; Thierry et al., 1999). Demonet and colleagues (1992, 1994) found that the left posterior IFG was active when subjects had to monitor for two phonemes in a specified sequence and suggested that this activity could result from a strategy of "sequencing and rehearsing" the two phonemes in order to make a response decision. In our study, both the sequential manipulation (reverse and delete) and recognition (match) tasks required working memory and rehearsal of stimulus sequences. Additionally, subvocal articulation of phonemes likely constitutes a different process than subvocal rehearsal of hummed notes, given that these two stimulus types have very different acoustic characteristics. Thus, a pure rehearsal account seems unlikely to explain the result that the left posterior IFG showed a relative increase in activity during the sequence manipulation tasks as compared to the match task for both stimulus types. Possibly, left posterior IFG is involved in concatenating sequences for input into a vocal rehearsal loop.

Table 4. Post-Hoc and Conjunction Analyses in Left BA 44/6

Location	Significance		Coordinates			Secondary Coordinates		
	z test	Voxels	X	Y	Z	X	Y	Z
Reverse hums > match hums	3.98	44	-38	6	36	-50	8	36
Reverse syllables > match syllables	3.34	70	-48	8	28	-40	6	28
Delete hums > match hums	3.02	13	-36	8	30			
Delete syllables > match syllables	2.98	21	-36	10	30			
Conjunction: reverse > match	5.18	14	-48	8	34			
Conjunction: delete > match	4.97	11	-36	8	30			

Note: Coordinates are in millimeters, reflecting distance from anterior commissure, and express the peak activation of a cluster of voxels in a particular anatomical region, as determined by t test. Cluster size reflects the number of activated voxels above the chosen threshold. All reported regions were significant after random effects analysis. For the individual contrasts, activations survived a threshold of $p < 0.005$ at the voxel level and 13 voxels at the cluster level. Conjunction analyses were performed between syllables and hummed notes, and results were significant at a voxelwise conjoint threshold of $p < 0.0001$ and contained clusters larger than ten voxels. For peak activations within 8 mm of each other and situated in both the same Brodmann's region and anatomical region, the peak with the highest z value is reported.

However, our data indicate that such a rehearsal loop is not specific to speech sounds.

Broca's area may be involved in several other functions, including semantic and morphosyntactic processing of language. However, a recent review (Bookheimer, 2002) has argued for subspecializations of Broca's area. Specifically, semantic processes seem to involve the left anterior IFG at the border of Brodmann's regions 45/47 (Dapretto and Bookheimer, 1999; Demb et al., 1995; Wagner et al., 2001; Poldrack et al., 1999), while syntactic processes typically engage the middle portion of Broca's area (*pars triangularis*), located in Brodmann's regions 44/45 (Kang et al., 1999; Friederici et al., 2000; Just et al., 1996; Dapretto and Bookheimer, 1999; Caplan et al., 1998, 2000). In the present study, we observed activation during the sequential manipulation tasks, across stimulus types, in a posterior, superior region of Broca's area (BA 44/6), bordering the precentral gyrus posteriorly and the junction of the precentral and inferior frontal sulci superiorly. Although this circumscribed region is frequently engaged during phonological processing (Demonet et al., 1992, 1994; Zatorre et al., 1992, 1996; Burton et al., 2000), we suggest that it may have a more general role in concatenating discrete vocal units into a sequence. Within a modularity framework, the anterior and posterior regions of Broca's area likely have highly interactive functions during language processing.

Neuroimaging (Zatorre et al., 1992, 1994; Rao et al., 1997), lesion (Zatorre and Samson, 1991; Shapiro et al., 1981), and EEG (Auzou et al., 1995) studies have implicated the right inferior frontal gyrus when rehearsal of pitch or tonal information is required. However, none of these studies had explicit sequential processing requirements. Moreover, in tasks requiring judgments about speech prosody instead of the phonemes themselves, the right inferior frontal gyrus is consistently engaged (Bookheimer, 2002). In the present study, we found no right inferior frontal gyrus activation when comparing the hummed notes to the syllables in the reverse or delete tasks, nor when comparing the reverse and delete hums tasks to the match hums task. However, the right inferior frontal gyrus showed a robust increase for hummed notes as compared to syllables when no explicit sequencing was required, as in the match task. Thus, our results are compatible with the idea that functional lateralization of the inferior frontal gyrus results from the mode of processing rather than the perceptual qualities of the input stimulus (Gates and Bradshaw, 1977). Specifically, temporal information about pitch changes may engage the left hemisphere, while processing the entire sound gestalt engages the right hemisphere (Gates and Bradshaw, 1977) and its associated rehearsal mechanisms.

Others have argued that Broca's area functions specifically in verbal working memory (Baddeley, 1986; Paulesu et al., 1993), and neuroimaging studies have reported activation in Broca's area due to increased processing load (e.g., Rypma et al., 1999). If working memory is involved in the present study, it is not specific to verbal information. It seems unlikely that a basic working memory function such as processing load can entirely account for our data, as posterior Broca's area showed a relative signal increase in both sequence ma-

nipulation tasks, even though the reverse and match tasks contained the same number of tokens and the delete task included fewer tokens than the match task. It is more likely that posterior Broca's area is performing an active processing role in our study. Support for this hypothesis comes from the study of Burton and colleagues (2000), who compared two phonological tasks matched in mnemonic demands. These authors attributed the resulting posterior Broca's activation to the requirement to identify and segment out the initial phoneme of a syllable. It is possible that a similar but nonverbal mechanism is operating in our sequential manipulation tasks, in the sense that the extraction of discrete vocal elements from the whole string engages posterior Broca's area. An alternative possibility is that the sequential manipulation and recognition tasks differ intrinsically in working memory and rehearsal demands. However, subjects were comparably accurate on the delete and match tasks, so difficulty cannot explain the activation observed in the left posterior IFG during the sequence manipulation tasks across stimulus types.

Another model holds that the left inferior frontal gyrus is involved in processing rapid frequency changes, which occur both in speech and certain nonspeech stimuli (Poldrack et al., 2001; Fiez et al., 1995; Benson et al., 2001). These authors have suggested that this region responds when specific acoustic analysis or articulatory recoding of rapid temporal transitions is required. However, the changes between hummed notes are considerably slower (300 ms on average) than the changes between nonspeech stimuli (Fiez et al., 1995; Benson et al., 2001) and the changes between compressed speech stimuli (Poldrack et al., 2001) in the above-mentioned studies (tens of milliseconds). This argues against a rapid temporal processing interpretation of the Broca's activation observed in this study; rather, temporal sequencing on the cognitive level may also engage posterior Broca's area. Retrieving information about temporal structure via an articulatory representation may be a general function of the left inferior frontal gyrus, thematically integrating the role of posterior Broca's area in this study in rearranging temporal order with the above studies associating this region with rapid temporal processing. Other studies have found consistent increases for processing rapid frequency transitions in the left superior temporal gyrus and left middle frontal gyrus (Belin et al., 1998; Poldrack et al., 2001), and these regions may have a specialized role in operating on such specific acoustic characteristics.

A region in the left dorsal middle frontal gyrus (dorsolateral prefrontal cortex [DLPFC]) responded to the match task and was significantly anterior to the left middle frontal activation seen in the reverse and delete tasks. This more anterior region is implicated in aspects of working memory. For instance, Barch and colleagues (Barch et al., 1997) observed increased and sustained activity in a similar region of the left middle frontal gyrus during active maintenance in working memory over a long retention interval, independent of task difficulty. Raye and colleagues (Raye et al., 2002) found greater activation in this region when subjects had to refresh (reflect back to a single, just-seen stimulus), as compared to reading a novel or repeated word. These authors suggested that refreshing may function to prolong

(or increase) activation of a perceptual representation, is initiated and/or sustained by the left middle frontal gyrus, and ultimately links perception to working memory processes. Moreover, this region showed greater activation for items that later were correctly and quickly identified. Such a finding converges with our results; in the present study, the match task was the easiest across stimulus types. Anterior DLPFC activation during our match task may reflect the need for subjects to maintain the order of sequences of phonemes and hummed notes in working memory prior to initiating a response. In the reverse and delete tasks, we identified a more posterior region of activation in the left middle frontal gyrus, which borders on the precentral and inferior frontal sulci. Henson et al. (2000) have associated this region with the serial rehearsal of the temporal order of phonemes, and our results suggest that it may have a more general role in sequencing. A third region in the left middle frontal gyrus, more anterior and inferior to the activations observed in this study and cytoarchitecturally distinct, has been implicated in rapid auditory processing (Poldrack et al., 2001; Belin et al., 1998). Together, these results suggest a dissociation of function in the left middle frontal gyrus.

In the reverse task, a unique task-specific activation was seen in the left supramarginal gyrus, when pooling across stimulus types, that was not observed in the delete task, the other sequence manipulation task. Both syllables and hummed notes individually showed sub-threshold left supramarginal activation when comparing the reverse to the match task, although the fMRI response was somewhat larger for syllables than for hummed notes ($z = 3.41$ for syllables; $z = 2.58$ for hummed notes), and the conjunction for these two stimulus types was significant just below threshold ($p < 0.001$). The left supramarginal gyrus traditionally is considered part of the phonological loop (e.g., Paulesu et al., 1993; Zatorre et al., 1992, 1996), along with Broca's area. Hickok and Poeppel (2000) have suggested that a left frontoparietal network may represent a sensory-motor integration circuit that develops to allow young children to compare the sounds produced by others to those they produce themselves, in order to learn to correctly articulate the target language. Moreover, these authors have suggested that attention to sublexical speech segments is crucial to this process and that the frontoparietal network participates in accessing and operating on sublexical speech segments. The frontal component of this network appears to be stimulus independent, while there may be some specialization for phonemic content in the parietal portion. A role for the left supramarginal gyrus in maintaining and combining sublexical sound representations for further processing is supported by neuropsychological studies (Hantén and Martin, 2001; Bisiacchi et al., 1989). Since the left posterior IFG and left supramarginal gyrus show differential specialization for phonemic stimuli, a phonological processing explanation cannot integrate these regions as a distinct functional system. It is unclear whether this frontoparietal network is specific to segments involving only human vocal stimuli or whether other types of segmental nonvocal auditory stimuli might also engage this network.

Our results suggest that the left supramarginal gyrus

may respond to the process of manipulating phoneme segments in working memory and that it may participate in manipulation of nonspeech vocal segments when the load increases in working memory. The observed increases are not likely due solely to maintaining order information in the phonological loop (Martin and Caramazza, 1982), since our baseline task, match, also involved order maintenance. In the neuroimaging literature, the left supramarginal region has been ascribed a role in the coding and retrieval of order information in verbal working memory (Marshuetz et al., 2000), an interpretation that may in part extend beyond the language domain. An active processing role for the left supramarginal gyrus seems likely, given its activation for syllable stimuli in the delete task and also its subthreshold activation for syllable stimuli and hummed notes individually in the reverse task, when order manipulation of three and not two elements was required. Studies requiring subjects to monitor pure tone sequences in order to make a response decision have also found activation of the left inferior parietal lobule (Demonet et al., 1994; Zatorre et al., 1994; Binder et al., 1997), and one interpretation is that some sort of associative transformations on nonspeech stimuli are also a function of the left supramarginal gyrus (Price, 1997). However, it remains possible that the left supramarginal gyrus does have a distinctive role in the organization of sequences for speech output (Bub et al., 1987).

The right anterior, superior temporal lobe demonstrated a specific role in processing hummed notes, in contrast to phonemes. Several neuroimaging studies have suggested that the anterior and middle portions of the right superior temporal sulcus may process the spectral characteristics of the human voice, independent of linguistic content (Belin et al., 2000, 2002). The right anterior temporal region also responds when human vocal stimuli have a clear pitch or intonation (Scott et al., 2000). However, other neuroimaging studies suggest that this region is not particular to processing human vocal sounds but, rather, general to analyzing pitch sequences. For example, Binder and colleagues observed activation during pitch detection with sequences of pure tones (Binder et al., 1997). Additionally, Patterson et al. have observed a stream of processing emanating anterolaterally from the right primary auditory cortex for evaluating and integrating sequences containing discrete pitch contours (Patterson et al., 2002). In Brodmann's area 42, somewhat posterior to the peak of right superior temporal activation in our study, Tervaniemi et al. (2000) found activation for passive listening to sequences containing chords with varying but not sustained pitches. They suggested that this region mediates an automatic comparison process between musical sounds. Similarly, in a somewhat more posterior region of the right superior temporal gyrus, Halpern and Zatorre (1999) found activation for imagery of tonal patterns in familiar melodies. One hypothesis, integrating these findings across complex and simple pitch stimuli, is that cortical asymmetries may have developed for pitch and speech processing due to dedicated functional properties of the auditory system (Zatorre et al., 2002). Specifically, these authors have proposed that the left auditory cortical area resolves rapid temporal events relevant for speech discrimination. In contrast,

they suggested that the right homolog has a complimentary role in processing complex spectral distributions, with the anterior region particularly selective for integrating subtle frequency changes over time (Zatorre and Belin, 2001). The present results confirm the role of the right anterior, superior temporal region in implementing pitch comparisons across an interval; however, the interaction analyses revealed a significantly greater response in this region for hummed notes as compared to syllables only in the match task, in which direct perceptual identification was required. Thus, our results suggest that temporal sequencing on the cognitive level may also modulate the degree of right anterior temporal participation in a top down fashion. It is possible that a concentration of cognitive resources to sequential processing occurred in the subjects of the present study during performance of the reverse and delete tasks.

In contrast to previous neuroimaging studies comparing normal speech processing to processing of nonphonological human vocal stimuli (Scott et al., 2000; Belin et al., 2002), we did not find evidence for greater activation of the left superior temporal lobe during speech processing. Since these previous studies either did not compare natural speech to natural nonphonological human vocal stimuli or used a passive listening task, it is possible that this region is sensitive to the spectral characteristics of natural human vocal structure or to the specific type of processing required by our tasks. Recent functional imaging studies have suggested that the left posterior superior temporal gyrus may transiently represent the temporally ordered elements of a heard or internally produced phonological sequence, preceding whole-word representation (Scott et al., 2000; Wise et al., 2001). Such a role in sequence maintenance may extend to the hummed notes in the present study, which are species-specific vocalizations that can be mimicked (Wise et al., 2001). The left superior temporal lobe is also thought to respond to the rapid auditory transitions present in speech (e.g., Binder et al., 2000). Our speech tasks did not emphasize the segmentation of individual phonemes from the rest of the sequence, and thus, subjects were not forced to distinguish between rapid auditory transitions belonging to distinct phoneme categories. Rather, syllables were always separated by 300 ms and could be easily distinguished during the manipulation tasks, so the tasks may not have emphasized processing of rapid temporal transitions. A related possibility is that the syllables were not treated as language, and we may have observed left temporal activation at our chosen statistical level if we had used syllables with semantic content. Alternatively, the loud noise of the fMRI scanner may have produced widespread activation over the auditory region, masking differences between regions modulating the acoustic decoding of speech and nonspeech. However, the left posterior superior temporal sulcus showed a trend to being more active for syllables than hummed notes. We observed activation in this region when we lowered the statistical threshold to $p < 0.05$, for syllables in contrast to hummed notes, pooled across tasks, demonstrating some support for the rapid auditory processing hypothesis.

In summary, we found evidence that the posterior portion of Broca's area and the left supramarginal gyrus, the putative components of the phonological loop, do

not have an integrated role in phonological processing per se but rather in the sequential manipulation of discrete units. Specifically, hummed notes, which have different articulatory requirements than phonemes, activated canonical language regions. Our results suggest that posterior Broca's area responds to the mode of processing rather than to the type of stimulus, while the left supramarginal gyrus may have a more direct function in operating on the sound units of language.

Experimental Procedures

Participants

Twelve native English-speaking, right-handed volunteers (mean age = 16.3 years, range = 15–18, eight males and four females) participated in this study after giving written informed consent to the protocol approved by the University of California, Los Angeles, Institutional Review Board. All participants had normal hearing and none reported a history of neurological disease or psychiatric illness or were taking medication affecting the central nervous system. No subjects were professional musicians; however, some had received basic musical training in childhood.

Paradigm Design

During the language trials, subjects performed three different tasks that varied in their sequencing demands (match, reverse, and delete), using strings of three different CVC syllables as stimuli. In the match task, a sequence recognition task, participants heard an initial syllable sequence and then determined whether a second sequence presented the syllables in the same order as the first. The reverse and delete tasks required subjects to manipulate a sequence. In the reverse task, subjects decided if the second sequence represented the syllables in the opposite order as the first. In the delete task, subjects were asked to mentally remove the middle syllable of the first sequence and then to determine if the second sequence of two syllables matched the order of the first sequence with the middle syllable deleted. Subjects also performed the same tasks (match, reverse, and delete) using sequences of three hummed notes of differing pitches. Table 1 presents example pairs of syllable and hum sequences for each task. During a rest condition, subjects were simply instructed to remain motionless. In each task, syllables or hums within a sequence were separated by approximately 300 ms, and corresponding sequences were separated by 1000 ms and followed by a 2000 ms response period.

Each task was presented in one of three runs (match, delete, or reverse), and each run was composed of three activation blocks presenting one stimulus type each (CVC syllables, hummed notes, and Chinese syllables). Data on Chinese syllable processing were collected for a separate experiment and are mentioned here only to describe subjects' complete experience during fMRI scanning. Experimental blocks alternated with rest blocks within each run. The order of runs and stimulus blocks was counterbalanced across subjects in a Latin Square design. Each run lasted 4 min, 22.5 s and contained three activation blocks of 57.5 s each in the match and reverse tasks and three activation blocks of 50 s each in the delete task. Every activation block presented seven trials, each lasting 8000 ms in the match and reverse tasks and 7000 ms in the delete task. The delete trials were shorter because the second sequence consisted of only two syllables or hummed notes.

Syllables and hums were individually recorded on a Macintosh computer using a microphone and were concatenated into sequences and matched for intensity and duration in SoundEdit (Macromind, Paracomp, Inc). Syllables were recorded by a male native English speaker and hums were recorded by a female vocalist, and although this is a potential confound, we are aware of no evidence suggesting that differences in voice gender would affect our results. This potential confound is further mitigated by the fact that the key comparisons are within the syllable and hums conditions. Each of the seven syllables was presented three times within each task, once in each of the first, middle, and last positions within a string. No three-element sequence was repeated within or across tasks.

Experimental Protocol

Before fMRI scanning, all participants completed a practice session using one of two stimulus sets, which were counterbalanced across subjects and between the fMRI and practice sessions. Stimulus presentation and behavioral data collection were controlled by a Macintosh computer using the MacStim program (David Darby, <http://airto.loni.ucla.edu/BMCweb/SharedCode/SharedSoftware.html#Anchor-MacStim-18197>). In the scanner, subjects heard the stimuli through MR compatible stereo headphones (Resonance Technologies, Inc., Van Nuys, CA) and responded with their right hand using a button box.

fMRI Data Acquisition

Images were acquired using a 3 Tesla GE scanner equipped with echo-planar imaging (EPI) from Advanced NMR (Wilmington, MA). First, we acquired a conventional T2-weighted sagittal scout scan, and then we obtained coplanar high-resolution EPI spin-echo images (TR = 4000 ms, TE = 65 ms, matrix size 128 × 128, flip angle = 90°, FOV = 20 cm), consisting of 26 slices for later coregistration and spatial normalization of each participant's data into a standard coordinate space, using an in-house Talairach-compatible MR template (Woods et al., 1999). Finally, 315 functional images were collected over 16 axial slices (4 mm thick/1 mm gap) for each subject, using an EPI gradient echo sequence (TR = 2500 ms; TE = 45 ms; matrix size 64 × 64; FOV = 20 cm), with 105 images acquired in each of three runs at each slice location.

Image Analysis

Each subject's coplanar high-resolution images were first registered and spatially normalized into a standard reference system (Talairach and Tournoux, 1988) using linear transformations and polynomial nonlinear warping, with AIR (Woods et al., 1998, 1999). We then used a six-parameter rigid body transformation model and a least-square cost function with intensity scaling to correct for head motion, by realigning each subject's functional image series to the middle image of the second run. Third, functional images were resliced into Talairach space using combined parameters from coplanar image warping and spatial normalization. Finally, images were smoothed using a 6 mm full-width half-maximum (FWHM) isotropic Gaussian kernel, producing a final voxel size of 2 × 2 × 2 mm.

Statistical comparisons on functional images were performed using SPM-99 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>). A fixed boxcar design with a 6 s lag to allow for the delay in the hemodynamic response was employed, and global normalization was used in each individual subject. Two steps were completed in order to generate the contrast images. First, a fixed effects model was created for each individual subject, and each run was entered as a separate study in the design matrix. Task-specific contrasts (match versus delete + reverse, reverse versus match, delete versus match), pooling across stimulus types, and stimulus specific contrasts (Syllables versus Hums, Hums versus Syllables), pooling across tasks, were calculated using the general linear model (Friston et al., 1995) across the entire brain for each subject. Additionally, we calculated interaction effects by contrasting stimulus-specific activations within each task. Second, these individual difference images were entered into random effects analysis, with a one-sample t test comparing each voxel in the brain across all subjects, in order to determine significant activations present in all subjects. Random effects analyses are inherently more conservative than fixed effects analyses because the variance is between subjects rather than within subject, and thus, the degrees of freedom depend on the number of subjects rather than on the number of scans (Friston et al., 1999). Since the variability across subjects is generally greater for fMRI data than the variability within subjects, activations will be less significant in a random effects analysis than a fixed effects analysis for a particular effect (Friston et al., 1999). All reported regions of activation were significant at $p < 0.005$ uncorrected at the voxel level and survived a cluster threshold of 13 voxels.

In order to confirm that the posterior, dorsal region of Broca's area was indeed active during the sequence manipulation tasks for both stimulus types, a post-hoc analysis was performed, comparing each sequence manipulation task (reverse, delete) to the match task for each stimulus type (four contrasts) in a one-sample t test in random effects. We also sought to determine if the left supramar-

ginal gyrus activation observed in the reverse versus match comparison (pooling across stimulus types) could be replicated in individual comparisons for each stimulus type during performance of the reverse task. Activations were significant at $p < 0.005$ and 13 voxels.

Next, to ensure that the left posterior inferior frontal region identified in the sequence manipulation tasks was identical for both syllables and hummed notes, we performed a conjunction analysis (Price and Friston, 1997) between syllables and hums for the reverse and delete tasks, respectively, as compared to the match task. Individual difference images calculated in fixed effects for each subject were entered into a two-sample t test without a constant term in random effects. The conjunction was over a test for each of the Sequence Manipulation versus match effects for syllables using contrast weights of [1 0] and the equivalent effect for hums with [0 1]. The conjunction procedure assumes sphericity, namely that the intersubject variability in the reverse versus match and delete versus match effects is the same for syllables and hums. This is simply motivated by noting that, under the null hypothesis, there is no reverse versus match or delete versus match effect. Conjunctions were significant at a voxel-wise conjoint threshold of $p < 0.0001$, and reported activations contained clusters larger than 10 voxels.

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