



Selective speech motor, syntax and cognitive deficits associated with bilateral damage to the putamen and the head of the caudate nucleus: a case study

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Abstract—Deficits in speech production, sentence comprehension and abstract reasoning occurred in a subject having profound bilateral damage to the putamen and the caudate nucleus. Acoustic analyses indicated that the subject's speech was degraded due to inappropriate sequencing of articulatory gestures that involve different articulatory structures. Transitions between sounds were slow and often did not achieve target configurations. The subject had a 14% error rate comprehending distinctions in meaning conveyed by syntax in English sentences; normal controls make virtually no errors in this test. Cognitive deficits involving impaired sequencing occurred: the subject had a 70% error rate on the Odd Man Out test when making decisions within a single category. Cognitive perseveration occurred when the subject was asked to shift categories. In contrast, performance was within normal ranges in tests of lexical access and memory. The pattern of deficits provides evidence for basal ganglia involvement in the regulation of sequencing across modalities. © 1998 Elsevier Science Ltd. All rights reserved

Key Words: basal ganglia; sequencing; language; timing; frontostriatal circuits; speech deficits.

Introduction

It has become apparent that the neural bases of higher human cognition involve subcortical structures traditionally associated with the regulation of motor control. Studies of aphasia resulting from damage to subcortical structures show agrammatism and losses in 'abstract' reasoning ability, as well as deficits in the production of speech [6, 40]. Studies of Parkinson's disease (PD), which primarily affects basal ganglia function, likewise reveal deficits in the comprehension of distinctions of meaning conveyed by syntax [25–28, 34, 48], as well as in reasoning and speech production [31, 36]. Deficits in 'executive' functions, such as planning and the ability to shift selective attention between sensory modalities, generally thought to be regulated by the frontal neocortex, may result from damage to the basal ganglia [20, 21, 31]. In contrast, other aspects of cognition, such as memory, are relatively preserved when basal ganglia structures are damaged or degenerate [2, 20, 31].

Involvement of subcortical structures in higher-level

cognitive processes is supported by anatomical data. Comparative anatomical and physiological studies of animals have revealed that the basal ganglia form a number of circuits that regulate various behaviors (e.g., [4, 5, 20]). Among these circuits are those connecting the caudate nucleus to frontal neocortical regions of the brain that appear to be implicated in higher cognition [49]. Recent tracer studies show other circuits to the 'cognitive' prefrontal cortex involving the globus pallidus as well as the cerebellum [46]. Assessments of neural activity derived by mapping the metabolic activity of the brain using positron emission tomography show reductions in frontal lobe neocortical activity occurring with damage to the head of the caudate nucleus [43]. It is unclear whether effects of damage to the basal ganglia derive from the processing of information in basal ganglia structures, from the disruption of information that is transmitted to and from the neocortex through subcortical pathways, or from damaged frontal cortex following reduced input from the basal ganglia (cf. [31, 44, 45, 49]).

In this context, subject CM, a 45-year-old woman who

suffered extensive bilateral damage to her putamen with some involvement of the caudate nucleus, provides an opportunity to assess the premise that basal ganglia structures operate across several domains due to their participation in different neural circuits. A range of deficits associated with damage to the putamen and caudate have been reported [18, 23, 41, 42, 52, 53], but for the most part, these studies are atheoretic, reporting deficits as revealed by gross cognitive and affective evaluations. Moreover, although language abnormalities have been noted [41], no rigorous assessment of syntactic ability has been performed. We report here the performance of CM on tests designed to assess speech production and perception, syntactic ability, and cognitive functions including memory, attention and frontal/executive functions.

Case history

CM, a 45-year-old left-handed woman with a history of hypertension and asthma, graduated college and began teaching high school English before developing a schizo-affective illness at age 24 requiring continuous treatment with neuroleptic drugs. No tardive dyskinesias, Parkinsonism, dysarthria or other neuroleptic-induced dysfunction had been noted. In December of 1992 she was placed on verapamil, 240 mg per day, for hypertension, precipitating a syncope spell due to cardiac pauses of up to 5 sec, followed by agitated behavior. She was admitted to a local hospital. Despite insertion of a cardiac pacemaker she remained hypotensive and required assisted ventilation and pressors. On extubation she was noted to have severe dysarthria and impaired cognition. When better recovered, she had difficulty walking. She remained in hospital for 1 month. Over the following 18 months she gradually improved and when first evaluated in June 1994, while taking insulin, ranitidine, reserpine (1.2 mg daily), was alert, cooperative, fully oriented with a normal affect and attention span, and had dysarthric speech. The psychosis appeared to have resolved, but subsequent to our test sessions, has recurred. Cranial nerves were normal. Motor exam revealed mild Parkinsonism and mild oral-lingual-buccal dyskinesias. Brain magnetic resonance imaging (MRI) revealed marked bright signal intensity in the putamen, with slight signal increase in the caudate (see Fig. 1). This symmetric abnormality was thought to be most likely due to hypoxemia.

Evaluation

In order to assess CM's speech, cognitive and linguistic function, she was interviewed and tested in seven 1-hr sessions over a period of 3 months, 21 months after the coma. All sessions were recorded using a Sony digital audio tape recorder with a Sennheiser condenser microphone positioned approximately 100 cm from the subject. Four gender-matched normal controls (average age 42.5;

range 38–46) were administered the same battery of tests. Because the overall speaking rate of these four controls was slower than CM's, an additional control (female, age 38) whose speaking rate more nearly matched CM's was included in the speech production analysis. For purposes of comparison, data from a pilot study of PD and Alzheimer's disease (AD) subjects are included in the presentation of the results of the language evaluation. The subjects in the PD group ($n = 10$) were evaluated as having stage III PD according to the Hoehn–Yahr scale [29]. The subjects in the AD group ($n = 5$) had MMS scores ranging from 17 to 22, average 19.6.

Speech

Speech production. CM's relatives reported that her speech had changed after the event and friends had sometimes remarked that she now had a 'foreign accent'. We found her speech difficult to comprehend and attempted to quantify the abnormalities in her articulation. The production of human speech involves three physiologically distinct systems: the subglottal airway consisting of the lungs and the trachea, the larynx, and the supralaryngeal airway formed by the pharynx, mouth and nasal cavity. The subglottal system generally produces a steady alveolar air pressure throughout the course of a sentence-like unit during discourse. The muscles of the larynx position the vocal folds to produce quasiperiodic phonation (when vibrating) or non-periodic noise (when the air constriction makes the airflow turbulent). Finally, the supralaryngeal articulators (i.e. tongue, lips, jaws and soft palate) can modify the shape and length of the supralaryngeal vocal tract to generate noise sources (at constrictions) and the formant frequency patterns that specify the sounds of human speech [22].

The three aspects of CM's speech motor control that we investigated were timing, coordination between the larynx and supralaryngeal vocal tract, and control over articulators. Timing in CM's speech was assessed by measuring the length of vowels before voiced and before unvoiced consonants. Vowel length is a cue to the following consonant's voicing (i.e. the distinction between the 'voiced stops' /b/, /d/ and /g/, and their 'voiceless stop' counterparts /p/, /t/ and /k/, respectively [37]). Coordination between the larynx and supralaryngeal vocal tract was assessed by measuring the voice onset time (VOT), i.e. the time between the articulatory release of the closure of the vocal tract (seen in the waveform as a burst of noise) and the onset of phonation caused by laryngeal vibration (identified by a quasiperiodic waveform). VOT is the primary cue, word initially, for the voicing distinction of stop consonants [37]. For a given speaker and speaking rate, a difference of at least 20 msec is found between VOTs of segments with the same place of articulation that belong to different voicing categories. The two categories are known to approach and even overlap in PD patients, Broca's aphasics and

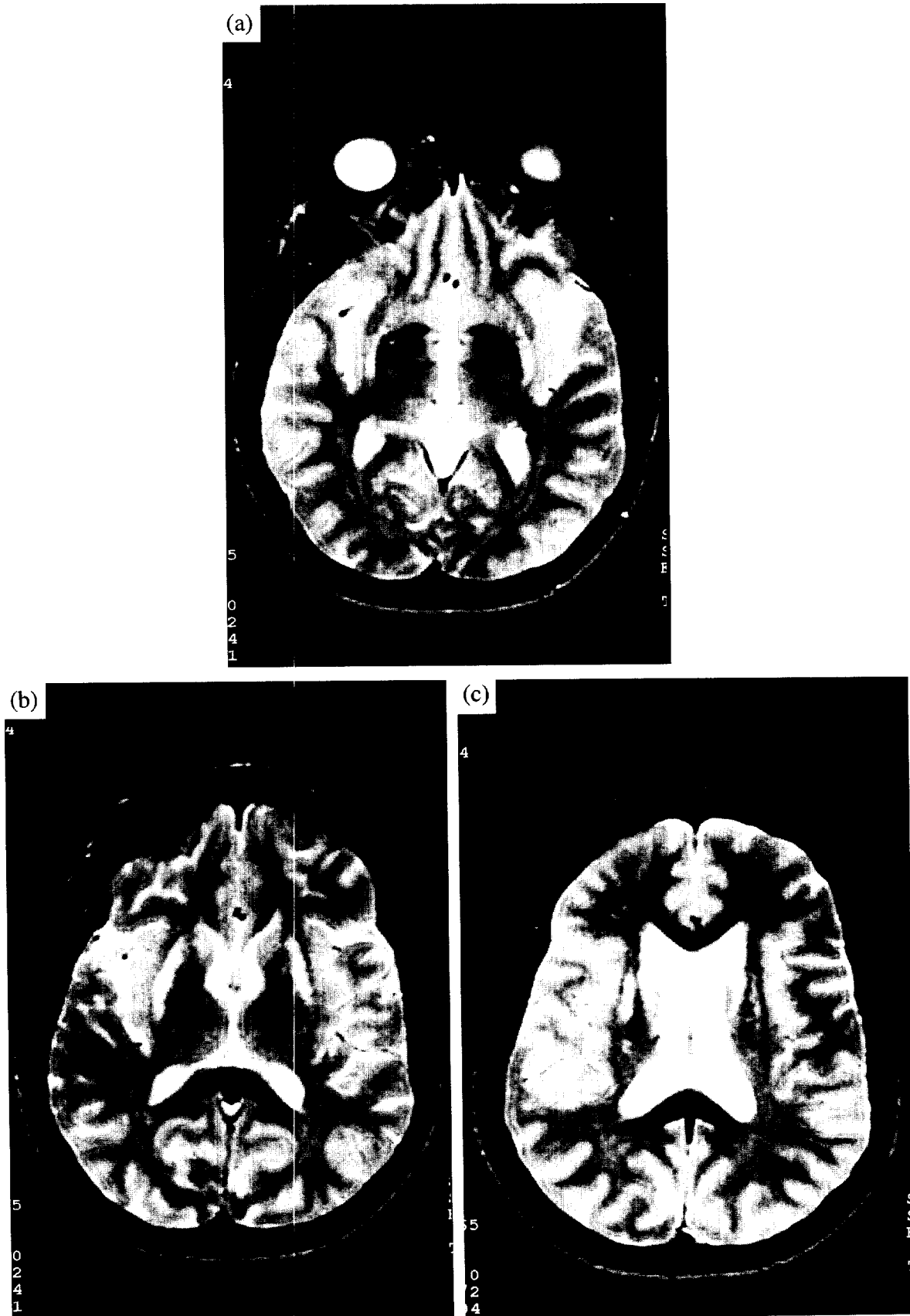


Fig. 1. MRI of subject CM showing marked bright signal intensity in the putamen and slight signal increase in the caudate.

healthy subjects under oxygen deprivation [11, 14, 35, 36]. Connor *et al.* [19], in a kinematic study of sequential multi-articulate movements in PD speech, found motor coordination disorders in the presence of normal durations. Likewise, the deficits in coordination of articulatory movements found with anterior aphasics (e.g., impaired VOT and nasal consonant production) have been attributed to impaired coordination of activity across articulators, rather than a temporal deficit *per se* (e.g., [15]). Finally, articulatory accuracy was assessed by spectral analysis using Fourier spectra and by visually examining the speech waveform for the acoustic events that occur in normal speech.

Method. A list of 30 monosyllabic words was read by CM three times during two separate testing sessions. Each word consisted of an initial stop consonant, a vowel and a final stop consonant. The stop consonants were balanced for voicing, place of articulation and phonetic context. Five normal controls, as described above, read the same list twice each under similar conditions.

The recorded speech was sampled at 20 kHz with 12-bit linear quantization and stored in computer readable format. Aided by a graphical waveform editor, we determined the lengths of the vowels, the lengths of the words and the VOT of the word-initial stop consonants. We marked regions of interest to be subjected to analysis of fundamental frequency of phonation and Fourier spectra.

Results. Vowels: Gross timing was relatively unimpaired, as temporal relations between vowels were appropriately preserved. Intrinsically longer vowels, such as /æ/ (as in 'bat'), were, on average, longer than intrinsically shorter vowels, such as /i/ (as in 'bit'). Vowels preceding unvoiced consonants were, on average, shorter than vowels preceding voiced consonants, as is the case in normal speech. Table 1 shows the lengths of CM's vowels /æ/ and /i/ before voiced and unvoiced final stop consonants separately for each session and the corresponding average values for the five normal controls.

The variability between subjects is due to differences in speech rate. The relative lengths between short and long vowels and between vowels preceding voiced and unvoiced consonants are similar for all subjects, including CM. The differences between vowel types and between voicing types of following consonants are statistically significant ($P < 0.0001$) for CM and for each of the five controls. Overall, the pattern of vowel lengths indicates that CM's timing of a single articulatory configuration is relatively unimpaired.

Spectral analysis did not reveal any gross abnormalities in CM's vowels. The analysis did show a dip in acoustic energy between 1 and 2 kHz (Fig. 2a), confirming the perceived nasal quality of CM's speech. While this nasality could indicate impaired control of the velum, which allows air to pass between the oral and nasal cavities, it is not necessarily an abnormal characteristic. Nasality is not distinctive in English vowels and some English speakers routinely nasalize their vowels. Thus, the nasal quality of CM's speech may have existed premorbidly. Figure 2b shows a normal control's non-nasalized production of the same vowel.

Voice onset timing: The VOT measurements indicate that CM generally maintains voicing categories. However, her VOT distributions, i.e. the shapes of the categories, were quite atypical. Figure 3 shows the VOT distributions of CM's productions from a single session (two repetitions of each of 30 words). This distribution is unlike those typically produced by normal speakers in this production context, i.e. when all VOTs are produced word-initially in monosyllabic words with balanced phonetic contexts spoken in isolation at a constant speaking rate during a single recording session. Figure 4 shows a representative distribution produced by normal control NA. The primary differences between CM's and the normal control's distribution are CM's widely dispersed VOT values and the small separation width between voiced and unvoiced categories. Overall, the separation width between voiced and unvoiced categories in CM's

Table 1. Mean vowel length (in msec) and its standard deviation (in msec, in parentheses) for CM (each recording session presented individually) and the five controls: the measurements were performed on tokens obtained using the same word list, read twice by each subject

| Vowel | Final stop | CM | | Normal controls | | | | |
|-------|------------|-------------|-------------|-----------------|-------------|-------------|-------------|-------------|
| | | 1 | 2 | DL | KK | NA | SN | JO |
| /æ/ | Voiced | 189 (35) | 246 (59) | 257 (34) | 372 (36) | 384 (45) | 401 (19) | 402 (69) |
| /æ/ | Voiceless | 126 (20) | 169 (19) | 180 (29) | 178 (34) | 238 (30) | 346 (41) | 243 (34) |
| /i/ | Voiced | 112 (21) | 161 (31) | 135 (10) | 213 (41) | 219 (21) | 318 (54) | 414 (36) |
| /i/ | Voiceless | 73 (23) | 91 (21) | 88 (10) | 102 (9) | 136 (18) | 268 (28) | 177 (45) |

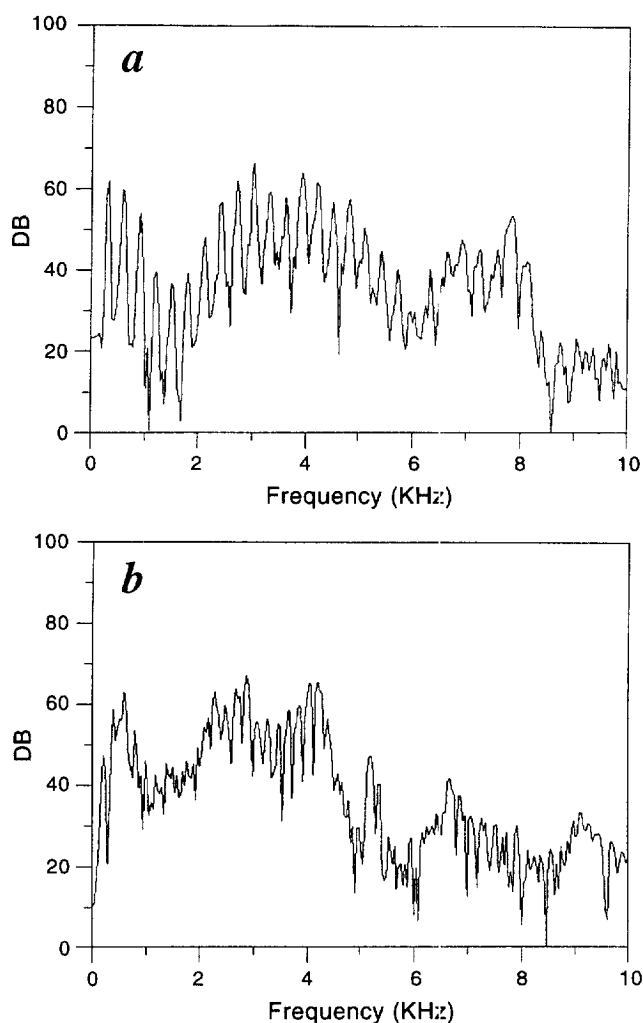


Fig. 2. CM's production (a) of the vowel in 'pick', showing a nasal dip in energy between 1 and 2 kHz, and control JO's production (b) of the same vowel in the same word.

productions was less than 20 msec in three of nine cases (3 places of articulations \times 3 list readings).

The prevoicing pattern in CM's VOT productions is also atypical. Although prevoicing is found in the productions of normal speakers, it tends to be concentrated around long (negative) times and does not affect the well-contained peak of the distribution between 0 and 20 msec. Figure 5 shows the VOT distributions of the one normal control that routinely prevoiced her consonants. With normal speakers, prevoicing typically occurs as a result of overly careful articulation, and is accompanied by a sharp peak at small positive VOTs and a wide separation between the voiced and unvoiced categories. In the case of CM, however, VOTs seem to be dispersed almost uniformly over a wide range.

Figure 6 shows the VOT distributions of CM's productions for the three places of articulation pooled across all three list readings. Her abnormal distribution is even more striking in comparison with the pooled VOT distributions from the five normal controls (Fig. 7). Even with the large amount of variability introduced by differ-

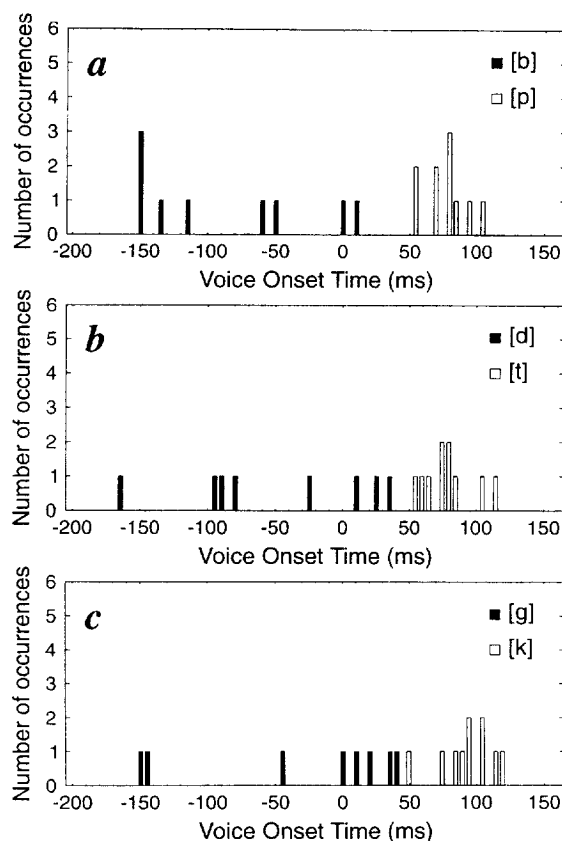


Fig. 3. VOT distributions from CM's productions (two list readings from a single session). The productions do not add up to 60 (twice the number of words in the list), because in many cases with no burst visible it was not possible to define and measure a VOT.

ences in speaker identity and in speaking rate (as demonstrated by the wide range of vowel durations reported in Table 1), this pooled distribution shows well separated categories, with a peak around optimal values. CM's VOT productions are similar to those of PD patients and Broca's aphasics, although her impairment is less severe. This degree of impairment exceeds that of high-altitude, oxygen-deprived climbers [35].

Articulatory precision: CM's speech showed prolonged voicing and extraneous reduced syllables between words, e.g., the three words 'cab', 'dig' and 'bag' were pronounced without stopping as 'cab-uh-dig-uh-bag' (Fig. 8). Vocalic activity instead of silence between words is never observed in normal speakers in the condition of this speech production task. The presence of such vocalizations in CM's speech suggests a lack of laryngeal and subglottal control with respect to supralaryngeal configurations.

The articulation of consonants was often imprecise. In particular, complete stop closures and the associated air pressure build-up and abrupt release were often absent, resulting in a gradual increase of noise amplitude (Fig. 9a) without a visible initial burst (Fig. 9b) or visible final release (Fig. 9c). Such consonants sounded breathy in the word-initial position and often like the corresponding

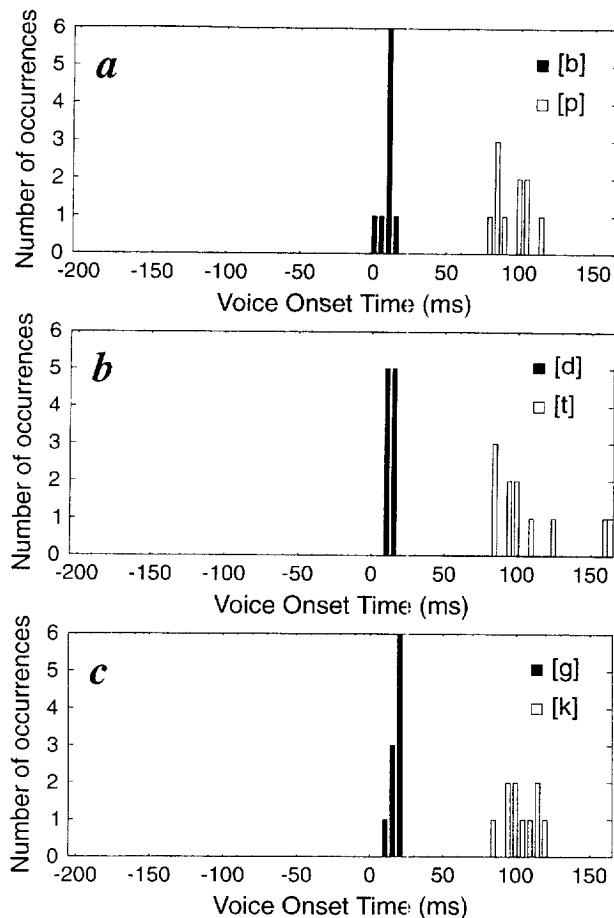


Fig. 4. VOT distributions typical for normal speakers (control NA).

fricative consonants in the word-final position. Other unusual characteristics of CM's productions include prolonged nasal vocalizations preceding partially realized word-final stop consonants (Fig. 10a), indicating poor control of the velum relative to other articulators, and the production of 'double bursts' (Fig. 10b), indicating poor control of phonation relative to articulation. Although such productions can be found in normal, and especially rapid, conversational speech, these characteristics are extremely rare in this speech production task. None of the normal control productions showed these characteristics.

In addition to the slow build-up and decay and the extensive prevoicing that were frequently observed, frequent transient amplitude changes over intervals of 50 msec or more marked CM's phonated segments in 20–30% of her productions (see example in Fig. 10c). These amplitude modulations were greater than any fluctuations produced by the normal controls, suggesting an impairment in coordinating alveolar pressure with respect to the larynx and the supralaryngeal articulators. The drops in amplitude were not correlated with drops in fundamental frequency, suggesting that control of the larynx was relatively unaffected.

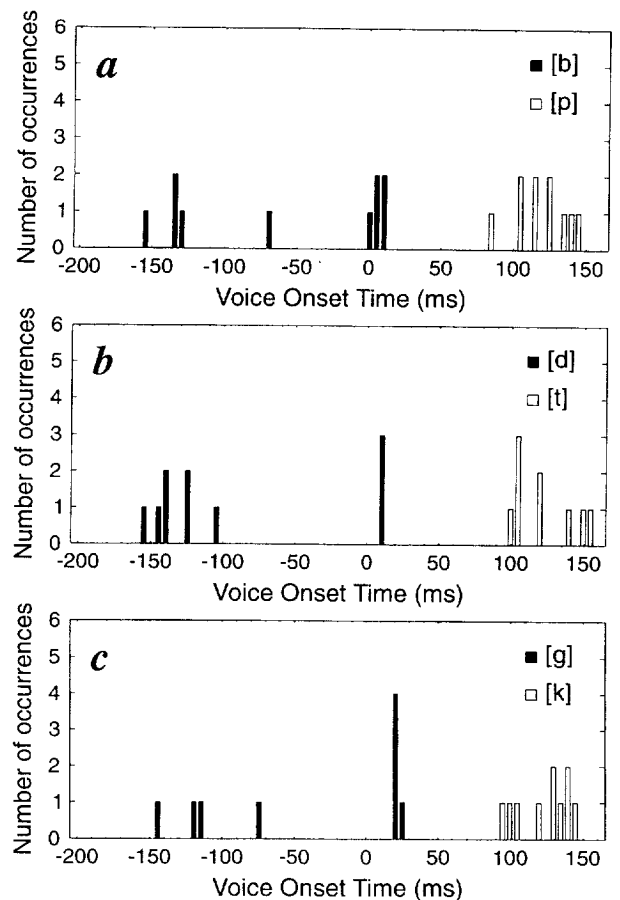


Fig. 5. VOT distributions of the one normal control who often prevoiced her voiced consonants (KK). Note the peak at small positive values and the wide separation between VOTs from the voiced and unvoiced categories.

Speech perception. CM's ability to correctly label the voiced consonant /b/ and the minimally distinct voiceless consonant /p/ in word-initial positions was tested in a categorization task using stimuli that varied along a VOT continuum (a fine temporal distinction). In English, VOT is the primary cue for the distinction between these two consonants. The temporal delay between burst and phonation needs to be determined in order to perform the categorization correctly. Inability to categorize the stimuli correctly could indicate a deficit in temporal processing.

Method. Fifteen synthesized 'bee'-'pee' syllables, with VOTs ranging from 10 to 100 msec in steps of 5 msec up to 50 msec and of 10 msec thereafter were kindly provided by Peter D. Eimas, and were presented to CM twice over loudspeakers in different random orders. CM indicated which consonant she perceived by pressing one of two labeled buttons.

Results. CM labeled all seven stimuli with VOT less than 40 msec /b/ and all seven stimuli with VOT greater than 40 msec /p/. The one stimulus with a VOT of exactly 40 msec was labeled /b/ once and /p/ once. CM's performance on this task was identical to normal performance as reported in the literature (e.g., [33]).

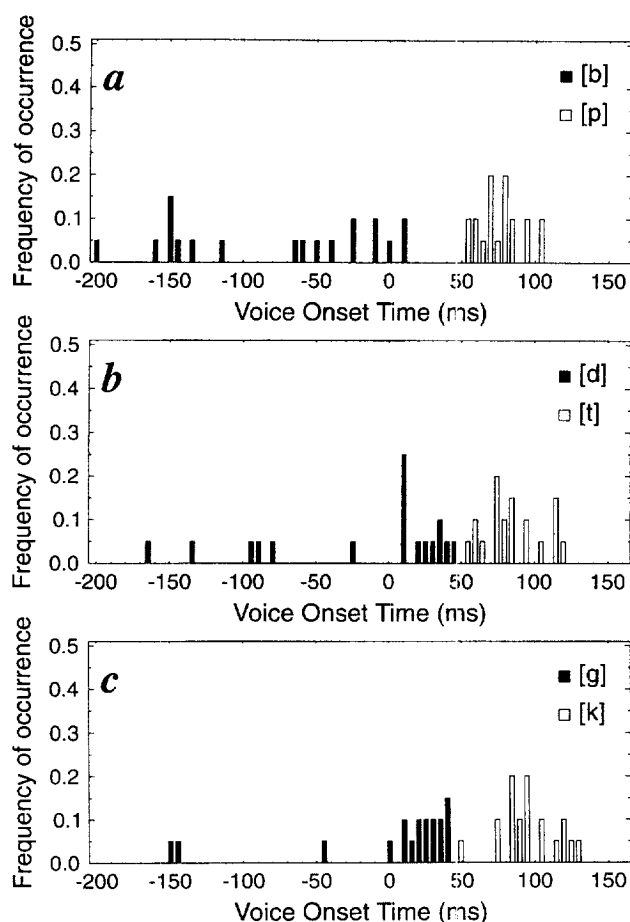


Fig. 6. CM's VOT distributions pooled from both sessions (three repetitions of the list total).

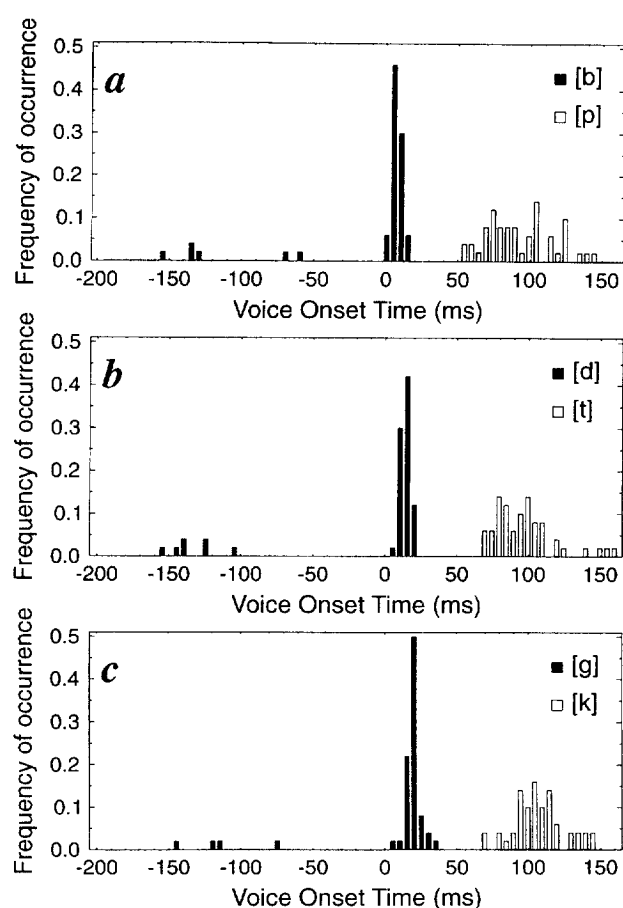


Fig. 7. VOT distributions from five controls plotted together.

Language evaluation

The Boston Diagnostic Aphasia Examination. The Boston Diagnostic Aphasia Examination (BDAE) is a widely used test which assesses conversational and expository speech, auditory comprehension, oral expression, and written language comprehension. CM had perfect scores on all subtests of the BDAE, with the exception of articulation. Her articulation was described by the examiner as "stiff, with occasional slurring", with a rating of 6.7 on a scale of 1 (poor) to 7 (perfect).

The Test of Meaning from Syntax. The Test of Meaning from Syntax (TMS) is a more rigorous assessment of the ability to use information conveyed by syntax in the comprehension of sentences. This test is a modified version of one used by Grossman *et al.* (e.g., [26, 27]) in their investigations of sentence comprehension in PD. Those investigators found a reliable pattern of errors on the task across PD patient groups and test sessions.

The test consists of 96 sentences, each of which is followed by a simple probe question. Three features of the target sentences are manipulated: syntactic complexity, semantic constraint, and voice correspondence between target and probe (see Table 2).

Syntactic complexity is varied by the use of three syn-

tactic structures. One-third of the sentences have a simple declarative single clause structure. One-third have a more complex structure, with a sentence final relative clause. The remaining one-third have the most complex structure, a center embedded relative clause. These final two types are of equal length and have the same amount of information, contrasting with the simple sentences.

Semantic constraint refers to the use of reversible or non-reversible nouns in a target sentence. Half of the sentences are semantically constrained in that the meaning of the verb is such that the subject and object nouns cannot switch places. In the non-constrained sentences, both nouns can be either the subject or the object of the verb. For example, *The cow licked the cup* is semantically constrained because part of the meaning of 'lick' is that only animate things can do it. In contrast, *The mouse followed the boat* is semantically non-constrained. Either a mouse or a boat may be the subject of the verb *follow*. In general, all of the sentences in the TMS are equally (im)plausible. However, the semantically constrained sentences can be interpreted based on lexical semantics, without recourse to syntactic processing. In contrast, the semantically non-constrained sentences can only be interpreted through syntactic processing.

Voice correspondence refers to the relationship between the target and probe sentences. For half the sentences,

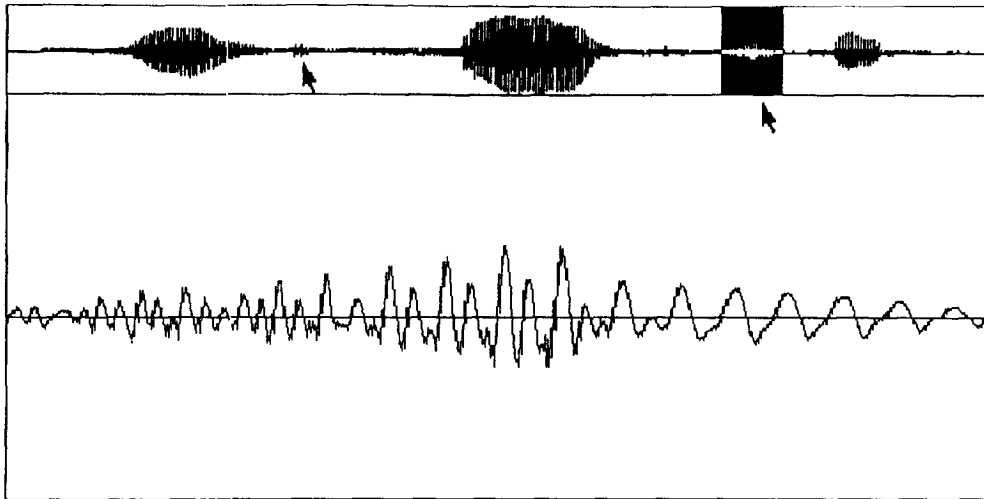


Fig. 8. Extraneous phonation between the words 'dig' and 'bag' (lower panel and shaded area in upper panel). The arrow on the left of the upper panel shows more extraneous vocalization preceding 'dig'.

the target and probe are in the same voice, either active or passive. The remaining half have differing voices in the target and probe sentences, either active target, passive probe or passive target, active probe.

The sentences were presented in random order, with each sentence read aloud by the experimenter. A practice session of eight sentences of increasing complexity preceded the administration of the task.

Results. Error rates for CM, the normal controls, and the AD and PD groups are presented in Table 3. The normal controls' 95% confidence interval was calculated for each condition. CM's errors fell outside this interval in each condition except center embedded, where she fell just inside. CM had an overall error rate of 14%. This contrasts with an average error rate of 2% for the normal control group. Rather, it falls between the error rates obtained in a pilot study with PD and AD subject groups. In that study, the overall PD error rate was 10% and the AD error rate was 21%.

CM did not show progressively higher error rates with increasing syntactic complexity. Her 16% error rate for simple sentences was in fact marginally greater than her 15% for subordinate sentences, and substantially greater than her 9% for center embedded sentences. This pattern of errors differs from the normal control, PD and AD subjects, all of whom had their lowest error rates for simple sentences. The normal control and PD groups both show the expected progressively increasing errors with increasing complexity. The AD group had fewest errors on simple sentences and roughly equally high error rates for the two complex structures. The center embedded condition is the one condition in which CM's error rate was not outside the normal controls' confidence interval, due to the fact that CM had relatively few errors while the controls had relatively many errors, bringing their error rates closer together.

CM made more errors on semantically non-constrained (17%) than on constrained (10%) sentences, as

did all three comparison groups. This result suggests that a significant component of the sentence comprehension impairment is due to syntactic processing. That is, when constraining lexical semantic information is available, CM is able to make use of it to determine the meaning of the sentence as a whole. The absence of such information results in greater difficulty in processing a sentence.

Voice mismatches between target and probe yielded high error rates (19%), more than double the 8% of voice matches. Of the three comparison groups, only the PD group showed an effect of this manipulation. It is not simply the case that CM has difficulty with one or the other voice. She made nearly equal numbers of errors in the Passive-Active case (20%) as in the Active-Passive case (17%), and equal numbers of errors in the matched Passive-Passive (8%) and Active-Active (8%).

Cognitive tasks

Formal neuropsychological testing performed at the hospital prior to our examination revealed a verbal IQ of 107, performance IQ of 84 and a full-scale IQ of 96 on the Wechsler Adult Intelligence Scale, Revised. Lezak [32] reviewed a series of studies demonstrating that verbal and performance scale discrepancies such as CM's are attributable to a wide variety of factors (including sociological), and as such, should not be used to draw inferences about neuropsychological status. CM's performance on the Stroop test was in the normal range on all three subtests (word reading: $T=50$; color naming: $T=50$; color-word naming: $T=58$). CM's performance on the Trails A test, which requires visual attention and graphomotor speed was normal (scaled score: 9, $T=55$), with completion of the task in 28 sec, reflecting normal psychomotor speed in response. Her performance on Trails B, which requires divided attention in alternating between two sets, was mildly impaired (scaled score: 7,

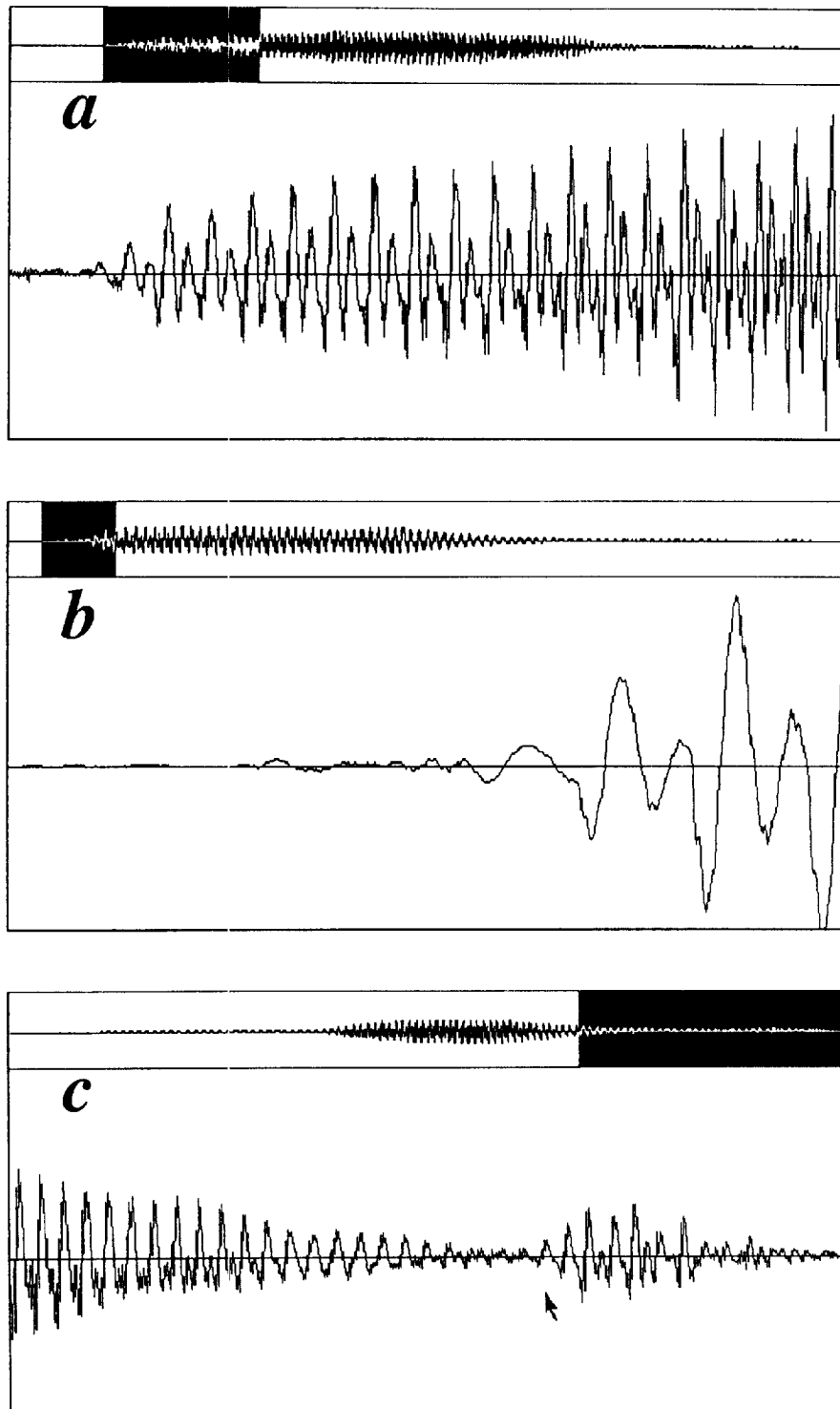


Fig. 9. The upper panel in each figure shows the waveform of the entire word and the shaded area corresponds to the portion displayed in the lower panel. (a) Gradual amplitude build-up in CM's production over more than 100 msec. (b) Lack of a closure-release burst in CM's production of a /d/ cor. sonant. (c) Gradual amplitude decay and incomplete closure with consequent lack of a release burst for a word-final /g/ consonant. This token sounded like ending with a voiced velar fricative.

$T=66$), as she completed this task in 105 sec and made three errors. Performance on the card sorting test (WCST) was also mildly impaired according to the available norms adjusted for age and education. On this test she obtained five categories (11–16 percentile) and pro-

duced 21 perseverative and 29 non-perseverative errors ($T=64$, $T=70$, respectively). Based on these standard neuropsychological tests, it appears that CM has intellectual functioning in the average range, but she has some mild frontal/executive deficits including mental flexibility

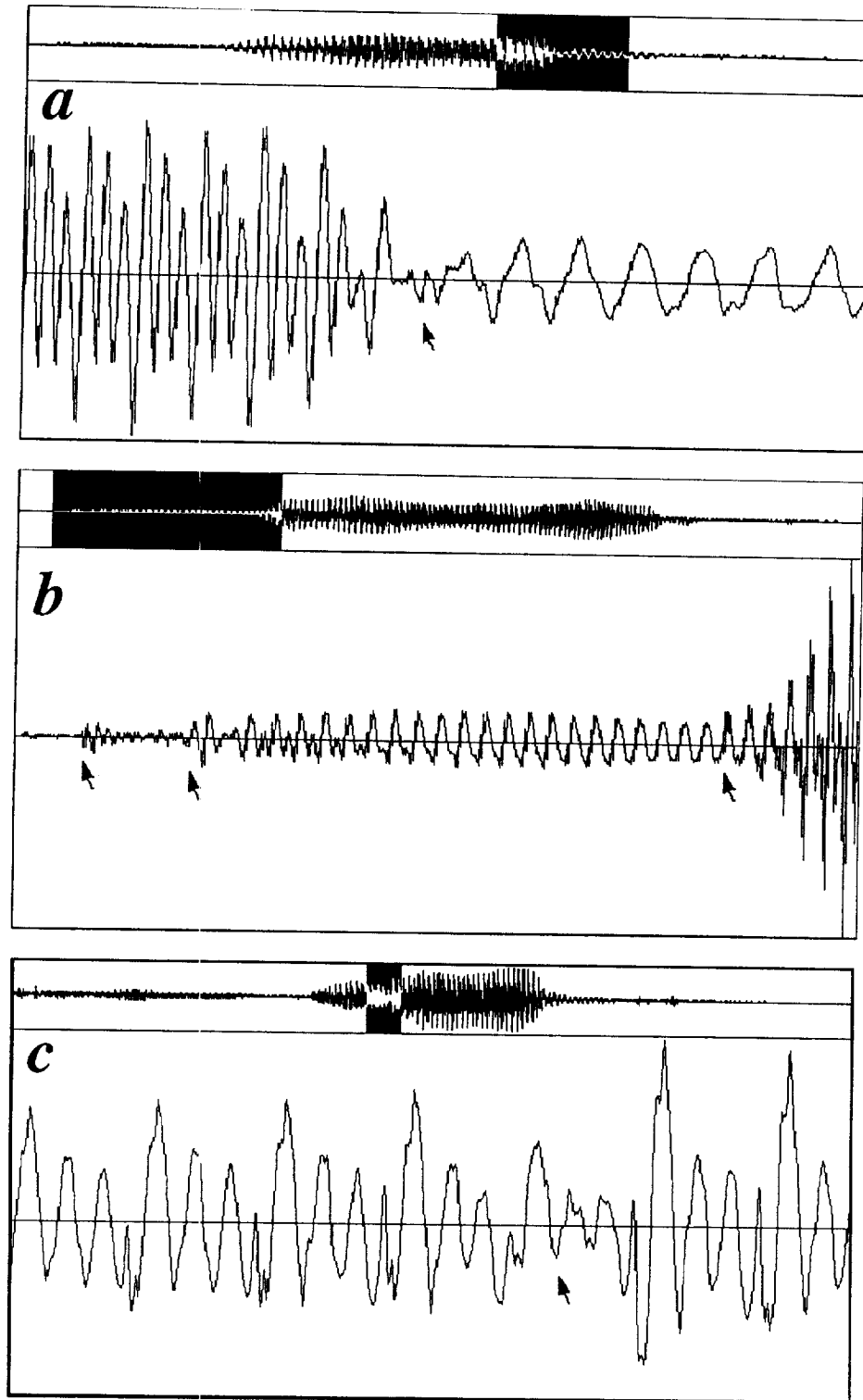


Fig. 10. (a) Abrupt vowel offset in CM's speech followed by nasal phonation and no release burst of the final stop consonant. (b) A double burst with abnormal prevoicing picture from CM's productions. From left to right, the first arrow points at an initial release burst followed by aspiration noise. Vocalization begins at the second arrow and carries through to the third arrow, where a second burst occurs and the vowel waveform first appears. (c) Amplitude fluctuations in CM's speech.

and capacity to shift task sets, with a tendency to perseverate in her response.

In addition to the neuropsychological examination, we administered three tasks to test cognitive processes that

may play a role in sentence comprehension in order to investigate whether CM's comprehension impairment could be attributed to specific non-language deficits. We used standard neuropsychological tasks which assess

Table 2. Example target sentences and probes from the Test of Meaning from Syntax, showing each condition of syntactic complexity, semantic constraint, and target-probe voice correspondence

| | Corresponding voice | | Non-corresponding voice | |
|-----------------|---------------------|---|-------------------------|---|
| Simple | | | | |
| Constrained | T: | The cow licked the cup. | T: | The cup was licked by the cow. |
| | P: | What did the licking? | P: | What did the licking. |
| Non-constrained | T: | The mouse was followed by the boat. | T: | The boat followed the mouse. |
| | P: | What was followed? | P: | What was followed? |
| Subordinate | | | | |
| Constrained | T: | The cup was licked by the cow that was thirsty. | T: | The cup was licked by the cow that was thirsty. |
| | P: | What was licked? | P: | What did the licking? |
| Non-constrained | T: | The boat followed the mouse that was gray. | T: | The mouse was followed by the boat that was gray. |
| | P: | What did the following? | P: | What did the following? |
| Center embedded | | | | |
| Constrained | T: | The cup that was licked by the cow was tasty. | T: | The cow that licked the cup was thirsty. |
| | P: | What was licked? | P: | What was licked? |
| Non-constrained | T: | The boat that followed the mouse was gray. | T: | The mouse that was followed by the boat was gray. |
| | P: | What did the following? | P: | What did the following? |

P, probe; T, target.

Table 3. Test of Meaning from Syntax errors (%): CM, Parkinson's patients, Alzheimer's patients and normal controls

| | CM | PD (n=10) | AD (n=5) | NC (n=4) |
|----------------------|----|--------------|-------------|-------------|
| Total errors | 14 | 10 | 21 | 2 |
| Syntactic complexity | | | | |
| Simple | 16 | 7 | 14 | 0 |
| Subordinate | 15 | 11 | 26 | 2 |
| Center embedded | 9 | 14 | 23 | 3 |
| Semantic constraint | | | | |
| Constrained | 10 | 8 | 18 | 1 |
| Non-constrained | 17 | 14 | 24 | 3 |
| Voice correspondence | | | | |
| Same | 8 | 6 | 20 | 2 |
| Different | 19 | 15 | 22 | 2 |

AD, Alzheimer's patients; NC, normal controls; PD, Parkinson's patients.

attention, expressive language and structured response initiation, and maintenance and shifting of cognitive sets.

Performance on the Digit Span task [50] provides a measure of attention, concentration and memory. The Digit Span task consists of two subtasks: Digits Forward and Digits Backwards. Both tests consist of seven pairs of random number sequences that the examiner reads aloud at the rate of one per second. The subject repeats the sequence in the order presented, in the case of Digits Forward, and in the reverse order, in the case of Digits Backwards. The score is calculated as the number of correct sequence lengths correctly repeated.

The Verbal Fluency test [50] provides a measure of structured response initiation and expressive language, and is thought to be a measure of frontal lobe function. The examiner asks the subject to say as many words as

she can think of that begin with the given letter of the alphabet, excluding proper nouns, numbers and the same word with a different suffix. The three letters used were V, I and P. The score is calculated as the total number of words produced.

The Odd Man Out task [50] tests a subject's ability to form and then shift abstract categories. The test consists of two packs of 10 cards, each of which has three figures, e.g., a large oval, a small oval and a large triangle. The task is to form a criterion (e.g., shape) and then pick the 'odd' figures for the first set of cards. After the initial sort, a new criterion must be developed (e.g., size) and the second set of cards is sorted. The subject is then asked to re-sort the first set, using the first criterion, and then to re-sort the second set, using the second criterion. Thus, the subject is required to switch criteria three times. The score is calculated as the total number of correct responses (100% = 40). The task was administered twice at two different test sessions.

Results. CM was normal on the Forward Digit Span (11), and slightly below normal on the Backwards Digit Span (5). The normal control averages were 10.5 (range 8-12) and 8.5 (range 6-10).

CM was normal on verbal fluency, generating a total of 43 words for the three letters. The normal control group produced an average of 46 (range 33-54).

CM was impaired on the Odd Man Out task. During the first administration of the task, she formed an initial criterion and correctly applied it. She was then unable to form a new criterion, perseverating her initial criterion for the remaining sorts, resulting in a score of 20. During a subsequent test session, CM again performed correctly on the first pass. However, although she insisted that she had formed a new criterion for the alternate sets, she sorted the cards with a 70% error rate, for a score of 26.

The normal control group average was 39.2 (range 38–40).

Discussion

This report describes CM 21 months after receiving extensive bilateral damage to the putamen with associated damage to the head of the caudate nucleus. CM's spontaneous language is apparently normal.† Her good performance on the BDAE demonstrates that she is not aphasic. Measures of attention, memory, lexical access and speech perception indicate no impairment in these areas. Her IQ indicates her current intellectual functioning to be in the average range. In contrast, CM showed deficits in three areas: speech production, sentence comprehension and cognitive set shifting.

In many respects, specifying the precise nature of the impairment in each of these areas is problematic. For example, CM's speech production is clearly abnormal; understanding her speech requires concentration and practice. Yet quantifying the perceived abnormality is not straightforward. The measures taken from CM's productions were sometimes indistinguishable from normal and other times were quite abnormal, suggesting that there is no particular component of speech production that she is not able to produce, at least sometimes. CM's performance on TMS is similarly inconsistent. In particular, the lack of an effect of syntactic complexity in the presence of a clear overall comprehension deficit is an unusual and puzzling finding. Finally, CM showed mixed performance on the cognitive tests. Her performance was normal on Stroop, Trails A, Digits Forward and Verbal Fluency. In contrast, her performance ranged from mildly to severely impaired on Digits Backward, Trails B, WCST and Odd Man Out.

A sequencing hypothesis

A review of a known role of the basal ganglia in motor functions points towards one possible interpretation of CM's deficits. Studies using a diverse set of methodologies have shown that subcortical structures, including the basal ganglia, are involved in behavioral sequencing [7, 8, 30, 51, 54, 55]. Activation of the putamen has been shown in humans during sequence learning or during retrieval of an overlearned sequence of keypresses [30]. PD has been reported to cause a deficit in motor sequencing [1, 12, 28, 38, 39, 47], characterized as a "deficit in the capacity to switch from one motor

program to another within an overall motor plan" [12] or as "defective cue production leading to impaired preparation for submovements performed in a sequence" [39]. Impaired performance of sequential structures of behavior resulted from carbachol and atropine injection in monkey caudate nucleus [56]. Aldridge *et al.* [3] have demonstrated that the coding of the 'syntax' of grooming in rodents occurs in the basal ganglia. Cooling of the caudate nucleus in cats resulted in a lost ability to perform the appropriate sequence leading to reinforcement [13]. Graybiel *et al.* [24] provide evidence that striatal neurons may perform the temporal binding necessary for sequencing.

Given the large body of data demonstrating that the basal ganglia, including the putamen and caudate, are involved in motor sequencing, we hypothesize that CM has a single basic impairment, a sequencing impairment, which underlies her apparently dissimilar deficits. In order for this hypothesis to be evaluated, it is necessary to develop a characterization of sequencing sufficiently general to be applied across the three domains of speech, syntax and cognition. In the motor domain, sequencing is commonly thought of as the execution of a behavioral sequence involving a series of actions and movements that must be selected and coordinated in accordance with a goal. Although in theory the timing component and the ordinal component of a behavioral sequence are dissociable processes, in practice it is extremely difficult to tease them apart, and it is unclear whether they are in fact functionally distinct. For present purposes, we will use sequencing in a general, inclusive sense to mean the ability to switch from one subtask to another at the appropriate time to achieve an intended goal. In other words, both timing and ordinality contribute to successful performance of a sequence. In order to apply this to cognitive domains, we intend 'subtasks' to refer both to physical and mental events.

According to this characterization, sequencing in speech production refers to the production of a specific articulatory gesture, or subtasks (e.g., vocal fold vibration), at the appropriate time with respect to another specific articulatory gesture (e.g., lip closure) in order to produce an intended goal, i.e. a specific phonetic segment. Applying our characterization to the cognitive domain is less straightforward. Again, however, the extensive knowledge accumulated about motor sequencing gives some pointers. In the motor domain, switching from one behavior to another is decomposed into at least two distinct processes: ending the first behavior and initiating the second. Both must be successfully accomplished in order to produce a sequence. This appears analogous to the cognitive process of set-shifting, i.e. changing from one mental set to another. In order to achieve this, it is necessary to first suppress a dominant or active set and then initiate or activate a different one. Failure to suppress an active set is perseveration. According to our characterization then, a perseverative set-shifting deficit can be viewed as a sequencing deficit, i.e. an inability to

† It is possible that more rigorous testing of CM's syntactic production would reveal systematic syntactic production deficits, as has been found with patient groups such as AD and Wernicke's aphasics, who both have superficially intact syntax production which upon closer examination is found to differ from normal in several respects (e.g., [9, 10]).

switch from one subtask (e.g., developing a criterion in Odd Man Out) to another (e.g., developing a different criterion) to achieve the task determined goal. More generally, a cognitive sequencing deficit might be realized as an inability to rapidly change cognitive strategies to suit the demands of a particular task. We propose that although CM is able to perform each of the individual actions comprising the tasks, be it generating an abstract rule or vibrating her vocal folds, her control over their sequencing into larger chains of behavior is compromised. The variability in her performance may result from imperfect *control* over the chaining of individual actions, rather than from loss of either the ability to sequence or the actions themselves. We next examine this hypothesis for each of the areas in which CM shows deficits.

Sequencing in speech

The overall pattern of speech production errors noted here is consistent with a breakdown in the subject's ability to properly sequence independent articulatory structures. Specifically, CM's pattern of VOT productions, with imperfectly separated and widely dispersed consonant categories, and her frequent inability to achieve complete constriction of stop production, with the associated abnormally gradual build-up and decay of aspiration or frication noise or vowel amplitude, are consistent with an impaired ability to rapidly switch from one articulatory target to the next. In the case of VOT, CM's impairment results in degraded control of timing the release of stop consonants with respect to the onset of voicing. Likewise, the production of voiced segments after word-final stops indicates degradation in controlling activity of the subglottal structures with respect to laryngeal and supralaryngeal structures.

CM's normal production of appropriate vowel lengths and normal VOT perception suggests that her VOT production impairment is not a timing impairment. CM showed normal control of linguistically significant timing in the context of steady-state vowels and intact perception of the VOT distinction. A deficit in generating behavioral sequences accounts for this pattern better than some more specifically linguistic deficit such as degraded phonemic representation or loss of knowledge of the voicing distinction. If the locus of the VOT impairment is outside of specifically linguistic knowledge, the dichotomy between production and perception is not surprising. Unlike producing an appropriate VOT, perceiving the difference between, e.g., 20 and 40 msec of aspiration noise does not require coordinating two actions.

The pattern of impairments observed in CM's speech production is comparable to motor coordination disorders observed with PD patients. Based on such observations, Connor *et al.* [19] suggested that "sequential movements for behaviors such as speech are inherently controlled with primary emphasis on relative movement

durations" (p. 1005). Again, the emphasis is on coordination between structures and not on timing *per se*.

Sequencing in language

CM showed moderate deficits in her ability to comprehend distinctions in meaning conveyed by syntax. Sentence comprehension is a complex multi-component process, involving, at the least, phonological decoding, lexical access, morphological processing, the extraction of structural information from syntactic facts such as word order, and the mapping of this information onto semantic or conceptual knowledge. A comprehension deficit can involve any one or more of these processes. The fact that CM's performance was better on semantically constrained than non-constrained sentences, together with her normal performance on the naming components of the BDAE, indicates that her lexical access and lexical semantics are unimpaired.† A surprising finding was a lack of effect for syntactic complexity. One explanation that has been put forward for complexity effects in patient populations is that they are in fact short-term verbal memory effects (see [17] for a review). That is, processing more complex structures such as the center embedded constructions in TMS involves holding the unresolved or uninterpreted subject noun phrase in memory while processing the embedded clause. The lack of a complexity effect may thus be due to CM's intact short-term verbal memory, as evidenced by her normal score on Digit Span Forwards. Rather, her overall comprehension deficit may be attributable to a more general process used in the comprehension of both simple and complex sentences.

The condition in which CM had the highest error rate was the voice mismatch condition. In light of our sequencing hypothesis, a possible interpretation of this result is that CM has difficulty switching comprehension strategies inside the single-goal event that the target-probe pair comprises. This 'syntactic perseveration' may involve the mechanisms that underlie syntactic priming (e.g., [16]), in which exposure to a syntactic structure increases the likelihood of subsequently producing that structure, regardless of content. So, for example, CM may be unable to rapidly suppress an activated structure, thereby preventing an alternative structure from becoming available to guide interpretation of the probe question. According to this interpretation, CM's relatively high error rate on simple sentences is not due to her inability to comprehend simple sentences. Instead, it may be attributable to the nature of the comprehension task, i.e. having to comprehend two sentences (the target and the probe) immediately after one another in order to

† Worth noting in this context is that CM is a prolific and accomplished punster, taking great pleasure in her plays on word meaning.

provide a correct answer. In fact, 80% of CM's errors on simple structures were voice mismatches. Thus, CM's overall deficit in sentence comprehension may reflect a non-linguistic deficit involving a compromised ability to rapidly switch from one cognitive strategy to the next.

Sequencing in cognition

CM's mixed performance on the cognitive tasks is also consistent with this interpretation. The tasks on which she was impaired have in common the necessity of switching from one set to another in response to an internally generated cue. For example, in *Odd Man Out*, CM was unable to develop and act on a new criterion following the successful application of her initial criterion. CM was also mildly impaired on WCST, Trails B and Digits Backwards, each of which requires an internal switching from one set to another.† In contrast, none of the tasks on which she showed normal performance require this same type of internal switching: *Trials A* requires visual attention and graphomotor speed, *Digit Forward* requires memory, *Verbal Fluency* tests expressive language and *Stroop*, although requiring shifting perceptual sets, differs from the other switching tasks in that the switch is in response to an externally provided cue. In sum, it is plausible that both CM's linguistic and cognitive deficits are attributable to a common processing impairment, specifically, poor control over cognitive sequencing.

Taken together, CM's neuropsychological test results clearly indicate a mild frontal lobe impairment. Although the imaging data show the basal ganglia to be the primary site of pathology, her frontal syndrome may in fact be attributable to her long history of schizophrenia and neuroleptic use. It is possible, then, that two distinct pathologies underlie CM's diverse set of deficits, frontal/cognitive and basal ganglia/motor. However, our point here is that it is not necessary to resort to a two-pathology explanation. Rather, we propose that our single-impairment sequencing hypothesis is a viable alternative explanation. In fact, our explanation provides a principled explanation for CM's mixed performance on frontal-type tasks.

CM's deficits are consistent with a growing body of evidence that the behavioral domains of cognition, language and speech production share neural mechanisms. For example, subcortical aphasia, PD and Huntington's disease may result in co-occurrence of deficits in these three domains [6, 26, 31, 34, 36, 40]. However, the precise role subcortical structures play in these activities has not been clear. The pattern of behavioral deficits observed

in CM following extensive damage to the putamen and caudate provides evidence for one role these structures might play, the regulation of sequencing across a number of modalities.

CM shows impaired performance in the production of speech, the comprehension of sentences, and the ability to generate and then switch between abstract concepts. The nature of her deficits in these diverse domains can be relatively well specified in terms of an impairment in a single process, sequencing. Given the traditional understanding of the role of the basal ganglia in motor control, additional evidence for our proposal of a global sequencing deficit may be provided by an investigation of her motor skills, which is currently in progress.

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† It is unclear why CM's performance on *Odd Man Out* was substantially worse than on these other tasks; it does not appear to be due simply to variability in CM's performance, as her responses were nearly identical on *Odd Man Out* across the two administrations of the task.

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