Prefrontal Cortex Guides Context-Appropriate Responding during Language Production

John G. Kerns,¹ Jonathan D. Cohen,^{2,3} V. Andrew Stenger,⁴ and Cameron S. Carter^{2,5,*} ¹Department of Psychological Sciences University of Missouri-Columbia Columbia, Missouri 65211 ²Department of Psychiatry University of Pittsburgh Pittsburgh, Pennsylvania 15213 ³Center for the Study of Mind, Brain, and Behavior Department of Psychology Princeton University Princeton, New Jersey 08544 ⁴Department of Radiology University of Pittsburgh Medical Center Pittsburgh, Pennsylvania 15213 ⁵Department of Psychology Department of Psychiatry University of California, Davis Sacramento, California 95817

Summary

Although language processing is thought to frequently require cognitive control, little is known about the cognitive and neural basis of the control of language. Here, we demonstrate that processing of context by the PFC plays an important role in the control of language comprehension and production. Using a missing letter paradigm and fMRI, we found that increased activation in the PFC (but not in posterior regions), while encoding and maintaining context information, predicted context-appropriate responses. Furthermore, greater selection demands increased activity during responding in the same regions engaged during the encoding and maintenance of context. Overall, as in other cognitive task domains, these results suggest that PFC context processing plays an important role in the control of language.

Introduction

Humans characteristically produce complex, goaldirected behavior. For example, language comprehension often involves remembering a previous passage in order to understand current text (Martin, 2003), and discourse requires the ordered selection and production of multiple speech acts in order to reach a particular conversational goal (Dell et al., 1997). Understanding the precise cognitive and neural mechanisms that underlie cognitive control (without resorting to a homunculus, that is, a source of unexplained intelligence in the brain) is an important goal of cognitive neuroscience. Prefrontal cortex (PFC) has been strongly associated with cognitive control (e.g., Leung et al., 2002; MacDonald et al., 2000; Pessoa et al., 2002). Thus, understanding the processing mechanisms associated with PFC would contribute to our understanding of human cognitive control.

The guided activation theory offers one account of the role of PFC in cognitive control and is consistent with findings from a broad range of computational modeling, animal, neuropsychological, and brain imaging studies (Cohen et al., 1996; Miller and Cohen, 2001). According to this model, patterns of activity in PFC represent taskcritical information (e.g., rules, goals, instructions, or intentions). These patterns of activity in PFC bias the flow of activity along pathways in other brain systems that are responsible for task execution, favoring the processing of task-relevant stimuli, associations, and responses. The influence of such top-down biasing, or control, is particularly important when task-appropriate behavior demands selection among competing responses or when task-relevant information must be maintained over delays. This theory has been preliminarilv applied to language processing, where it is assumed that the PFC represents and maintains information received earlier in discourse, as a constraint on interpretation and response to subsequent input (Cohen and Servan-Schreiber, 1992; Cohen et al., 1992, 1999). In this case, representations of prior discourse-what we refer to more generally as internal representations of context-perform the same role as rules, goals, etc., in other task domains, by serving to bias processing in favor of task-relevant behavior. In this work, a computational model based on the guided activation theory has been used to explain subjects' ability to access the weaker meaning of lexical ambiguities (e.g., "fenced enclosure" for the word PEN), when a preceding sentence provided context consistent with that meaning (e.g., "to keep her chickens the farmer needed a PEN"), as well as impairments of this ability in individuals with presumed disturbances of prefrontal function.

In the current research, we sought to more directly test predictions of the guided activation theory concerning the role of PFC in language processing by using fMRI to examine the relationship of PFC activity to context processing in a language task. Previous theory and behavioral research on both language comprehension (e.g., Just and Carpenter, 1992) and production (Dell et al., 1997; Levelt et al., 1999) suggest that cognitive control mechanisms play an important role in language processing (Gernsbacher and Kashak, 2003; Martin, 2003). For example, using PET, Nathaniel-James and Frith (2002) reported greater dorsolateral PFC activity in a sentence completion task in a low contextual constraint condition (i.e., when the rest of the sentence did not clearly predict a final missing word). They interpreted their findings as support for a role of dorsolateral PFC in selection, which some have argued should be distinguished from the role of PFC in active maintenance (e.g., Rowe et al., 2000). In contrast, the guided activation theory proposes that these are one and the same function: the representation and maintenance of context information in PFC is the mechanism by which selection occurs (Miller and Cohen, 2001). Thus, in a language task, context information encoded, represented, and



Figure 1. Correspondence between Timing of Trial Events and Timing of Staggered Acquisition Scanning that Allowed for Recording of Behavioral Responses

1.5 s of active scanning alternated with 1.5 s of silence (no scanning). Probe onset occurred 500 ms before a period of silence, allowing a 1.5 s window for participants to make a response to the probe.

maintained by the PFC during sentence processing provides a source of top-down control that biases processing in other structures responsible for language processing, favoring activation of the context-relevant meaning of words and phrases and the selection of corresponding responses. Thus, according to the guided activation theory, maintenance of context information and selection represent the operation of a single underlying mechanism. This makes the strong prediction that activity associated with the encoding and maintenance of context should colocalize to the same areas of PFC associated with selection. The findings from previous studies (such as the PET study described above) do not address this prediction, as they have not distinguished between activity during sentence processing (presumably associated with the encoding and maintenance of context information) and response selection. This was the primary goal of the present study.

To examine the neural mechanisms underlying cognitive control in language processing and to test the guided activation theory regarding the role of prefrontal cortex in this domain, we used the missing letter task (Figure 1). This task has been used in previous behavioral studies of the influence of context processing on language in normal subjects and people with schizophrenia (Cohen et al., 1999). In this task, participants are presented auditorily with a sentence. On some trials, this is followed by a true-false question about the content of the sentence, in order to insure that subjects encode its meaning. However, on most trials, the sentence is followed by presentation of a visual probe with one letter missing (e.g., w_ist). Participants are instructed to say out loud the first word they can think of that fits the probe letters (e.g., "wrist" or "waist"). Probes are used that have been shown in previous work to have at least two common completions (e.g., "wrist" or "waist"), the frequencies of which have been normed (Cohen et al., 1999).

The experiment involves two critical manipulations designed to probe the representation and maintenance of context information and its influence on language processing. First, some sentences provide context supporting a particular completion (context condition; e.g., "The dancer was fond of bracelets and light fabric" related to "wrist"; "The dancer was fond of wearing belts of light fabric" related to "waist"), while others do not provide context relevant to any completion (neutral condition; e.g., "The dancer was fond of wearing light fabric"). Thus, comparing completions generated in the context versus neutral conditions provides an index of the extent to which participants use the context provided by the sentence in responding to the probe. The second manipulation varies the delay between termination of the auditorily presented sentence and visual presentation of the probe (short delay, 1–3 s, versus long delay, 8–10 s). This manipulation, together with the context manipulation, permits an examination of those brain areas involved in the maintenance of context information.

In a previous behavioral validation study (Cohen et al., 1999), performance in the missing letter task was compared with performance in two other tasks that involve the representation and maintenance of context: the A-X CPT and a task-switching version of the Stroop task (in which a cue instructed participants to perform either color naming or word reading, followed by a delay and then the Stroop stimulus). We found that the number of context-appropriate responses in the missing letter task was strongly and significantly associated with measures of context processing in these other two tasks (e.g., the effect of prior letter in the AX-CPT and the effect of the instruction in the Stroop task). In contrast, missing letter performance was not associated with psychometrically matched (i.e., difficulty, reliability, and variance) measures that were insensitive to context effects. The results of this behavioral study strongly suggest that context-appropriate responses in the missing letter task reflect the capacity to represent and maintain context. An important difference between this task and many of the verbal production tasks used in previous imaging research (e.g., word generation [Petersen et al., 1988; Wise et al., 1991; Buckner et al., 1995a] and standard stem completion tasks [Buckner et al., 1995b; Desmond et al., 1998; Ojemann et al., 1998; Palmer et al., 2001]; these studies reported activation in the left ventrolateral PFC) is that the missing letter task permits a controlled and systematic examination of the effect of context processing on word production.

Using this design, we examined whether PFC is involved in the representation and maintenance of context in language processing. To do so, we analyzed brain activity during three different epochs of a trial: (1) encoding of the auditory context sentence, (2) maintenance of context (which occurred only on long delay trials), and (3) overt verbal responding to missing letter probes. According to the guided activation theory, PFC activity should predict the production of context-appropriate responses.

Results

Behavioral Results

Participants exhibited large and significant effects of context on language production at both short and long delays [F(1,15) = 52.73, p < .00001] (increase in context-appropriate completions in context versus neutral conditions: short = 16.5%, SD = 11.2; long = 20.5%, SD = 14.9). However, the effect of delay was not significant (p > .35). Thus, at both short and long delays, participants were influenced by the sentence context and made a significant number of context-appropriate verbal responses.



Figure 2. Dorsolateral PFC Activity

(A) Area of left dorsolateral PFC, Brodmann's area (BA) 46, activated during the maintenance of context information that predicted making context-appropriate verbal responses (Talaraich coordinates, -35, 36, 16).

(B) Percent signal change (compared to baseline fixation) for the dorsolateral PFC (BA 46) during short-delay trials.

(C) Percent signal change (compared to baseline fixation) for context-appropriate and context-inappropriate long-delay trials in left BA 46.

Summary of fMRI Results

As predicted by the guided activation theory and shown in Figure 2, greater activity was observed in two areas of PFC in association with context-appropriate responses rather than context-inappropriate responses (dorsolateral PFC, BA 9/46; and ventrolateral PFC, BA 45). Furthermore, as shown in Figure 2, activity in these areas followed a time course consistent with the representation and maintenance of context information: activation began during sentence encoding, remained elevated during maintenance (in long-delay trials), and resolved during the response phase. Interestingly, activity during the response phase was greater for context-inappropriate responses than context-appropriate responses. As discussed below, this finding may shed light on the role of PFC in selection and its relationship to context processing.

Areas of temporal cortex were also reliably associated with task performance but with a different profile of responses than PFC. As shown in Figure 3, at the short delay, a region of left superior temporal cortex was active during sentence encoding but not during the response. At the long delay, this area was again active during encoding, showed reduced activity during the



maintenance interval, and then reactivated during responding. As discussed below, this pattern of results is consistent with a role for temporal cortex in the encoding and retrieval of semantically relevant information but is not consistent with a role in the active maintenance of task-related information.

Relationship of fMRI Measurements to Task Performance

Activity during Encoding. PFC activity during sentence encoding predicted context-appropriate responding for both short- and long-delay trials (short-delay trials, left Brodmann's area [BA] 9 and right BA 9/46; for longdelay trials, as seen in Figure 2C [right], left BA 46 as well as left BA 45). In addition, as can be seen in Figure 3B, increased activity bilaterally in the superior temporal gyrus (BA 22) during encoding on short-delay trials predicted context-appropriate verbal responses. However, as seen in Figure 3C, activity in the temporal lobes did not predict context-appropriate verbal responses, nor did any other region outside of PFC.

Activity during the Delay Period. PFC activity (in both dorsolateral and ventrolateral areas) during the maintenance interval on long-delay trials also predicted context-appropriate verbal responses (see Figure 2C). In

Figure 3. Temporal Lobe Activity

(A) Area of temporal lobe (peak of activity in the superior temporal gyrus, BA 22/42, Talaraich coordinates, -51, -18, 7) active during sentence encoding on short-delay trials that predicted making context-appropriate verbal responses (the same region was activated bilaterally, but only the left region is shown in the figure). This same region exhibited both increased and decreased activity during different portions of the task.

(B) Percent signal change (compared to baseline fixation) for temporal regions during short-delay trials.

(C) Percent signal change (compared to baseline fixation) for temporal regions during longdelay trials.



Figure 4. Anterior Cingulate Activity

Area of anterior cingulate cortex (Talaraich coordinates, -1, 23, 35) more active during inappropriate than during appropriate responses.

contrast, increased temporal lobe activity during the maintenance interval did not predict context-appropriate responding, nor did any other region outside of PFC. However, decreased activity bilaterally in the superior temporal gyrus did predict context-appropriate responding.

Activity during Responding. As can be seen in Figures 2B and 2C, there was significantly increased activity in left dorsolateral PFC during the response epoch for context-inappropriate trials. This activity was in the same region that exhibited activity during encoding and maintenance on context-appropriate trials. A similar pattern of activity was observed in left PFC, BA 45. As will be discussed below, these findings are consistent with the prediction of the guided activation theory that the same regions of PFC are involved in maintenance and selection.

We also observed activity in a caudal portion of the anterior cingulate cortex (ACC; BA 32) that was significantly greater for context-inappropriate than for context-appropriate responses (Figure 4). This region has been consistently associated with response conflict (e.g., Buckner et al., 1995b; Kerns et al., 2004; Raichle et al., 1994), suggesting that response conflict was greater on context-inappropriate trials. This finding is consistent with the idea that a failure to encode or adequately maintain context information in PFC produced an underdetermined response to the probe.

In temporal cortex, context-appropriate responses were associated with decreased activity bilaterally in the superior temporal gyrus on short-delay trials (see Figure 3B) but increased activity in these same areas on long-delay trials (see Figure 3C). Thus, responseperiod activity in temporal regions was associated with context-appropriate responses but in opposite ways for short and long trials. We consider the meaning of these patterns of results with respect to the guided activation theory, and other theories of PFC function, in the discussion that follows.

Discussion

The primary finding of this study was that PFC activity during encoding and maintenance (in the long-delay condition) was associated with context-appropriate verbal responses, while this was not observed for any posterior structures. This finding is consistent with predictions of the guided activation theory, which asserts that a critical function of PFC is to represent and maintain context information that exerts control over behavior by biasing processing in posterior structures in favor of task-appropriate stimuli and responses. In the sections that follow, we consider how this hypothesis, and the additional findings of our study, relate to other theories concerning the role of PFC in cognitive control and language processing.

The Role of PFC in Selection, Maintenance, and the Processing of Context

Greater activity in the PFC during the encoding and maintenance of context anticipated making contextappropriate responses, as predicted by the guided activation theory. Alternatively, one might imagine that perhaps participants processed context perfectly well on context-inappropriate trials but that they just happen to maintain the wrong context. However, if this explanation was correct, then there should be no differences in brain activity between context-appropriate and -inappropriate trials (because context is being equally well maintained on both types of trials). Instead, the results are consistent with our prediction that PFC activity should be greater for context-appropriate trials than for context-inappropriate trials. The results are also consistent with previous behavioral research indicating that missing letter performance is associated with performance on other tasks that involve the representation and maintenance of context (Cohen et al., 1999) (moreover, performance on these other context processing tasks have also been associated with PFC activity [Barch et al., 2001; MacDonald et al., 2000]).

Another possible interpretation of our results is that perhaps on context-inappropriate trials, participants may not have read the sentence very deeply, thus leading to a failure to use the context to guide responding. Such an explanation is entirely consistent with our hypothesis that subjects failed to represent and maintain context on these trials, perhaps offering an explanation for how this came about. Thus, our finding of greater PFC activity for context-appropriate than for contextinappropriate trials suggests that when subjects fail to read and deeply encode the meaning of the sentence, they fail to generate an adequate representation of that meaning in PFC, and therefore fail to respond in a context-appropriate manner. In further support of this interpretation, the PFC regions we found to be active during encoding have consistently been found to be associated with deep encoding of semantic information in previous research (e.g., Wagner et al., 2001a). It is also worth noting that the specific areas of PFC identified in this study (left BA 46 and BA 45) have been implicated consistently in previous studies of verbal working memory (Chein et al., 2002). We have argued that maintenance of context represents a specific form of working memory (e.g., Cohen and Servan-Schreiber, 1992; Servan-Schreiber et al., 1996; O'Reilly et al., 1999), and thus it is reassuring that the areas that conform to our predictions regarding the maintenance of context in a language task are similar to those that have been identified in other verbal working memory tasks.

The same regions of PFC that were active during encoding and maintenance also showed increased activity during the response epoch for trials in which subjects made context-inappropriate responses. This finding is consistent with a role for PFC in response selection. As just discussed, our results suggest that when participants produced context-inappropriate responses, they did so because they failed to adequately represent and maintain context information given by the preceding sentence. As a consequence, when the probe was presented they were faced with competing response alternatives and little basis for deciding between these. The conflict produced by this competition served to recruit additional top-down control for selection (Botvinick et al., 2001). The greater PFC activity observed in this condition reflected the response to this demand.

This interpretation is supported by several of our findings. First, it is consistent with the observation of greater ACC activity (indicating greater conflict) during responding on context-inappropriate rather than contextappropriate trials. It is also supported by the results of an additional analysis that we conducted of PFC activity on neutral trials. This compared activity for probes associated with a single, prepotent response (low selection demand) to activity for probes with equiprobable responses (demanding selection; see Experimental Procedures, Image Acquisition and Analysis). The same regions of PFC (left BA 46 and 45) that showed an increase in activity during context-inappropriate responses were also significantly more active for probes associated with high versus low selection demands (a result similar to previous findings by Desmond et al. [1998]). Finally, these findings corroborate the results of previous studies suggesting that dorsolateral PFC is involved in the selection of verbal information (e.g., Nathaniel-James and Frith, 2002).

Some investigators have proposed that dorsolateral PFC activity is associated with selection but not active maintenance (Rowe et al., 2000). This runs counter to the guided activation theory, which asserts that maintenance and selection are two reflections of the same underlying mechanism and therefore should rely on the same areas of PFC. Our findings are consistent with this prediction. The area of dorsolateral PFC associated with demand for selection on context-inappropriate and neutral trials was the same as the one that showed increases in activity during encoding and maintenance and correlated with context-appropriate responses.

It could be argued, however, that our results do not determine whether PFC activity during the maintenance interval uniquely reflects the representation and maintenance of context information or other types of selection mechanisms. For example, Rowe et al. (2000) have argued that rehearsal may contribute to selection. However, previous research has not supported an association between verbal rehearsal and dorsolateral PFC (e.g., Chein and Fiez, 2001). Rather, rehearsal seems to engage more caudal areas of PFC (such as Broca's Area, BA 44) and posterior cortical structures (e.g., parietal cortex [Smith and Jonides, 1999]). None of these were observed to be active during the maintenance interval in our study. (Interestingly, this suggests that participants did not retain information about the previous sentence in phonological form [i.e., using rehearsal] but rather in a semantic form that served to bias subsequent responses in accord with the context of the sentence, as our hypothesis suggests.) It is possible that some other mechanism of selection could have been operating during the delay (e.g., controlled retrieval, as has been proposed by Wagner et al. [2001a]). However, the precise nature of such mechanisms has yet to be specified. In contrast, the guided activation theory proposes an explicit mechanism for selection: the representation and active maintenance of context information in PFC that serves to bias processing in other structures in favor of task-relevant stimuli and responses. This mechanism has been implemented in a computational model of the missing letter task (Cohen and Servan-Schreiber, 1992) that explains performance in this task in a manner that is consistent with many of the known properties of PFC (Miller and Cohen, 2001).

Functions of Dorsolateral and Ventrolateral PFC

Our findings suggest that regions within both dorsolateral (BA 9/46) and ventrolateral (BA 45) PFC contribute to the representation and maintenance of context in our task, as the patterns of response and their relationship to behavior was very similar in these two areas. In contrast, other areas of the PFC, such as left ventrolateral BA 44 (which was active during maintenance and selection for all trials, as reported in the Experimental Procedures, Image Acquisition and Analysis), did not appear to be specifically associated with making context-appropriate responses. Both dorsolateral BA 9/46 and ventrolateral BA 45 have previously been implicated in the control of behavior, and in particular response selection in language tasks (e.g., Gabrieli et al., 1998; Desmond et al., 1998; Hashimoto and Sakai, 2002; Thompson-Schill et al., 1999; Wagner et al., 2001b). This raises the intriguing question of what functional differences, if any, there may be between these two areas.

One possibility is that they might differ in the level of semantic information that they represent, with ventrolateral PFC representing simpler or more specific information (e.g., single words or simple concepts) and dorsolateral PFC supporting more abstract information (e.g., discourse or sentence level representations). Consistent with this view, activation of ventrolateral PFC has frequently been observed in single word processing tasks (e.g., Gabrieli et al., 1998; Petersen et al., 1988; Wagner et al., 2001a). In contrast, dorsolateral PFC activity has less frequently been observed in single word studies and, in at least one case where it has, the task involved a more abstract level of semantic processing (elaborative encoding coupled with a maintenance component [Wagner et al., 2001b]). In this study, activity of a region in middle frontal gyrus was observed that is quite similar to the region of dorsolateral PFC found in the current study. Conversely, in tasks involving sentence processing, dorsolateral PFC activity has been observed more frequently than VLPFC. For example, Hashimoto and Sakai (2002) found dorsolateral PFC activity during whole sentence but not single word semantic processing. Similar explanations for apparent differences in the function of ventrolateral and dorsolateral PFC-in terms of the abstractness of representations in these areas—have been made previously (e.g., Koechlin et al., 2003; O'Reilly et al., 2002).

In the current study, the representation and maintenance of discourse information (i.e., pertaining to the meaning of the entire sentence) could not be distinguished from memory for individual words or concepts. Therefore, unfortunately, our findings do not directly address the hypothesis that activity in dorsolateral and ventrolateral PFC can be distinguished based on the level of semantic representations that they support. Furthermore, it should be noted that this hypothesis does not provide an obvious or straightforward explanation of some results that have been reported in the literature. For example, Desmond et al. (1998) reported greater DLPFC activity in a simple stem completion task (involving single words) when the stem was associated with many versus fewer possible completions. It is not immediately clear whether such conditions demand more abstract PFC representations for selection or how they compare to the demands of the task used by Thompson-Schill et al. (1999), in which multiple possible completions was associated with greater activity in ventrolateral rather than dorsolateral PFC. These findings indicate that it will be important, in future research, to specifically manipulate the type of information that participants represent and use for selection when required to choose between multiple responses, in order to better understand (and more carefully test hypotheses regarding) the differential contributions of VLPFC and DLPFC to language processing.

Temporal Lobe Findings

In contrast to PFC, activity in superior temporal cortex showed a more complex and less easily interpreted time course and relationship to behavior. On the one hand, activity during encoding in the short-delay condition and during responding in the long-delay condition predicted context-appropriate responding. This suggests that temporal lobe activity plays a role in mediating the effects of context on verbal responding. According to the guided activation theory, this occurs under the influence of topdown bias signals from PFC. Consistent with this hypothesis, we observed that temporal lobe activity was reduced during the maintenance interval in the longdelay condition, suggesting that context information could not be maintained in temporal areas and that this relies on PFC. On the other hand, however, temporal lobe activity exhibited a number of other challenging features

First, although activity was reduced in temporal areas during the long-delay condition, the degree of activity was nevertheless significantly associated with contextappropriate responding. This could reflect a subtle but sustained influence of representations maintained in PFC on temporal cortex during the delay. Alternatively, it could reflect delay period activity within temporal cortex that was more focused and therefore appeared as an overall decrease in activity when averaged at the spatial scale of fMRI measurements. Although possible, this explanation does not seem entirely consistent with the increased activity observed in temporal regions during responding in the long-delay condition. If reduced activity reflects the active maintenance of more focused activity, then why did activity *increase* at the time of response? This remains a question for future research.

Another puzzling feature of temporal lobe activity was the increase during responding in the long-delay condition but decrease during responding in the short-delay condition. As noted above, the increased activity in the long-delay condition was associated with contextappropriate responding and could thus reflect reactivation of verbal representations required for a contextappropriate response. Why, then, should activity be decreased during responding at the short delay?

One possibility is that this reflects a form of primingrelated suppression of activity. Decreased activity associated with primed responses is consistent with previous brain imaging studies of priming (e.g., Karni et al., 1995; Rossell et al., 2003; Thompson-Schill et al., 1999) and may indicate repetition-induced suppression of neural activity (Wiggs and Martin, 1998) or a faster peak latency (without decrease in firing rates) of the BOLD response (Henson and Rugg, 2003). Thus, it is possible that activation of context-relevant verbal representations during encoding may have served to prime areas involved in responding. This priming may have suppressed activity during the actual response, which followed shortly after encoding in the short-delay condition. On this view, responding in the long-delay condition occurred well enough after encoding to allow this suppressive effect to resolve. It should be noted that priming effects can occur even over long delays (e.g., up to 3 days [van Turrennout et al., 2000]). However, it is not known whether such long-term priming effects rely on the same neural mechanisms as shorter lasting ones, and therefore it is not clear whether they too are associated with suppression of activity. In any case, increased temporal activity on long-delay trials suggests that some mechanism, other than priming, may have contributed to making a response. One possibility is the influence from context processing by the PFC. Assuming that temporal cortex did not actively retain context information during the delay, these areas might have been reactivated by PFC areas at the time of response.

Engagement of Episodic Memory

We have interpreted our findings primarily in terms of short-term or "active" memory mechanisms (in PFC) and their interaction with long-term semantic memory (in temporal cortex). However, it is possible that episodic memory also plays a role in our task, encoding sentence constituents and retrieving these at the time of response. Indeed, as we and others have suggested (Cohen et al., 1996; Gabrieli et al., 1998; Barch et al., 2002), it is likely that episodic memory contributes to the reinstatement of representations in PFC when they are situationally appropriate—for example, in recruiting PFC during responding on context-inappropriate and neutral trials. Conversely, representations in PFC may serve to guide the encoding and retrieval of task-relevant information in episodic memory. Although this study did not focus on such interactions and our results do not illuminate them, an interesting direction for future research would be to contrast activation in the current design with activation involving much longer delays (e.g., 30 min), to more directly contrast the contributions of active and episodic memory mechanisms to language performance.

Language Processing

The results of this study provide strong evidence that the control functions of PFC extend to the processing of language. Current models of language processing suggest that responses to the missing letter probes in our task could have been influenced by several levels of processing, including interactions between orthography and phonology (e.g., Martin, 2003) as well as semantic processes involved in language comprehension and production (Martin, 2003). Furthermore, as proposed above, activation of ventrolateral and dorsolateral regions of PFC may reflect the engagement of different levels of semantic processing. Our results indicate that language comprehension, which demands that the listener (or reader) be sensitive to information over an extended period of time, may rely on the representation and maintenance of context information in PFC. Correspondingly, our findings suggest that this function of PFC may serve to guide language production in accord with the contextual constraints.

Previous studies that have identified dorsolateral PFC activity associated with language processing have done so using a variety of tasks involving disparate processing demands (e.g., BA 9, whole sentence processing versus syntactic judgments [Hashimoto and Sakai, 2002]; BA 9/46, delayed interpretation of earlier processed information [Newman et al., 2002]; and BA 46, high selection demands [Nathaniel-James and Frith, 2002]). We propose that the representation and maintenance of context information is a common requirement in these tasks that accounts for the mutual finding of PFC activation.

The current research may also have important implications for understanding disorders of speech. It has been consistently reported that individuals with PFC damage have deficits in language comprehension and production (Ferstl et al., 2002). For example, an individual with a tumor impinging on BA 45 exhibited a dynamic aphasia, with difficulty speaking when the speech context was not constrained (Robinson et al., 1998). This was interpreted in terms of an impairment of context processing in language production. Similarly, disorganized speech in schizophrenia has been associated with poor performance on tasks that rely on prefrontal cortex (e.g., Cohen et al., 1992; Kerns and Berenbaum, 2002) and interpreted in terms of a disturbance in the processing of context (Cohen and Servan-Schreiber, 1992). The present findings provide evidence for the engagement of PFC in the representation and maintenance of context in normal language processing. This provides strong convergent support for the hypothesis that language deficits associated with disturbances of PFC can be explained in terms of impairment in the processing of context.

Conclusions

In a language-processing task, PFC activity during encoding and maintenance predicted making contextappropriate responses. Moreover, the same regions of the PFC were activated by increased selection demands. These results are consistent with the guided activation theory of PFC function, according to which a primary function of PFC is the representation and maintenance of context information used to guide processing in other brain areas, leading to the selection of context-appropriate responses. These results suggest that PFC plays a similar role in the control of language as it does in other domains of behavior.

Experimental Procedures

Participants and Task

Participants were 16 (10 female) right-handed adults (ages between 21 and 34, mean = 25.2) who participated after giving informed consent. They were scanned while performing the missing letter task, which has been used in previous behavioral studies of context processing and language in normal subjects and patients with schizophrenia (Figure 1). At the beginning of each trial, participants heard a context sentence that was presented through headphones (e.g., "The dancer was fond of bracelets and light fabric"). Then, after either a short delay (between 1 and 3 s) or after a long delay (between 8 and 10 s; the delay period was variable depending on the length of the sentence, which lasted between 1.5 and 3.5 s). participants saw a string of letters that could make up a word, except that one letter was missing (e.g., w ist). Participants were instructed to say out loud the first word they could think of that fit the probe letters (e.g., "wrist" or "waist"). Thus, the auditory sentence acted as verbal context that could influence participants' responses to the probe. There were two different trial conditions used: context and neutral. On context condition trials, context provided by the sentence was related to a possible word completion (e.g., "The dancer was fond of wearing belts of light fabric" is related to the word "waist"). On neutral condition trials, the meaning of the sentence was unrelated to the possible completions of the probe. These materials had been pilot tested and used extensively in previous research to determine the response frequencies for the context and neutral conditions (for the actual materials used, see Supplemental Data at http://www.neuron.org/cgi/content/full/43/2/283/ DC1). The dependent variable was the percentage increase in context-appropriate completions in the context versus neutral conditions. Participants successfully made a coherent verbal response to the probe on 99% of trials. Although not directly relevant to the current study, for completeness we note that there were two types of context-related trials: dominant (when context provided by the sentence was related to the dominant response completion. e.g., "The dancer was fond of wearing bracelets and light fabric" is related to the dominant completion "wrist") and subordinate (when context provided by the sentence was related to the less common response completion). On neutral trials, participants made the dominant response about 65% of the time. On dominant trials, participants made the dominant response about 85% of the time. On subordinate trials, participants made the dominant response about 45% of the time. These results are consistent with the results of previous studies using these materials (Cohen et al., 1999).

Trials occurred in miniblocks of either short or long delay. There were seven trials within each miniblock: four context, two neutral, and one catch trial to insure that participants were encoding the meaning of the context sentences. On catch trials, after hearing the sentence, 8 s later participants would see a sentence (e.g., "He left the door open") and participants needed to decide if the sentence. Thus, the catch trials insured that participants were encoding and maintaining the content of the auditory context sentences. Short-and long-delay miniblocks varied throughout the task. There were four larger blocks of trials consisting of four miniblocks and three 30 s periods of baseline fixation. A brief rest period occurred after each block.

Image Acquisition and Analysis

A 3.0 T scanner (General Electric Company) with a standard head coil acquired all images. Three gradient echo functional scouts were used to localize the anterior commissure and the posterior commissure. T2* spiral scans (3.2 mm³ voxels, repetition time = 1.5 s of active scanning preceded by 1.5 s of silent scanning, echo time = 18 ms, flip angle = 70°) acquired 28 axial slices. Incremental (scan to scan) and total movement were corrected using AIR (Woods et al., 1998). Structural images were crossregistered to a reference brain by minimizing signal intensity differences with 12 parameter AIR, after which images were set to a standard mean intensity and smoothed (8 mm FWHM).

Scanner noise can make it difficult to record verbal responses during scanning. In the current research, we were able to collect verbal responses by using a staggered pulse sequence in which every 1.5 s of scanning alternated with 1.5 s of silence. Probe onset occurred 500 milliseconds before a period of silence (and we knew from pilot testing that the fastest response latencies in this task would be around 500 milliseconds or greater). Hence, this created a 1.5 s verbal response window in which participants could speak and be clearly heard (Figure 1).

Imaging data were analyzed with a random effects single-subjects general linear model, using AFNI (Cox, 1996) and NIS (Clinical Cognitive Neuroscience Laboratory, University of Pittsburgh) software. We were particularly interested in examining what brain regions were associated with making context-appropriate responses. Thus, in our analysis, we included five covariates that were based only on those trials in which participants selected a context-appropriate verbal response (i.e., when the meaning of the sentence matched the meaning of the verbal response): (1) short-delay sentence encoding, (2) long-delay sentence encoding, (3) long-delay sentence maintenance, (4) short-delay missing letter probe presentation/verbal response, and (5) long-delay missing letter probe presentation/ verbal response (we included both short-delay and long-delay response covariates after it became obvious early on in data analysis that the results for these two conditions were very different).

In addition to the covariates for trials in which a context-appropriate response was given, there were five additional covariates for all trials: (1) auditory context sentence presentation, (2) missing letter visual probe presentation/verbal response, (3) long-delay sentence encoding (we included this covariate to be conservative in case there was unique encoding activity in order to maintain information during the delay; results were even more significant if it was removed), (4) long-delay sentence maintenance, and (5) visual truefalse visual sentence presentation on catch trials. The results for the basic all trial covariates were as expected. For example, auditory context sentence presentation was associated with activation of bilateral temporal regions (BA 22/42) and of left inferior frontal gyrus (BA 45), regions associated in previous research with language and semantic processing (Michael et al., 2001; Gernsbacher and Kashak, 2003; Palmer et al., 2001). Missing letter visual probe presentation and making a verbal response was associated with activity in the supplementary motor area (BA 8), anterior cingulate cortex (BA 32), the left dorsolateral PFC (BA 46), bilateral premotor areas (BA 6), and the left inferior PFC (BA 44 and BA 45/47), all areas associated in previous research with making and selecting motor responses and, for the left inferior (BA 44) frontal area, specifically with making verbal responses, and in bilateral regions in the occipital lobe (BA 17/ 18/19), regions associated with visual processing (e.g., Gernsbacher and Kashak, 2003; Nathaniel-James and Frith, 2002; Palmer et al., 2001; Thompson-Schill et al., 1999). Long-delay sentence encoding (left BA 9, left BA 44/6, and right BA 10/46) and long-delay sentence maintenance (left BA 9, left BA 46, and left BA 44) were both associated with activity in the PFC.

The above analyses provide information regarding activity associated with particular trial types (e.g., general maintenance period activity) as well as providing activity regarding unique associations with context-appropriate trials. In order to directly compare activity for context-appropriate, context-inappropriate, and neutral trials, we also examined the results by directly comparing context-appropriate and context-inappropriate trial types; the results were identical (this analysis included the following regressors: neutral short encoding, context-appropriate short encoding, context-inappropriate short encoding, neutral short response, context-appropriate short response, context-inappropriate short response, neutral long encoding, context-appropriate long encoding, context-inappropriate long maintenance, context-appropriate long maintenance, context-inappropriate long maintenance, neutral long response, context-appropriate long response, and context-inappropriate long response, and context-inappropriate long response). Note that there were no differences between either word length or duration of the sentences for context-appropriate trials (p > .50).

To display activation in the task (in Figures 2 through 4), we calculated percent signal change difference from baseline (the average of the fifth through the tenth baseline fixation scans; note that the fifth baseline fixation scan begins at least 12 s after the last trial event). We then calculated average time series data for encoding by summing the second and third scans of each trial (note that averaging the second and third scans essentially captures the peak of the bold response for encoding, or roughly from 3 s to 9 s). We calculated short-delay responding by summing the fourth and fifth scans of each short-delay trial. We calculated long-delay maintenance by summing the fourth and fifth scans of every long-delay trial. We calculated long-delay response activity by summing the sixth and seventh scans of every long-delay trial. We do not argue that this averaging of scans perfectly characterizes activity specific to each of these particular trial events. Nonetheless, we do think that it captures as adequately as possible the raw peak level of activity associated with each particular trial event.

To examine selection demands on neutral trials, we divided probes by whether they had a relatively high or low prepotent response frequency. Low selection demand probes were defined as those having a single response with a frequency of greater than 80%; high selection probes were those with no response exceeding a frequency of 70%.

Acknowledgments

We thank Gary Dell for his helpful comments on this research and the members of the Clinical Cognitive Neuroscience Laboratory and the staff at the Department of Radiology at the University of Pittsburgh for their assistance. This research was supported by NIMH (C.S.C.).

Received: July 21, 2003 Revised: May 3, 2004 Accepted: June 23, 2004 Published: July 21, 2004

References

Barch, D.M., Carter, C.S., Braver, T.S., Sabb, F.W., MacDonald, A.W., III, Noll, D.C., and Cohen, J.D. (2001). Selective deficits in prefrontal cortex function in medication-naïve patients with schizophrenia. Arch. Gen. Psychiatry 58, 280–288.

Barch, D.M., Csernansky, J.G., Conturo, T., and Snyder, A.Z. (2002). Working and long-term memory deficits in schizophrenia: is there a common prefrontal mechanism? J. Abnorm. Psychol. 111, 478–494.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., and Cohen, J.D. (2001). Conflict monitoring and cognitive control. Psychol. Rev. *108*, 624–652.

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R., and Raichle, M.E. (1995a). Functional anatomical studies of explicit and implicit memory retrieval tasks. J. Neurosci. *15*, 12–29.
Buckner, R.L., Raichle, M.E., and Petersen, S.E. (1995b). Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. J. Neurophysiol. *74*, 2163–2173.

Chein, J.M., and Fiez, J.A. (2001). Dissociation of verbal working memory system components using a delayed serial recall task. Cereb. Cortex *11*, 1003–1014.

Chein, J.M., Fissell, K., and Fiez, J.A. (2002). Functional heterogeneity within Broca's area during verbal working memory. Physiol. Behav. 77, 635–639.

Cohen, J.D., and Servan-Schreiber, D. (1992). Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol. Rev. 99, 45–77.

Cohen, J.D., Targ, E., Servan-Schreiber, D., and Spiegel, D. (1992). The fabric of thought disorder: a cognitive neuroscience approach to disturbances in the processing of context in schizophrenia. In Cognitive Science and Clinical Disorders, D.J. Stein and J.E. Young, eds. (San Diego, CA: Academic Press), pp. 99–127.

Cohen, J.D., Braver, T.S., and O'Reilly, R.C. (1996). A computational approach to prefrontal cortex, cognitive control, and schizophrenia: recent developments and current challenges. Philos. Trans. R. Soc. Lond. B Biol. Sci. *351*, 1515–1527.

Cohen, J.D., Barch, D.M., Carter, C.S., and Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated tasks. J. Abnorm. Psychol. *108*, 120–133.

Cox, R.W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.

Dell, G.S., Burger, L.K., and Svec, W.R. (1997). Language production and serial order: a functional analysis and a model. Psychol. Rev. *104*, 123–147.

Desmond, J.E., Gabrieli, J.D.E., and Glover, G.H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. Neuroimage 7, 368–376.

Ferstl, E.C., Guthke, T., and von Cramon, D.Y. (2002). Text comprehension after brain injury: left prefrontal lesions affect inference processes. Neuropsychology *16*, 292–308.

Gabrieli, J.D.E., Poldrack, R.A., and Desmond, J.E. (1998). The role of left prefrontal cortex in language and memory. Proc. Natl. Acad. Sci. USA *95*, 906–913.

Gernsbacher, M.A., and Kashak, M.P. (2003). Neuroimaging studies of language production and comprehension. Annu. Rev. Psychol. *54*, 91–114.

Hashimoto, R., and Sakai, K.L. (2002). Specialization in the left prefrontal cortex for sentence comprehension. Neuron *35*, 589–597.

Henson, R.N.A., and Rugg, M.D. (2003). Neural response suppression, haemodynamic repetition effects, and behavioural priming. Neuropsychologia *41*, 263–270.

Just, M.A., and Carpenter, P.A. (1992). A capacity theory of comprehension: individual differences in working memory. Psychol. Rev. 99, 122–149.

Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., and Ungerleider, L.G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377, 155–158.

Kerns, J.G., and Berenbaum, H. (2002). Cognitive impairments associated with formal thought disorder in people with schizophrenia. J. Abnorm. Psychol. *111*, 211–224.

Kerns, J.G., Cohen, J.D., MacDonald, A.W., III, Cho, R.Y., Stenger, V.A., and Carter, C.S. (2004). Anterior cingulate conflict monitoring and adjustments in control. Science *303*, 1023–1026.

Koechlin, E.T., Ody, C., and Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. Science *302*, 1181–1185.

Leung, H.C., Gore, J.C., and Goldman-Rakic, P.S. (2002). Sustained mnemonic response in the human middle frontal gyrus during online storage of spatial memoranda. J. Cogn. Neurosci. 14, 659–671.

Levelt, W.J.M., Roelofs, A., and Meyer, A.S. (1999). A theory of lexical access in speech production. Behav. Brain Sci. 22, 1–75.

MacDonald, A.W., III, Cohen, J.D., Stenger, A.V., and Carter, C.S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science *288*, 1835–1838. Martin, R.C. (2003). Language processing: functional organization

and neuroanatomical basis. Annu. Rev. Psychol. 54, 55-89.

Michael, E.B., Keller, T.A., Carpenter, P.A., and Just, M.A. (2001). FMRI investigation of sentence comprehension by eye and by ear: modality fingerprints on cognitive processes. Hum. Brain Mapp. *13*, 239–252.

Miller, E.K., and Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.

Nathaniel-James, D.A., and Frith, C.D. (2002). The role of the dorso-

lateral prefrontal cortex: evidence from the effects of contextual constraint in a sentence completion task. Neuroimage *16*, 1094–1102.

Newman, S.D., Just, M.A., and Carpenter, P.A. (2002). The synchronization of the human cortical working memory network. Neuroimage *15*, 810–822.

Ojemann, J.G., Buckner, R.L., Akbudak, E., Snyder, A.Z., Ollinger, J.M., McKinstry, R.C., Rosen, B.R., Petersen, S.E., Raichle, M.E., and Conturo, T.E. (1998). Functional MRI studies of word-stem completion: Reliability across laboratories and comparison to blood flow imaging with PET. Hum. Brain Mapp. *6*, 203–215.

O'Reilly, R.C., Braver, T.S., and Cohen, J.D. (1999). A biologicallybased neural network model of working memory. In Models of Working Memory, P. Shah and A. Miyake, eds. (Cambridge: Cambridge University Press), pp. 375–411.

O'Reilly, R.C., Noelle, D.C., Braver, T.S., and Cohen, J.D. (2002). Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. Cereb. Cortex *12*, 246–257.

Palmer, E.D., Rosen, H.J., Ojemann, J.G., Buckner, R.L., Kelley, W.M., and Petersen, S.E. (2001). An event-related fMRI study of overt and covert word stem completion. Neuroimage 14, 182–193.

Pessoa, L., Gutierrez, E., Bandettini, P.A., and Ungerleider, L.G. (2002). Neural correlates of visual working memory: fMRI amplitude predicts task performance. Neuron *35*, 975–987.

Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M., and Raichle, M.E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature *362*, 585–589.

Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.M., Pardo, J.V., Fox, P.T., and Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb. Cortex 4, 8–26.

Robinson, G., Blair, J., and Cipolotti, L. (1998). Dynamic aphasia: an inability to select between competing verbal responses. Brain *121*, 77–89.

Rossell, S.L., Price, C.J., and Nobre, A.C. (2003). The anatomy and time course of semantic priming investigated by fMRI and ERPs. Neuropsychologia *41*, 550–564.

Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S.J., and Passingham, R.E. (2000). The prefrontal cortex: response selection or maintenance within working memory. Science 288, 1656–1660.

Servan-Schreiber, D., Cohen, J.D., and Steingard, S. (1996). Schizophrenic deficits in the processing of context: a test of a theoretical model. Arch. Gen. Psychiatry 53, 1105–1112.

Smith, E.E., and Jonides, J. (1999). Storage and executive processes in the frontal lobes. Science 283, 1657–1661.

Thompson-Schill, S.L., D'Esposito, M., and Kan, I.P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. Neuron 23, 513–522.

van Turrennout, M., Ellmore, T., and Martin, A. (2000). Long-lasting cortical plasticity in the object naming system. Nat. Neurosci. *3*, 1329–1334.

Wagner, A.D., Pare-Blagoev, E.J., Clark, J., and Poldrack, R.A. (2001a). Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. Neuron *31*, 329–338.

Wagner, A.D., Maril, A., Bjork, R.A., and Schacter, D.L. (2001b). Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. Neuroimage *14*, 1337–1347.

Wiggs, C.L., and Martin, A. (1998). Properties and mechanisms of perceptual priming. Curr. Opin. Neurobiol. *8*, 227–233.

Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., and Frackowiak, R. (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. Brain *114*, 1803–1817.

Woods, R.P., Grafton, S.T., Holmes, C.J., Cherry, S.R., and Mazziotta, J.C. (1998). Automated image registration: I. General methods and intrasubject, intramodality validation. J. Comput. Assist. Tomogr. *22*, 139–152.