functions. Rapid neuron-NG2 cell signaling may allow rapid feedback regulation of neuronal functions by Ca^{2+}-dependent secretion of neuroactive factors, and the strength of such feedback regulation will increase after the induction of gLTP.

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Supporting Online Material

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Language Control in the Bilingual Brain

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How does the bilingual brain distinguish and control which language is in use? Previous functional imaging experiments have not been able to answer this question because proficient bilinguals activate the same brain regions irrespective of the language being tested. Here, we reveal that neuronal responses within the left caudate are sensitive to changes in the language or the meaning of words. By demonstrating this effect in populations of German-English and Japanese-English bilinguals, we suggest that the left caudate plays a universal role in monitoring and controlling the language in use.

People who communicate in more than one language can voluntarily control which language is in use at any given time. The bilingual brain can, for example, determine the language of heard or written speech, produce words in the selected language, and inhibit the production of words in the nonselected language. All of these processes necessitate language-sensitive neuronal activity. Contrary to expectation, however, whole-brain functional neuroimaging studies have shown that highly proficient bilinguals activate the same set of brain regions irrespective of which language is presented or produced; see (*1*) a for recent review. These findings suggest that the neural circuits for different languages are highly overlapping and interconnected but do not indicate how the brain determines or controls the language in use.

Our study was designed to identify language-dependent neuronal responses at the level of word meanings (i.e., semantics). By using whole-brain functional neuroimaging, semantic priming, and the neuronal adaptation technique (*2–4*), we expected to see regional reductions in left anterior temporal activation when two successively presented written words had similar meanings (e.g., trout-SALMON) compared with different meanings (e.g., trout-HORSE) (*5*, *6*). Critically, if semantic activation is independent of the language of the stimuli, then neuronal adaptation will be the same irrespective of whether the semantically related words are in the same or different languages (*2*). If, on the other hand, a region responds to both semantic content and the language of the stimuli, then neuronal adaptation will depend on whether semantically related words are presented in the same or different languages.

Our participants saw visually presented sequential word pairs (e.g., trout-SALMON). They were instructed to ignore the first (the prime) and to make a decision based on the meaning of the second [the target, printed in capitals (English and German) or a larger font (Japanese) (Materials and Methods)]. A short interval (250 ms) between the onsets of the prime and the target was chosen to minimize the likelihood that the prime could be used to predict the target word but to maximize the time available to activate semantic associations in both languages (*7*). The influence of the prime on the target was identified by comparing the response to prime-target pairs that were either semantically related (bathtub-SHOWER) or unrelated (spoon-SHOWER). We then identified language-dependent semantic responses by comparing the effect of semantic priming when prime and target were in the same language (trout-SALMON in English or forelle-LACHS in German) or different languages (e.g., trout-LACHS or forelle-SALMON). Lastly, to identify the semantic system that was common to all types of priming, we included a baseline condition with meaningless nonlinguistic symbols. Our two-by-two-by-two experimental design manipulated (i) the language of the target word and varied whether the prime and the target were (ii) semantically related or unrelated and (iii) written in the same or different languages.

The robustness and universality of the observed effects were ensured by including three groups of highly proficient bilinguals (table S1). One group of German-English bilinguals (n = 11) participated in a positron emission tomography (PET) experiment, whereas a second group of German-English bilinguals (n = 14) and a third group of Japanese-English bilinguals (n = 10) participated in functional magnetic resonance imaging (fMRI) experiments. The stimuli in all three experiments were carefully equated across languages (table S2). Therefore, language-dependent neuronal responses present in all three groups would provide strong evidence for the universality of the language mechanism, particularly because

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German and Japanese come from entirely separate linguistic families. The replication of effects across three different experiments is also important because previous reports of language-selective effects (*8*) have not been replicated subsequently.

To begin, we demonstrated equivalent behavioral and imaging effects for both languages spoken (Fig. 1). In the behavioral analysis, over all three subject groups, there were no significant effects of target language on accuracy or response times, [$F(1, 32) < 1.5$; $P > 0.1$] although the Japanese group were 92 ms faster with Japanese than with English targets [$F(1, 9) = 3.6$; $P = 0.09$]. The imaging data demonstrated that the same network of brain regions relative to baseline was activated for semantic decisions for both languages spoken (Fig. 1), and a direct comparison of the two languages did not reveal any significant differences when a correction was made for multiple comparisons across the entire brain. At a lower statistical threshold ($P < 0.001$, uncorrected), we found greater activation in the visual cortices for German compared with English words and for English compared with Japanese words. These effects are attributed to inevitable perceptual differences in the orthographies of the languages tested. Indeed, there were more letters in our German words (7.2 letters on average per word) compared with their English equivalents (6.1 letters on average per word) and in English compared with Japanese (three characters on average per word). Despite the different orthographies, however, a common set of frontal, temporal, and parietal regions were activated in each language (Fig. 1), consistent with previous studies of highly proficient bilinguals (*9–13*).

The influence of the prime on the target response was clearly demonstrated by both behavioral and imaging data from each bilingual group. Over subject groups, there was a 41-ms main effect of semantic priming on response times [1258 ms for unrelated and 1217 ms for semantically related; $F(1, 32) = 8.2$; $P = 0.007$], and this effect was observed irrespective of whether the prime and the target were in the same or different languages [$F(1, 32) < 1.2$ and $P > 0.3$ for all two-way and three-way interactions] (Fig. 2). At the neuronal level, responses on the ventral surface of the left anterior temporal lobe mirrored the behavioral data, with reduced activation for semantically related word pairs irrespective of whether the prime and the target were in the same or different languages (Fig. 3) This effect did not interact with the languages of the prime or the target ($P > 0.05$ for all two- and three-way interactions in each group of subjects). This suggests that semantic priming in the left ventral anterior temporal lobe (*5*, *6*) is language-independent, consistent with the notion that both languages converge on the same neuronal networks.

Most importantly, our whole-brain analysis revealed language-dependent semantic priming that was only observed in the head of the left caudate. Across all three of our subject groups, we found that semantically related words reduced activation in the left caudate when prime and target were in the same language but not when they were in different languages (Fig. 4). The group-specific P values for unrelated more than semantically related word pairs in the same language were 0.001 for the Japanese group and 0.003 and 0.008 for the German groups. The joint probability across groups ($P = 2.4 \times 10^{-8}$) corresponds to a Z score of 5.46, which is highly unlikely to arise by chance even for a whole-brain undirected search. In addition, we confirmed that the size of the effects in both PET and fMRI analyses reached significance ($P < 0.05$) after a small volume correction for multiple comparisons when the coordinates from the PET study were used as an independent region of interest (6-mm radius)

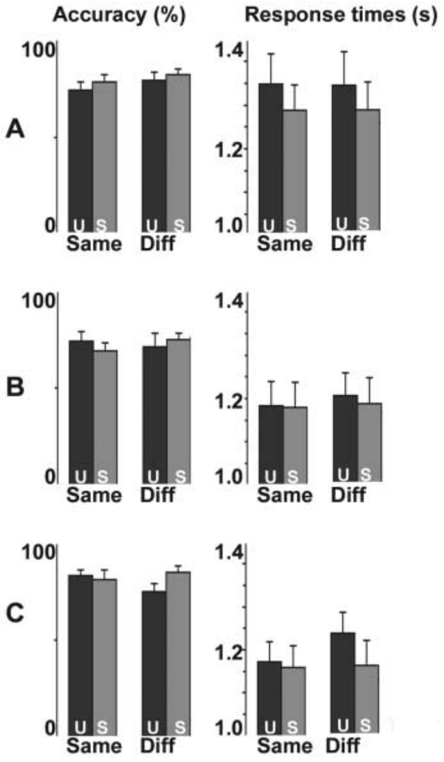

Fig. 2. The effect of semantic priming on behavioral responses. Response accuracy (left) and time (right) in each group of subjects. (**A**) German-English fMRI. (**B**) Japanese-English fMRI. (**C**) German-English PET. Prime and target were either in the same language (Same) or different languages (Diff) and unrelated (U) or semantically related (S). There was no significant effect of any variable on accuracy in any of the three groups of subjects or over all subjects ($P > 0.05$). The error bars show standard error of the mean.

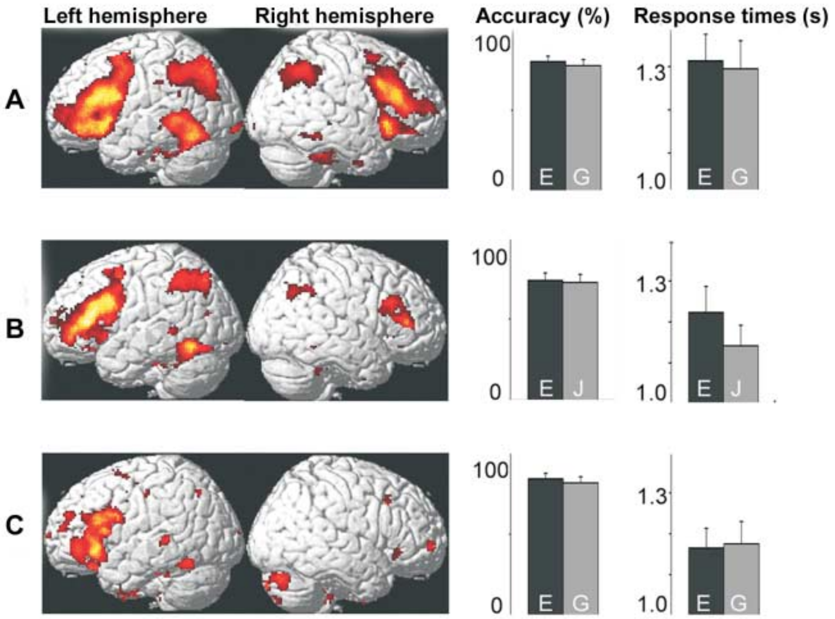

Fig. 1. Common neuronal and behavioral effects for both languages spoken. (Left) Activation for semantic decisions relative to baseline for both languages in each of the three groups of subjects (red to yellow colors correspond to significance values ranging from $P < 10^{-3}$ to $P < 10^{-6}$, uncorrected). (**A**) German-English fMRI (n = 14). (**B**) Japanese-English fMRI (n = 9). (**C**) German-English PET (n = 11). (Right) The accuracy and response times for semantic decision in each of the languages spoken. E indicates English; G, German; and J, Japanese. Over subject groups, the mean accuracy including trials where the response time was longer than 2 s was 79% in English and 77% in German and Japanese, whereas the mean response time excluding trials longer than 2 s was 1249 ms in English and 1232 ms in German and Japanese. The error bars show standard error of the mean.

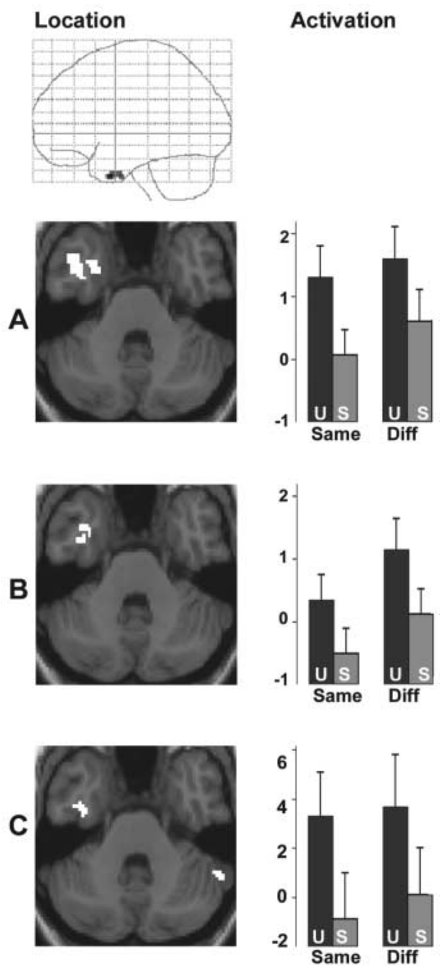

Fig. 3. Language-independent neuronal adaptation in the left anterior temporal lobe. (Left) Activation for unrelated minus semantically related word pairs for (top) all fMRI data ($P < 0.001$) on a sagittal view of a glass brain, to show that the most significant effect across the whole brain was located in the left anterior temporal lobe, and for each of the three bilingual groups on axial slices ($z = -36$ mm; the left side of the image corresponds to the left hemisphere). (**A**) German-English fMRI. (**B**) Japanese-English fMRI. (**C**) German-English PET. (Right) Parameter estimates, relative to baseline, at the peak of unrelated minus semantically related activation (see Fig. 2 for abbreviations). The error bars show standard error of the mean. Details of *x*, *y*, and *z* coordinates (Montreal Neurological Institute standard space); *Z* score; *P* value uncorrected; and number of voxels at $P <$ 0.05 uncorrected were –32, 4, –36; 3.1; 0.001; and 135 for all fMRI data; –34, –4, –38; 2.6; 0.005; and 151 for German fMRI data; –32, 4, –36; 2.4; 0.007; and 22 for Japanese fMRI data; and –32, –12, –36; 2.7; 0.004; and 62 for German PET data, respectively. The combined probabilities of the effects in each group were multiplied ($0.005 \times 0.007 \times 0.004$) to equal 1.4×10^{-7}, corresponding to a Z score of 5.14. Note the different location of the peak in the PET and fMRI results is likely to reflect distortion due to susceptibility artefacts in this region in the fMRI experiments (*37*).

in the fMRI study and vice versa. Critically, in all three subject groups, semantic priming was significantly greater when the prime and the target were in the same language than when they were in different languages ($P = 10^{-6}$, $Z = 5.1$), irrespective of the language of the prime. There were no other significant effects, not even in the frontal and the parietal regions that activate when the language of response switches (*2*, *14*). The key distinction here is that we had no explicit task-switching condition. Our subjects were instructed to respond only to the target word, and, within a block, the target language was held constant.

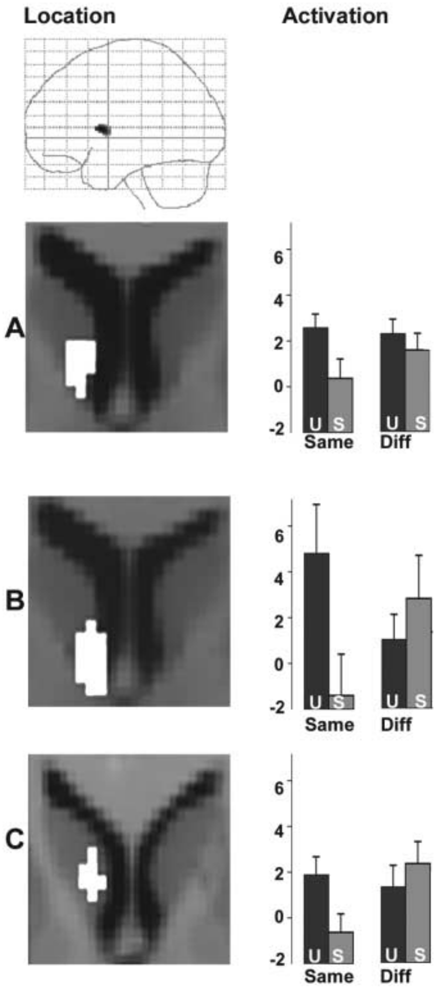

Fig. 4. (**A** to **C**) Language-dependent neuronal adaptation in the left caudate. Activation for unrelated minus semantically related word pairs in the same language only (see Fig. 3 for layout). The sagittal view of the glass brain (top) shows that the average of all fMRI data ($P <$ 0.001) and indicates that the only significant effect across the whole brain was located in the left caudate. Details of *x*, *y*, and *z* coordinates; *Z* score; *P* value (uncorrected); and number of voxels at $P < 0.05$ uncorrected were –6, 8, 8; 3.6; 0.001; and 171 for all fMRI data; –8, 12, 6; 2.4; 0.008; and 48 for German fMRI data; –6, 6, 8; 3.3; 0.001; and 146 for Japanese fMRI data; and –4, 14, 2; 2.9; 0.003; and 37 for German PET data, respectively. Lastly, the *Z* scores and probabilities for the interaction of (unrelated–semantically related) × (same-different languages) were 1.5 and 0.074 for German fMRI; 3.1 and 0.001 for Japanese fMRI; and 2.8 and 0.003 for German-PET, respectively. The combined probability for the interaction is 2.2×10^{-7}, corresponding to a *Z* score of 5.05.

The language-dependent neuronal responses that we have observed in the left caudate were highest when prime and target are either semantically different (unrelated) or in different languages (Fig. 4). This is consistent with language-dependent responses at the level of word meanings. Indeed, the response in the left caudate cannot be explained in terms of orthographic or perceptual differences in the scripts, because if this had been the case we would have seen reduced activation when unrelated words were in the same language (English-ENGLISH) than in different languages (e.g., English-日本語). Instead, we only saw reduced activation when words in the same language were semantically similar (Fig. 4). We can also exclude the possibility that our effects result from proficiency confounds, because the effect of semantic priming was observed within languages irrespective of whether the prime and the target were presented in English, German, or Japanese ($P < 0.03$ for each language) and there was no effect of semantic priming when the prime and target were in any combination of different languages ($P > 0.05$).

Our imaging results dissociate two effects of semantic priming in all three of our subject groups, despite cultural and linguistic differences between groups. In the left anterior temporal cortex, semantically related primes reduced activation irrespective of whether the prime and the target were in the same language or in different languages. This suggests that different languages converge on the same neuronal populations within this region as opposed to distinct populations embedded within the same area of the temporal cortex. In contrast, in the head of the left caudate, reduced activation for semantically related word pairs was only observed when the prime and target were in the same language.

There are two possible neuronal mechanisms that might generate the response profile we have observed in the left caudate. The first is that different languages are processed by different neuronal populations (i.e., language-selective neuronal populations) and semantic priming selectively adapts responses in the neuronal populations for the prime language (*3*). In this case, semantic priming between words in different languages does not reduce activation because the change in language activates a different (i.e., non-adapted) neuronal population. The second interpretation is that the same neurons respond to semantic input in both languages with increased neuronal firing when there is a change in language (*15*). Neuronal populations that respond to a change in language would indicate a possible mechanism for language control that regulates output whenever a change in input is detected. To dissociate the two contrasting explanations of language-dependent semantic priming, we turned to neuropsychological studies of bilingual patients with damage to the left caudate. If there are distinct neuronal populations in the left caudate for different languages, then damage to this region should disrupt all of these neuronal populations and impair word processing in all the patient's languages. If, on the other hand, the left caudate plays a role in language control and increases its firing when words in a pair are unrelated by meaning or language, then semantic processing after left caudate damage may remain intact for all languages, but the patient will have difficulties monitoring the language of input or controlling the language of output.

The results of neuropsychological studies of bilingual patients strongly suggest that the left caudate is involved in language control rather than language-selective semantic representations. The most notable case is a study of a trilingual patient with a lesion to the white matter surrounding the head of the left caudate (*16*). This patient had preserved comprehension in all three of her languages. Her picture naming was also above 80% accuracy. However, during language production tasks, she spontaneously and involuntarily switched from one language to another. These and other findings with bilingual patients (*17*) suggest that the left caudate is required to monitor and control lexical and language alternatives in production tasks.

In monolingual patients, left caudate damage is typically associated with confrontational naming and word-finding difficulties (*18*, *19*). This has led to suggestions that damage to, or stimulation of, the caudate will impair the patient's ability to select appropriate lexical-semantic responses (*20*, *21*). Recently, however, semantic priming experiments have demonstrated that patients with nonthalamic subcortical lesions also have lexical-semantic impairments when required to manipulate or control semantics during attention-demanding comprehension tasks (*22*, *23*). Likewise, functional neuroimaging studies of neurologically normal subjects have shown increased left caudate activation for semantic decisions, even when speech output is controlled, by comparing semantic decisions to phonologically complex baseline tasks (*24*, *25*). Together, these studies suggest that the left caudate plays a role in lexical-semantic control in both monolingual (*20*, *23*) and multilingual subjects (*16*, *17*). Lexical semantic processing may be regulated, for example, by increased left caudate responses when the distributed pattern of neuronal inputs changes (*26*). Indeed, our study shows that the left caudate responses are highest when there is a change in language or a change in meaning but lowest in the context of words that are related in both language and meaning.

Anatomically, the left caudate is the primary recipient of corticostriatal projections from frontal, temporal, and parietal association regions in the language-dominant hemisphere and, in turn, sends reciprocal connections via the thalamus that play a critical role in controlling and selecting automatic motor sequences such as those necessary for articulation (*27*, *28*). These motor patterns differ across languages and therefore require a mechanism sensitive to the language in use. The head of the left caudate may be ideally situated to serve this function.

By using functional neuroimaging, we have demonstrated that neuronal responses in the head of the left caudate are sensitive to both the semantic content and the language of written words. In contrast to previous functional imaging investigations of semantic processing in bilingual participants (*29*), we were able to dissociate language-dependent effects within a shared brain region by using semantic priming and a neuronal adaptation technique. In contrast to electrical stimulation studies of speech production in bilingual patients with craniotomies before surgery (*30*, *31*), our functional imaging technique allowed us to investigate the whole brain and avoid confounds from differences in the computational demands required for speech production in a second language (*32*–*36*). Moreover, in contrast to both neuropsychological and electrical stimulation studies, we were able to ensure the robustness and universality of our results by replicating the effects in three different populations of highly proficient bilinguals with different linguistic backgrounds. We conclude that the left caudate plays a critical role in language control and that future studies targeting the regions to which the left caudate connects will enable a more complete characterization of the neural circuits involved in the control of multiple languages.

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