letters to nature

Methods

Data

A literature search yielded 45 genes for which polymorphism had been surveyed in *D. melanogaster* and for which an outgroup sequence was available. Of these, 36 had a sample size of eight or greater, 32 had been surveyed in at least two African and two non-African individuals and 10 were of X-linked genes. The 45 genes and their references are listed in Supplementary Information.

Analysis

Polymorphism data was tabulated by hand or from GenBank accession numbers using SITES[21] or DNASP[22]. For each polymorphic site, the minor allele was classified as rare ($\leq 12.5\%$) or common ($> 12.5\%$). The cutoff of 12.5% was chosen to exclude deleterious mutations from the common frequency class and to include those genes with samples of eight or more in the analysis of rare compared to common polymorphism. Cutoffs of 10 and 15% produce similar results. We treated three alleles segregating at a single nucleotide as two segregating sites and excluded complex variations. Divergence data was obtained by comparing a randomly chosen sequence of *D. melanogaster* with that of *D. simulans* or, if unavailable, either *D. mauritiana* or *D. sechellia*. The number of amino-acid and synonymous substitutions between species was estimated using Kimura's two-parameter model to correct for multiple hits.

The contribution of each gene to the excess number of amino-acid substitutions was calculated as the excess number of amino-acid substitutions minus the excess number of amino-acid polymorphisms found in each gene. The excess for polymorphism and divergence is $A - S \times (65/224)$, where A and S are the number of amino-acid and synonymous substitutions, respectively, and 65/224 is the total number of amino-acid polymorphisms divided by synonymous polymorphisms. (Ideally, the excess of amino-acid divergence in each gene should be calculated using only polymorphism and divergence in that gene but there is rarely sufficient polymorphism in a single gene for comparison with divergence.) We also calculated the contribution to the excess separately for three groups of genes sorted by their rate of amino-acid divergence. The two methods produced a similar distribution so the simpler method using a single group of genes was used.

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Brain potential and functional MRI evidence for how to handle two languages with one brain

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Bilingual individuals need effective mechanisms to prevent interference from one language while processing material in the other[1]. Here we show, using event-related brain potentials and functional magnetic resonance imaging (fMRI), that words from the non-target language are rejected at an early stage before semantic analysis in bilinguals. Bilingual Spanish/Catalan and monolingual Spanish subjects were instructed to press a button when presented with words in one language, while ignoring words in the other language and pseudowords. The brain potentials of bilingual subjects in response to words of the non-target language were not sensitive to word frequency, indicating that the meaning of non-target words was not accessed in bilinguals. The fMRI activation patterns of bilinguals included a number of areas previously implicated in phonological and pseudoword processing[2–5], suggesting that bilinguals use an indirect phonological access route to the lexicon of the target language to avoid interference[6].

High-proficiency bilingual subjects manage to understand and speak one of their languages without apparent interference from the other. This is a remarkable ability in the face of the fact that neuroimaging studies have revealed, at least for high-proficiency bilinguals, that neuro-anatomical representations of both languages are
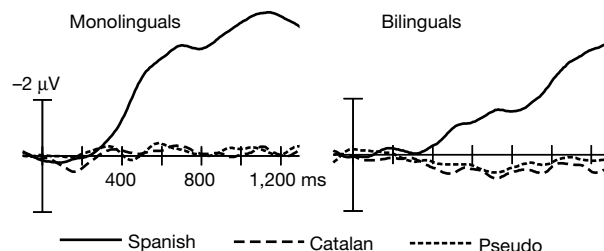

Figure 1 Lateralized readiness potentials (LRPs) from the main experiment indicating the preparation of motor responses. The onset latency of the LRP to Spanish words, estimated by the time at which the amplitude was significantly different from zero for at least 4 consecutive time points (sequential *t*-tests)[14], was 408 ms in the monolingual and 520 ms in the bilingual group. No LRP activity is observed for Catalan words, indicating an effective blocking of 'word' (go) responses in the bilingual group.

overlapping[7,8]. How, then, do bilinguals avoid interference between languages and maintain their attention focussed on the target language? In an experiment involving Spanish/English bilinguals who were shown a mixed list of Spanish, English and pseudowords (subjects were instructed to respond to words in the target language and reject both non-target words and pseudowords), non-target words were rejected as fast as pseudowords[9]. Furthermore, in contrast to words in the target language, no effect of word frequency on the rejection latencies of words in the non-target language was found[9]. This suggests that bilinguals effectively 'filter out' words of the non-target language, and are able selectively to shut down one lexicon when necessary[10,11]. However, other behavioural data have been thought to be compatible with a non-selective access to the two lexicons in bilinguals[12].

Thus, although it has been suggested that an automatic switching mechanism permits a rapid change between languages[1], this notion is ill-defined, and it is unclear to what degree words from the non-target language are processed by bilinguals.

To address this question we assessed behavioural, electrophysiological and brain-imaging measures during word processing in a group of bilingual Catalan/Spanish-speaking subjects, and in a second group of monolingual speakers of Spanish. Catalan, as with Spanish, is a Romance language and is mainly spoken in the north-eastern part of Spain[13]. It is one of two official languages in this region and is compulsory in school and at university. In our experiments, subjects were required to make a speeded button press in response to Spanish words presented on a video monitor, with response hand (left or right) determined by the first letter (vowel or consonant). Subjects were instructed to withhold responses to Catalan words and pseudowords. Both groups performed the task

with ease. The difference in reaction times to Spanish words (monolingual, 699 ms; bilingual, 738 ms, $F_{1,28} = 1.9$, $P = 0.17$) failed to reach significance, but the delayed onset latency of the lateralized readiness potential (LRP)—which indexes response preparation[14]—in bilingual subjects (Fig. 1) suggests that bilinguals were slower in preparing responses to words in the target language. Bilinguals also showed slightly more false-positive responses to high-frequency Catalan words (monolingual: high frequency, 3.8%, low frequency, 3.9%; bilingual: high frequency, 5.7%, low frequency, 3.7%; group by frequency interaction $F_{1,28} = 7.64$, $P < 0.01$), indicating that they had some difficulty suppressing button presses to high-frequency irrelevant words.

For the target (Spanish) words, event-related brain potentials (ERPs) showed a typical sensitivity to word frequency in both groups, as shown in Fig. 2. This effect results from a modulation of the 'N400' component[15], the frequency sensitivity of which is well known[16]—it receives contributions from semantic areas of the fusiform gyrus[17] and has been interpreted as reflecting meaning access[18]. Interestingly, neither of the groups showed frequency sensitivity for Catalan words. Also, ERP effects towards Catalan and pseudowords were virtually identical in both groups (Fig. 2c). This suggests that the meanings of most of the Catalan words are not accessed even in subjects who are highly proficient in that language, and that these words are rejected at a stage before semantic analysis.

To test the generality of these effects, a subset of the bilingual group was subjected to a control experiment with the instruction to press the button in response to Catalan words, and to ignore Spanish words and pseudowords. The pattern of ERPs was reversed, with a frequency effect now showing up for the Catalan words, whereas no frequency effect was seen for the Spanish stimuli
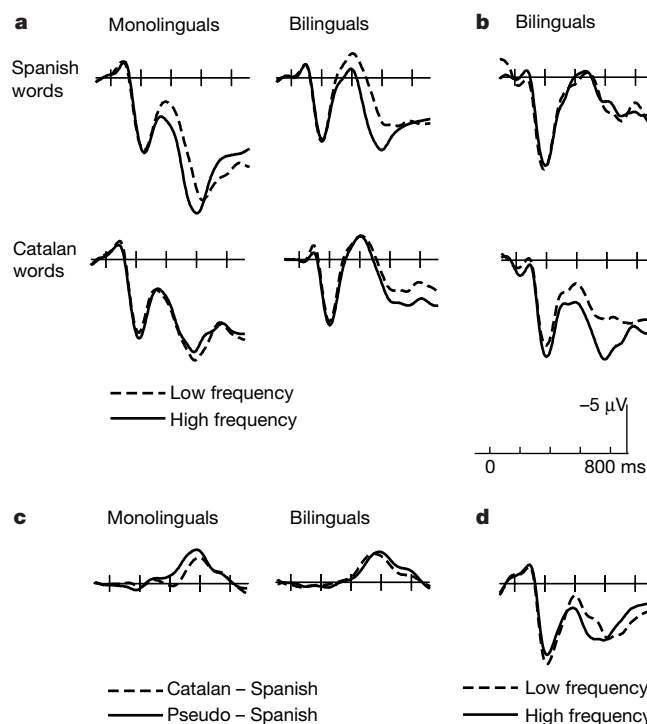

Figure 2 Event-related brain potentials (ERPs) from the main and two control experiments. **a**, ERPs from the main experiment: only Spanish words show a frequency sensitivity with an increased negativity for low-frequency words. No frequency effect is seen for the Catalan words (mean amplitude 350–500 ms, language × frequency interaction, $F_{1,28} = 70.8$, $P < 0.001$, centroparietal electrode sites). **b**, ERPs from the first control experiment performed in a subset of the bilingual group. A frequency effect is only seen for the (relevant) Catalan words (task × language × frequency interaction, $F_{1,3} = 37.05$, $P < 0.01$, task defines the relevant language). **c**, Difference waves obtained by subtracting the ERPs to the Spanish words from the ERPs to the Catalan words and

pseudowords, respectively. The resulting waveforms are very similar for both conditions, and for the Catalan group are virtually overlapping. Neither main effects of stimulus type (Catalan versus pseudowords) nor group by stimulus type interaction effects were obtained for ANOVA tests conducted on several successive 200-ms time windows between 100 and 700 ms. **d**, ERPs from the second control experiment. The frequency sensitivity of the ERPs in the 350–500-ms time window was preserved ($F_{1,11} = 17.9$, $P < 0.0014$, centroparietal electrode sites), even though only pseudowords required a response in this experiment. All waveforms are from the central midline site. Scale bar applies to all panels.

(Fig. 2b). To rule out the possibility that the lack of an ERP frequency effect for words from the non-target language could be due to the task characteristics, a second control experiment was conducted on monolingual Spanish subjects. Here, a discriminative (vowel/consonant) response was required for pseudowords occurring intermixed with Spanish words, which required no response (no-go). The frequency modulation of the N400 component was preserved for the Spanish words, indicating its independence of task requirements (Fig. 2d).

To examine the areas of the brain that are active during the task, we conducted an event-related functional MRI version of the experiment. Importantly, neither the monolingual nor the bilingual group showed reliable differences between pseudowords compared with Catalan words. The contrast between the three critical conditions (Spanish, Catalan and pseudowords) against a consonant string baseline (Fig. 3a, b) indicates how bilinguals may optimize performance during this task. Using responses to consonant strings (for example, dfmvr) as a baseline, activity in extrastriate visual cortex, which is usually found when contrasting words to a fixation baseline condition, is subtracted out[19]. Activity in the left primary motor cortex, left inferior parietal lobe and cerebellum, initiated by Spanish words, is attributable to the motor response. Only bilingual subjects exhibited an activation of the posterior inferior frontal area in response to the stimuli of Spanish words. This is evident when the pattern of activation between monolingual and bilingual groups is compared (Fig. 3c). This region of the brain is critical for pseudo-word reading[20], phonological processing[2,3] and subvocal rehearsal[4],

and was activated to a greater extent for Catalan (non-target) words and pseudowords in both groups. Furthermore, bilingual subjects showed a greater activation of the planum temporale (BA 22, 42) for all three critical conditions, a region of the brain that has also been linked to phonological processing[2–5].

A parsimonious interpretation of these results, in line with the electrophysiological data, can be derived from the dual route model of reading, which proposes two different pathways for lexical access: the 'lexical' route, which proceeds directly from orthography to lexical access, and the 'sublexical' or letter-to-sound route, in which the graphemic form is converted to its phonological representation before lexical access, by applying a specific set of graphemic–phonological spelling rules[6]. We propose that bilinguals perform the current task using the sublexical pathway, that is, activating only graphemic–phonological spelling rules of the Spanish language, and that use of this pathway is reflected in a greater activation of posterior inferior frontal cortex and the planum temporale. This would imply an inhibition of the direct access route from orthography to the lexicon, thereby reducing response conflict for non-target words. The greater activation in an anterior prefrontal region (BA45/9, Fig. 3c) of the brain in bilingual subjects in response to Catalan words and pseudowords is a likely correlate of this inhibition, as this region has recently been implicated in the selection of relevant information and interference resolution[21,22]. These stimuli have also been associated with an enhanced activation in the anterior cingulate cortex that has frequently been found in control and conflict tasks[23] (see Supplementary Information). However,
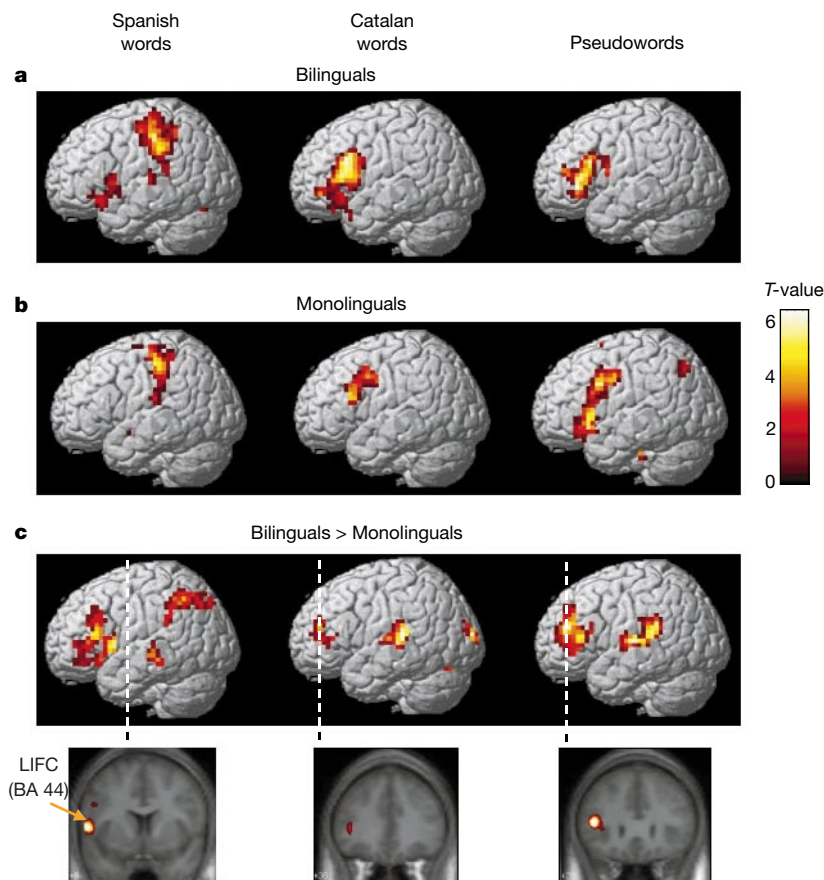

Figure 3 Rendering of group-averaged brain activations in standard stereotactic space identified for the Go condition (Spanish words) and the two no-go conditions (Catalan words and pseudowords). Each condition was contrasted against the baseline condition (consonant strings). **a**, The bilingual group ($n = 7$); **b**, the monolingual group ($n = 7$) ($P < 0.01$, 20 voxels). **c**, Group differences were identified using a t-test between groups for each of the conditions ($P < 0.02$, 40 voxels). Shown are regions with greater activations in the bilinguals. Corresponding coronal views superimposed on the mean anatomical image of the 14 participants are shown (bottom). The group comparison for Spanish words showed a reliable difference in the left posterior inferior frontal cortex (LIFC, BA 44; peak coordinates −60, 8, 8, $P < 0.001$, uncorrected). In the pseudoword condition the peak activity was located more anteriorly, near to the medial frontal gyrus (BA 45/9; −44, 28, 8, $P < 0.001$).

sometimes inhibition seems to have failed in our subjects, as demonstrated by the slight increase in commission errors for high-frequency words in the non-target language. Indeed, high-frequency words are thought to be processed using the direct access route[6].

Taken together, behavioural, electrophysiological and brain-imaging measures demonstrate a very efficient blocking of the non-target language in bilinguals, which is probably achieved through the use of an indirect access route to the lexicon. The meaning of stimuli in the irrelevant language seems not to be accessed under the current conditions. Further studies are needed to test the generality of these findings in other experimental tasks. □

Methods

Subjects

Monolingual speakers of Spanish and bilingual Catalan/Spanish subjects (age 18–30 years) were recruited from the foreign student population at Hannover and Magdeburg Universities, Germany. All bilinguals had acquired both languages during their first years of life, and a questionnaire[24] revealed a high proficiency in and regular usage of both languages.

ERP experiments

Fifteen monolingual and fifteen bilingual subjects participated in the main experiment. Six hundred Spanish words (300 high-frequency words, 95.0 occurrences per million; 300 low-frequency words, 2.45 per million[25]), 300 Catalan words (150 high-frequency words, 68.4 per million, 150 low-frequency words, 7.4 per million[26]) and 300 pseudowords (150 each derived from Spanish and Catalan by changing 1–3 letters) were presented in random order on a computer monitor (duration 400 ms, stimulus-onset asynchrony 1,750–2,250 ms). A fixation point appeared at the beginning of each trial in the centre of the screen 500 ms before imperative stimuli. Only Catalan words that were completely different (non-cognates) from Spanish words were selected. A speeded button press was required for Spanish words, whereas no response was to be given to Catalan and pseudowords. Spanish words with a vowel as the initial letter required a right-hand response, those starting with a consonant required a left-hand response (counterbalanced across subjects). This task was chosen to allow for the computation of the lateralized readiness potential (LRP). Several lists with different orders were generated and presented to subsets of the subjects. Event-related brain potentials (ERPs) and LRPs were computed from the electroencephalogram (EEG) using standard procedures[14]. Mean amplitude measures were obtained and entered into analysis of variance (ANOVA) statistics with the Huynh–Feldt epsilon correction applied as necessary. Before statistical analysis, error rates were replaced by the inverse sine transformation of the square root of the error proportions[27].

In the first control experiment (four bilingual subjects), the Catalan words used were the same as in the main experiment. These were presented together with a subset of the Spanish words (75 high- and 75 low-frequency words; 90 and 2.4 per million, respectively) and 150 pseudowords. The instruction was the same as in the main experiment, except that Catalan words were now to be responded to with the first letter (vowel or consonant) determining response hand.

In the second control experiment (12 additional monolingual Spanish subjects), 300 Spanish words (150 of each frequency level) and 300 pseudowords (all derived from Spanish words) were used with a left/right reaction to pseudowords, depending on the initial letter (vowel or consonant).

fMRI experiment

The fMRI session was conducted with the same timing as in the ERP session, but the number of stimuli was reduced (324 Spanish words, 108 Catalan words, 108 pseudowords and 108 consonant strings). The consonant strings were presented for further differentiation, and additional trials comprising the presentation of just a cross-hair served as a baseline condition. Imaging was performed with a GE Medical Systems 1.5 Tesla Signa Neurovascular MR scanner with a standard quadrature head coil. Visual images were back-projected onto a screen by an LED projector and participants (7 bilingual and 7 monolingual) viewed the images through a mirror on the head coil. Magnet-compatible response buttons were used. Conventional high-resolution structural images (rf-spoiled GRASS sequence, 60 sagittal slices, 2.8 mm thickness) were followed by functional images sensitive to blood oxygenation level-dependent contrast (echo planar T_2^*-weighted gradient echo sequence, repeat time = 2 s, echo time = 40 ms, flip = 90°). Each functional run consisted of 135 sequential whole-brain acquisitions (16 axial slices aligned to the plane intersecting the anterior and posterior commissures, 3.125-mm in-plane resolution, 7 mm thickness, 1 mm gap between slices). There were 4 trial types as in the ERP experiment plus the fixation control (cross-hair), and subjects performed 6 runs (mean stimulus-onset asynchrony of 2 s). Volumes were acquired continuously; the first four volumes were discarded to allow for T_1 equilibration effects. To allow precise co-registration of functional data a separate T_1-weighted echo-planar image was acquired covering the whole volume (inversion recovery prepared echo-planar imaging (EPI) sequence). Different preprocessing steps were implemented using statistical parametric mapping (SPM99)[28]. Functional volumes were realigned, corrected for movement-related effects, spatially normalized to an EPI template (Montreal Neurological Institute reference brain[29]), an approximation of canonical space[30], resampled into 4-mm cubic voxels, and finally spatially smoothed (8-mm gaussian kernel).

For the statistical model an event-related design matrix including all conditions of

interest was specified using the canonical haemodynamic response function for all event types[28]. The data was high-pass filtered, smoothed temporally with a 4-s full-width, half-maximum gaussian kernel, and rescaled to the global mean. Subject-specific contrasts were estimated using a fixed-effects model. Those contrast images were used to obtain subject-specific estimates for each effect. For group analysis, these estimates were entered in a second-level analysis treating subjects as a random effect, using a two-sample t-test at each voxel. Unless mentioned otherwise, resulting SPM-T maps were thresholded at $P < 0.001$, uncorrected for multiple comparisons, and only activations involving contiguous clusters of at least ten voxels are reported. Maxima and all coordinates are reported in MNI coordinates.

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Competing interests statement

The authors declare that they have no competing financial interests.

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