Inference for magnitudes and delays of responses in the FIAC data using BRAINSTAT/FMRISTAT

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Abstract

We used straightforward linear mixed effects models as described in Worsley *et al.*, 2002, together with recent advances in smoothing to control the degrees of freedom (Worsley, 2005a), and random field theory based on discrete local maxima (Worsley, 2005b). This has been implemented in BRAINSTAT (Taylor *et al.*, 2005), a Python version of FMRISTAT. Our main novelty is voxel-wise inference for both magnitude and delay (latency) of the hemodynamic response (Liao *et al.*, 2002). Our analysis appears to be more sensitive than that of Dehaene-Lambertz *et al.* (2006). Our main findings are greater magnitude ($1.08 \pm 0.16\%$) and delay (0.148 ± 0.035s) for different sentences compared to same sentences, together with a smaller but still significantly greater magnitude for different speaker compared to same speaker ($0.47 \pm 0.08\%$).

1 Introduction

Our main aim is to duplicate part of the analysis of Dehaene-Lambertz *et al.* (2006) (henceforth DL) so that their methods using SPM can be compared directly with ours using BRAINSTAT/FMRISTAT.

To do this, we approach the Functional Image Analysis Contest (FIAC) data set as a hierarchical study with three levels: runs, sessions and subjects. We analyse the event sessions separately from the block sessions, but our analysis method is the same in both cases. This common analysis method seeks to detect changes in magnitude and changes in latency or delay of the responses to the stimuli, and provide standard errors for these estimates.

The changes we looked at were 1) different minus same sentence (averaged over speakers); 2) different minus same speaker (averaged over sentences); 3) an interaction between the two. All these estimates, both of magnitudes and delays, are combined in a hierarchical mixed-effects analysis to produce one map of voxel-wise statistics for each of the three contrasts of scientific interest just described.

In addition to these contrasts, DL also looked at sentence effects separately for different and same speaker, and asymmetry differences between hemispheres, but only for magnitudes. Although BRAINSTAT/FMRISTAT can easily do these extra analyses, we chose to concentrate just on the two main effects of sentence and speaker and their interaction, both for magnitudes and delays.

2 Methods

The details of our approach are as follows. The fMRI data were corrected for motion and different slice acquisition times using the FSL package (Smith *et al.*, 2004). This data was then proportionally scaled to a percentage of the whole volume mean. The data were not smoothed spatially, unlike DL, who used 8mm smoothing before combining the data over subjects. Separate but identical analyses were conducted for the event data and the block data.

2.1 First level: frames

At the first level (frames or scans), the statistical analysis of the percentages was based on a linear model with correlated errors. The design matrix of the linear model was set up in exactly the same way as in DL. For the event experiment, we constructed 5 variables corresponding to all sentences except the first, separately for the 4 conditions, and to the first sentence pooled across all conditions. For the block experiment, we constructed 5 variables corresponding to the 2nd to 6th sentences in each block, separately for the 4 conditions, and to the first sentence pooled across all conditions. This fifth variable, which removes any effect due to the onset of the stimulus after a period of rest, was not used in any of the contrasts.

Each of the variables consisted of 1's and 0's for the presence/abscence of each of the conditions. The five variables were then convolved with a hemodynamic response function (HRF) modelled as a difference of two gamma functions. To estimate delays, the variables for each condition were shifted over a range of delays, and a singular value decomposition was used to extract two basis functions per condition that optimally captured each shifted variable (Liao *et al.* 2002). For each condition, these two basis functions, which closely match the unshifted variables and their derivatives, were added as covariates to the design matrix of the linear model, together with the fifth ("onset") variable, giving eight covariates for the conditions and one nuisance covariate (see Figure 1).

Information from their coefficients was used to estimate both the magnitude of the response and the shift in its delay for each of the four conditions. An inverse tangent transformation was used, very similar to that of DL for experiment 1. The advantage of our delay estimation method is that it can be applied to any experimental design, not necessarily periodic (as in DL), and either events or blocks. Another advantage is a theoretical Sd for the delay as well as the magnitude, so that both magnitudes and delays can be further analysed by the same statistical methods.

Temporal drift was removed by adding a cubic spline in the frame times to the design matrix (one covariate per 2 minutes of scan time), and spatial drift was removed by adding a covariate in the whole brain average to give 15 covariates in the design matrix (see Figure 1).

The correlation structure was modelled as an autoregressive process of degree 1. At each voxel, the autocorrelation parameter was estimated from the least squares residuals using the Yule-Walker equations, after a bias correction for correlations induced by the linear model (Worsley *et al.*, 2002). The autocorrelation parameter was first regularized by 3D spatial smoothing with a Gaussian filter to control the effective degrees of freedom (Df) to at least 100 (Worsley, 2005a). Smoothing was unnecessary for the event design since the effective Df was already greater than 100, but for the block design 2.2 to 2.6mm smoothing was used

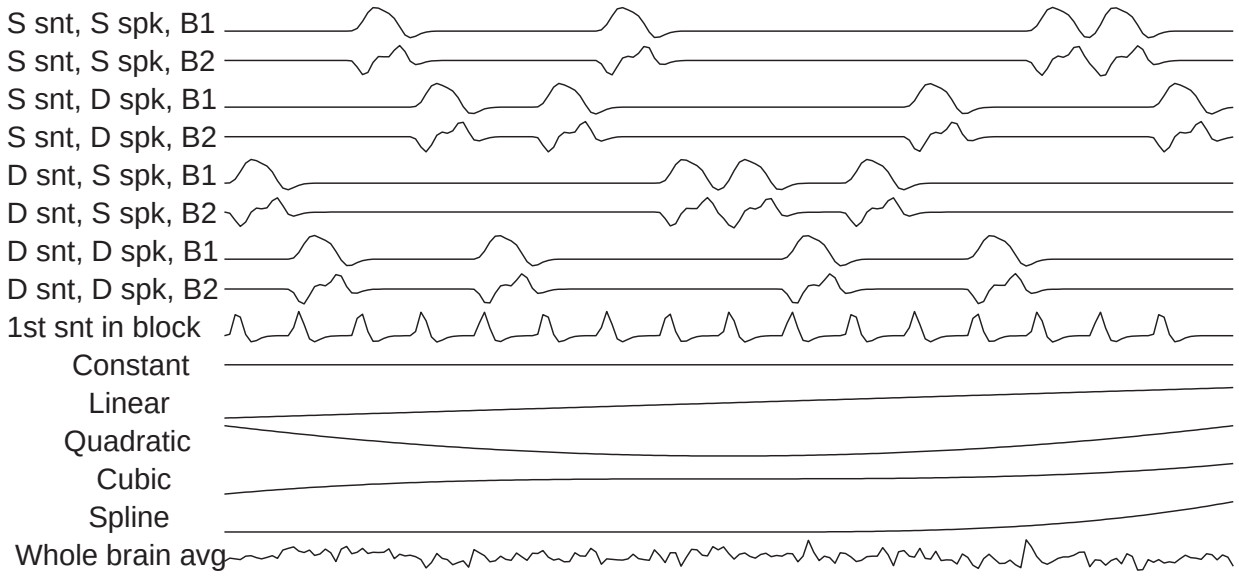

Figure 1: Covariates of the linear model for the first run on the first subject (block experiment). S=same, D=different, snt=sentence, spk=speaker, B=basis function. The first nine covariates model the conditions, and the remaining six model the drift. For each condition, the coefficient of the first basis function is the magnitude, and the coefficient of the second basis function is used to estimate the delay shift.

Contrast	Same sentence, same speaker	Same sentence, different speaker	Different sentence, same speaker	Different sentence, different speaker
Sentence	-0.5	-0.5	0.5	0.5
Speaker	-0.5	0.5	-0.5	0.5
Interaction	1	-1	-1	1

Table 1: Contrasts used for event and block designs, and for magnitudes and delays.

to achieve ∼100 effective Df for all contrasts. The smoothed autocorrelations were used to 'whiten' the data and the design matrix. The linear model was then re-estimated using least squares on the whitened data to produce estimates of effects (contrasts) and their standard deviations (Sd's). There were three contrasts of interest: different – same sentence, different – same speaker, and the interaction of the two (Table 1).

2.2 Second level: runs

The three effects in Table 1, both for magnitudes and delays, together with their estimated (fixed effects) standard errors, were transformed linearly to Talairach space using a transformation estimated by the FSL package (Smith *et al.*, 2004). Subjects 2 and 5 were dropped due to problems with this registration (FSL needed some manual intervention which we were not aware of), leaving 14 subjects for further analysis.

The contrasts from each of the 2 runs per subject were combined using a fixed effects analysis for the effects (as data) with fixed effects Sd's taken from the previous analysis, leaving 14 effects and their Sd's for further analysis.

2.3 Third level: subjects

The 14 effects, one per subject, were combined using a mixed effects linear model for the effects (as data), again with Sd's taken from the previous analysis. This was fitted using ReML implemented by the EM algorithm with a re-parameterization to avoid positivity constraints that would bias the Sd. We then estimated the ratio of the random effects variance to the fixed effects variance, then regularized this ratio by spatial smoothing with a Gaussian filter. The variance of the effect was estimated by the smoothed ratio multiplied by the fixed effects variance (Worsley *et al.*, 2002). The amount of smoothing was chosen to achieve 40 effective Df, and varied from 6.7 to 10.7mm.

2.4 Inference

The resulting T statistic images were thresholded at $P = 0.05$ using the minimum given by a Bonferroni correction, random field theory, and discrete local maxima (Worsley, 2005b), taking into account the non-isotropic spatial correlation of the errors (Hayasaka *et al.*, 2004). Both high and low values of the T statistic images were examined. For the magnitudes, the search region was taken as the whole brain (minimum functional image $>\sim$6000 BOLD units, volume $\sim$1400cm^3); for the latencies, the search region was the voxels where the T statistic image for the overall magnitude exceeded 5 (12cm^3 for the event design, 20cm^3 for the block design).

These higher level analyses were repeated 12 times, once for each combination of stimulus type (event or block), contrast (sentence, speaker or interaction, see Table 1), and parameter (magnitude or delay). No special code was added to BRAINSTAT to perform these calculations, apart from a script to repeat the analyses as above.

The third level analysis was validated by changing the sign of the effects on 7 subjects chosen at random from the 14. Such an analysis should give null results. In fact no false positive local maxima or clusters were detected at the $P = 0.05$ level on 16 such analyses of both magnitudes and delays. This gives us some assurance that the entire analysis is valid. If on the other hand the amount of smoothing was increased to achieve 100 effective Df then the excessive smoothing biased the Sd and resulted in too many false positives.

3 Results

3.1 Efficiencies

Before we start the analysis, it is worth looking at the efficiencies of the two designs (event, block) at estimating the 3 contrasts in a single run. Efficiencies are just the inverse of the Sd of a contrast; the lower the Sd, the more efficient is the design. Of course this depends on the underlying Sd of the errors, so we measure Sd relative to the Sd of the errors (but for delays it depends not on the Sd of the errors, but on the T statistic for the magnitude, which we fix at 5). This allows us to compare designs, and to get some idea of the sizes of effects we can hope to detect under ideal conditions.

The validity of the Sd's rests on the assumptions of the linear model. In particular, they depend on the constancy of the BOLD response throughout a block. Judging by the time-courses in DL, this seems to be a reasonable approximation, though there is some evidence of a steady decline in response after the 2nd event in a block.

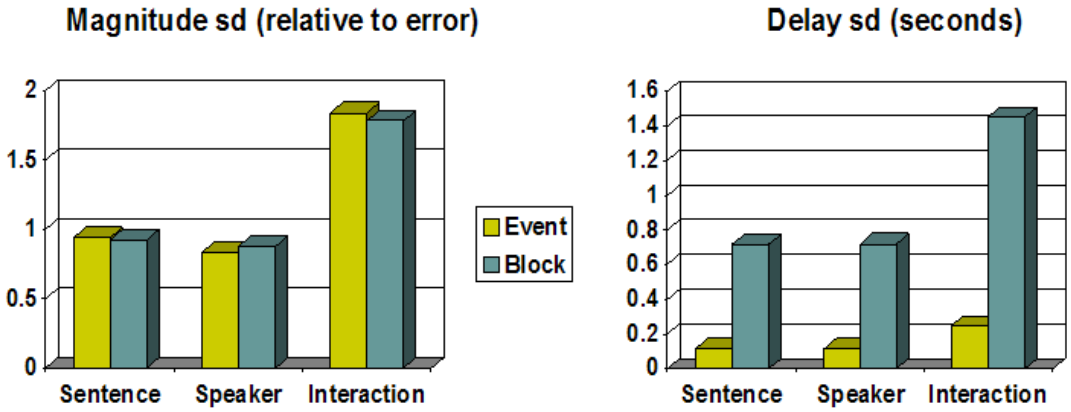

Figure 2: Sd of designs (lower is better) for a single run, assuming additivity of responses. Interactions are harder to detect than main effects. For delays, the event design is more efficient (lower sd) than the block design; the event design estimates sentence and speaker delays to within 0.12 seconds.

These Sd's depend only on the design matrix, the contrasts, and the temporal correlation structure (AR(1) lag 1 correlation taken as 0.6) so they can be calculated before the data is collected. This is useful at the planning stage to help choose the paradigm (event or block), and parameters of the paradigm (inter-stimulus interval, block length) that give smallest Sd, thus making best use of the time in the scanner.

Unfortunately it is only possible to do this at the first level in the hierarchy, that is within subjects, since we usually have no idea in advance of the variability of an effect from one subject to another, that is, the random subject effects. In the absence of random subject effects, Sd's will decrease as the square root of the number of subjects, but if random effects are present, they will add an unknown (and sometimes large) extra component of variability to the Sd's which we can usually never estimate in advance of doing the experiment.

The efficiencies for a single run are shown in Figure 2 as Sd's, relative to error (for magnitudes), or in seconds (for delays, assuming a T statistic for magnitude of 5). Assuming additivity of the responses, both designs are roughly equally efficient for all contrasts in the magnitudes. For the delays the event design is much better for all contrasts. Of course this is for a single run, and results may differ after combining effects in higher level analyses, depending on the strengths of the random effects.

3.2 Mixed effects analysis over subjects at the third level

To illustrate the analyses, we show in Figures 4 and 5 a display of the single subject results after level 2, and their combination in level 3. These figures are included only to show how a mixed effects analysis works, and how it combines variability both within and between subjects.

We chose just one contrast, different – same sentence, which shows the most interesting results. We show the analyses of the event and block data for both magnitude and delay. We chose part of just one slice ($-74 \leq x \leq 70$, $-46 \leq y \leq 4$, $z = -2$mm), rotated 90° so that left is uppermost. This slice is located on Figures 6 and 7. The contour of the search region is added to give some idea of anatomy.

The first row of each figure shows the estimated effect (Ef) for each of the 14 subjects

from the first two levels of the analysis (200 frames/run, 2 runs/subject). The last panel is the estimator combined over subjects using the mixed effects analysis at the third level.

The second row shows the estimated Sd of the first row and their effective Df. The Df's are substantially lower than $200 \times 2 = 400$ due to the randomness of the estimated temporal autocorrelations (Worsley *et al.*, 2005). They are not quite identical since they depend on the sequencing of the stimuli which varied from run to run.

The mixed effects Sd on the right is obtained by smoothing the ratio of random/fixed effects Sd by an amount chosen to give 40 effective Df (Worsley *et al.*, 2002). The amount of smoothing varies because it depends on the inherent smoothness of the effects (as data). The smoothed random/fixed effects Sd image is shown on the far right. A value of 1 indicates that the mixed effects Sd is the same as the fixed effects Sd, so that the random effect is zero and can be ignored. A value greater than 1 indicates the presence of a random effect. Only magnitudes for the block design show some evidence of random effects ($\sim$1.5), either due to different sentence effects for different subjects, or due to different locations of these effects.

The third row shows the T statistics, equal to the first row divided by the second. The $P = 0.05$ threshold for the final T image on the right is based on the minimum of Bonferroni, random field theory, and discrete local maxima (DLM) (Worsley *at al.*, 2005b). This requires calculation of the voxel-wise effective FWHM, shown in the panel at the far right, which averages $\sim$8.6mm. The threshold is lower for delays because the search region is much smaller (since it only makes sense to look at delays where there is some signal). The positive T statistics, particularly on the left, indicate increased magnitude and delay for different sentences over same sentences.

3.3 Comparison of block and event designs

Overall the block and event designs seem to be equally good for estimating the magnitude, but the block design has slightly lower Sd's, giving slightly larger T statistics. This is not surprising, since they have roughly similar efficiencies in Figure 2. Note that the Sd for the events design on subject 7 is high (and Df low) because only one run was available.

What is surprising is the delays. Here the block design gives T statistics as high as the event design, despite the fact that the Sd's are much lower (as anticipated by Figure 2). The explanation may lie with the assumed model. Delays are estimated from both the onset and termination of the BOLD response, which is assumed to be constant throughout a block. If the response diminishes over time or terminates early, then this will result in decreased latency (see Figure 3). It is reasonable to suppose that this might happen more for the same sentence condition (due to boredom) than with the different sentence condition (novelty will sustain interest). The time courses given by DL appear to show just this linear decline after the 2nd event in a block, more pronounced for the same sentence condition than for the different sentence condition. The result might be an apparent increase in latency for different sentences in the blocks design due perhaps to sustained response rather than delayed response (see Figure 3).

Can the event and block results be combined? The answer appears to be yes, at least for the magnitudes. The reason is that the magnitude effects are roughly equal between events and blocks (see also Table 2). In fact most cannot be rejected as being different by a two-sample T-test. Of course the delays cannot be combined because of the apparent delay shifts in blocks due to a decline in BOLD response within a block, as just discussed. Accordingly the events and blocks were combined at the second level of the hierarchy (over

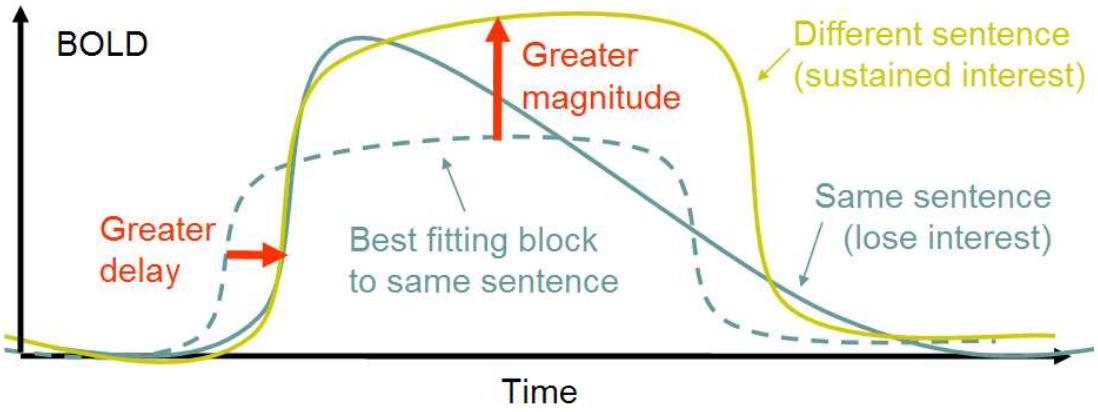

Figure 3: Illustration of how a decline in BOLD response during a block can alter both the apparent magnitude and delay of the block.

runs within subjects), then combined in the usual way at the third level (over subjects).

3.4 Inference

The complete results are shown in Table 2 for comparison with other analyses. Local maximum T statistics inside a significant cluster are indicated in bold face. Clusters were thresholded at $P = 0.001$ (uncorrected) for magnitudes, and $P = 0.01$ (uncorrected) for delays. P-values for clusters are based on their spatial extent measured in resels, which allows for spatially varying FWHM (Hayasaka *et al.*, 2004). Only the events data was used for detecting differences in delays.

There appear to be significant magnitude effects for sentence and speaker, but there is no evidence of an interaction. The sentence contrast shows both positive and negative effects. The combination of events and blocks detects more activation than either events or blocks alone, as expected, since the combined Sd's are lower. There is some evidence for a sentence effect on delay for the events data but this is not supported by a significant cluster.

4 Conclusions

The most prominent effects are increases of magnitude for different – same sentence. We estimate increases as high as $1.08 \pm 0.17\%$ if events and blocks are combined. These increases are spread all along the left mid-temporal gyrus, as reported in DL, and to a lesser extent in the right mid-temporal gyrus (see Figure 6). There is some evidence for a decrease in magnitude in the left and right inferior parietal lobule (Brodmann area 40), though it is about half that of the increases (-0.52 ± 0.08).

There is also evidence for a speaker effect on magnitudes in roughly the same part of the left mid-temporal gyrus as the sentence effect, Brodmann area 21. However the size of the speaker effect is about half that of the sentence effect, peaking at 0.47 ± 0.08 for the combined data.

Turning to delays, we note again that the delay local maximum is isolated and not supported by a significant cluster. Nevertheless there is some evidence for increased delay of 153ms for different sentences compared to same sentences in the right superior temporal

gyrus, Brodmann area 22. What is interesting here is that the delay can be estimated so accurately, to within 35ms.

Our conclusions can be summarized as follows:

- an increase of sentence magnitude in the left and right mid-temporal gyri, and in the left inferior temporal gyrus;
- a smaller decrease of sentence magnitude in the left and right inferior parietal lobule, Brodmann area 40;
- a smaller increase in speaker magnitude in the left mid-temporal gyrus, Brodmann area 21;
- an increase in sentence delay in the right superior temporal gyrus, Brodmann area 22.

5 Discussion: Comparison with Dehaene-Lambertz *et al.* (2006)

We chose covariates identical to those of DL: four covariates for each condition after the first in a block or run, and one for the first event in any block or run. We analysed exactly the same contrasts, though DL analysed several others that we did not attempt: sentence effects under same and different speaker conditions, and tests of asymmetry.

DL also looked at delays, but for a different data set (experiment 1) from the FIAC data analysed here. They reported increased delay in temporal poles and inferior frontal regions, compared to Heschl's gyrus. DL was more interested in differential regional delays of the same stimulus. These differences could be partly attributed to differences in hemodynamics, rather than neuronal activity, although DL argue that hemodynamics cannot explain all the observed delay differences. On the other hand, we were looking for differential stimulus delays in the same region, which is unaffected by regional differences in hemodynamics, and so presumably only attributable to neuronal activity.

We compared our results in Table 2 with those reported by DL in their Table 2. Overall we found more significant activations than DL, indicating that our analysis is more sensitive, while maintaining the same false positive rate. This is based on the fact that none of the local maxima reported by DL reached statistical significance, whereas we found four in the same blocks data set. DL reported only one significant cluster of 1.6cm^3, whereas we found three ranging in size from 2.7 to 7.9cm^3 at the same cluster threshold. Whereas DL only found evidence for an increase of sentence magnitude, we found evidence for a decrease as well. Yet this is despite that fact that we analysed 14 subjects, whereas DL analysed 16.

It is difficult to pin-point which aspects of our analysis make it more sensitive. Note first that there were several non-statistical factors that could come into play:

- different slice timing and motion correction;
- different registration;
- different smoothing (DL used 8mm smoothing, but we did not smooth the actual data).

Their are several minor differences on the statistical side, such as the shape of the HRF, but the main ones are:

- different drift covariates,
- different strategies for dealing with temporal correlation (DL used a spatially constant temporal correlation structure, whereas ours varied spatially);
- mixed effects rather than pure random effects at the subject level;
- spatial smoothing of the random/fixed effects Sd ratio to boost the effective Df from 13 to 40;
- the new DLM P-values (Worsley, 2005b) that reduced the P-values of local maxima by $\sim$43% for P-values near 0.05.

These last two factors may be one of the main contributors. We ran the same analysis as in Table 2 but with no smoothing, so that the effective Df was 13 (as in DL) rather than 40. Significant clusters were reduced from 20 to 14, and significant local maxima were reduced from 16 to 4, with one in the blocks data. This is still more than in DL, so smoothing of the random/fixed effects Sd ratio cannot be the only factor that contributes to the increased sensitivity of our analysis. We tried switching off the DLM P-values, using just the best of Bonferroni and random field theory (as in DL). This increased P-values by $\sim$10% but did not reduce the number of local maxima (switching off DLM without switching off the smoothing reduced the local maxima from 16 to 11, with 3 in the blocks data). This is still more than DL, so smoothing of the random/fixed effects Sd ratio and the new DLM P-values cannot be the only factors that contribute to the increased sensitivity of our analysis.

Finally, it is reassuring that the centres of activation that are reported by DL do coincide with ours.

Acknowledgement

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Magnitude

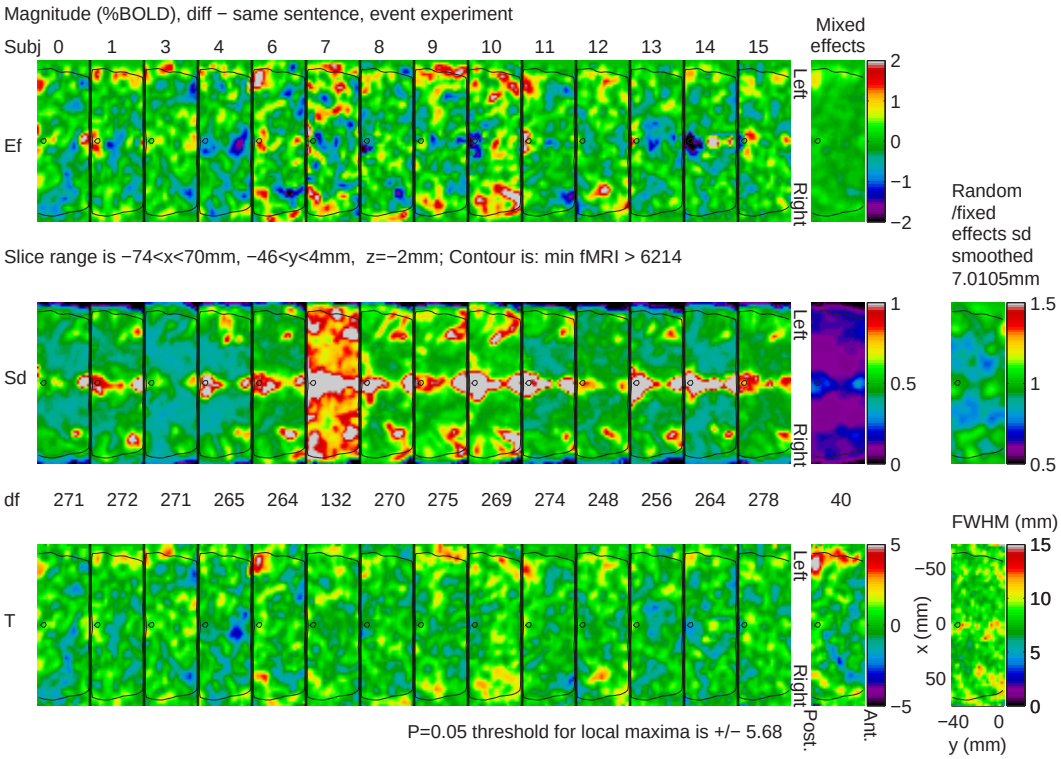
Contrast	Expt	T	Ef $\pm$ Sd(%)	P	x	y	z	Area
Sentence	Event	**6.57**	0.86 $\pm$ 0.13	0.003	-54	-12	-20	LITG
		6.08	0.88 $\pm$ 0.14	0.015	-58	-44	-2	LMTG
		5.43	0.64 $\pm$ 0.12	0.109	-18	-64	18	LPRE
		4.98	0.62 $\pm$ 0.12	0.426	54	-16	-14	RMTG
		-4.73	-0.48 $\pm$ 0.10	0.860	-58	-48	34	LSmG
	Block	**7.61**	1.00 $\pm$ 0.13	<0.001	-60	-10	-10	LMTG
		5.94	0.62 $\pm$ 0.10	0.021	56	-14	-6	RMTG
		5.69	1.17 $\pm$ 0.21	0.048	-56	-42	-2	LMTG
		-6.48	-0.58 $\pm$ 0.09	0.004	-52	-52	46	LIPl, B40
	Comb.	**7.85**	0.96 $\pm$ 0.12	<0.001	-60	-10	-10	LMTG
		6.30	1.08 $\pm$ 0.17	0.007	-56	-42	-2	LMTG
		5.93	0.79 $\pm$ 0.13	0.022	-52	-10	-22	LITG
		5.74	0.69 $\pm$ 0.12	0.039	56	-14	-12	RMTG
		5.69	0.51 $\pm$ 0.09	0.047	60	-10	-6	RMTG
		-6.65	-0.52 $\pm$ 0.08	0.002	-52	-56	44	LIPl
		-6.37	-0.38 $\pm$ 0.06	0.006	-50	-56	34	LIPl
		-5.61	-0.40 $\pm$ 0.07	0.060	50	-48	40	RIPl
Speaker	Block	**5.46**	0.58 $\pm$ 0.11	0.098	-64	-40	-2	LMTG, B21
	Comb.	**5.97**	0.47 $\pm$ 0.08	0.020	-64	-40	-2	LMTG, B21
		5.77	0.38 $\pm$ 0.07	0.038	-58	-34	-2	LMTG

Delay

Contrast	Expt	T	Ef $\pm$ Sd(s)	P	x	y	z	Area
Sentence	Event	4.33	0.153 $\pm$ 0.035	0.048	58	-18	2	RSTG, B22

Table 2: Local maximum T statistics (T = Ef/Sd, 40 Df), P-values ($P \leq 0.05$, corrected), effect (Ef) $\pm$ standard deviation (Sd), and x, y, z Talairach coordinates (mm). Only local maxima separated by more than one FWHM (8.6mm) are shown. Bold face indicates a local maximum inside a significant cluster ($P \leq 0.05$, corrected). Comb is the combination of the event and block data. Only the events data was used for delay. L=Left, R=Right, I=Inferior, S=Superior, M=Middle, T=Temporal, G=Gyrus, Sm=Supramarginal, Pl=Parietal lobule, B=Brodmann. The threshold for delay local maxima is lower than that for magnitude because the delay search region is much smaller (20-37cm^3) than the magnitude search region (1424cm^3). There were no significant activations for the interaction contrast, nor for the speaker contrast in the delays.

(a) Event design



(b) Block design

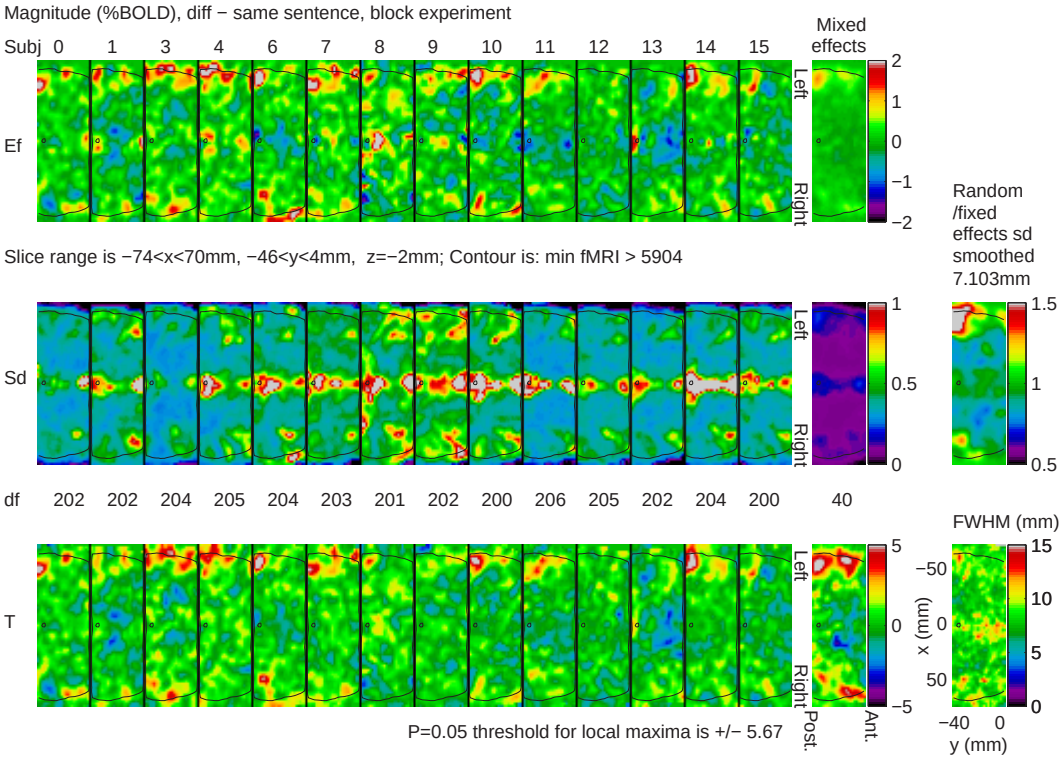


Figure 4: Single subject results after level 2, and their combination in level 3 for magnitudes of different – same sentence for (a) event design, and (b) block design, rotated 90° so that left is uppermost (located on Figures 6 and 7).

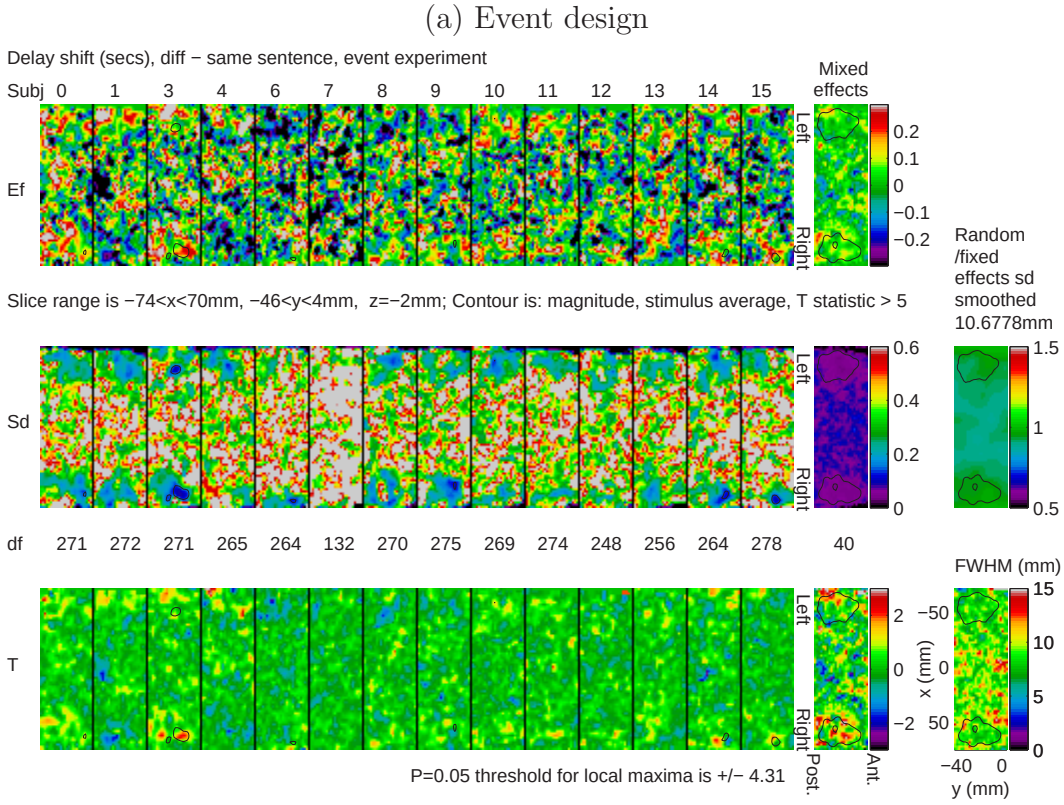


Figure 5: Single subject results after level 2, and their combination in level 3, for delays of different – same sentence for (a) event design, and (b) block design, rotated 90° so that left is uppermost (located on Figures 6 and 7).

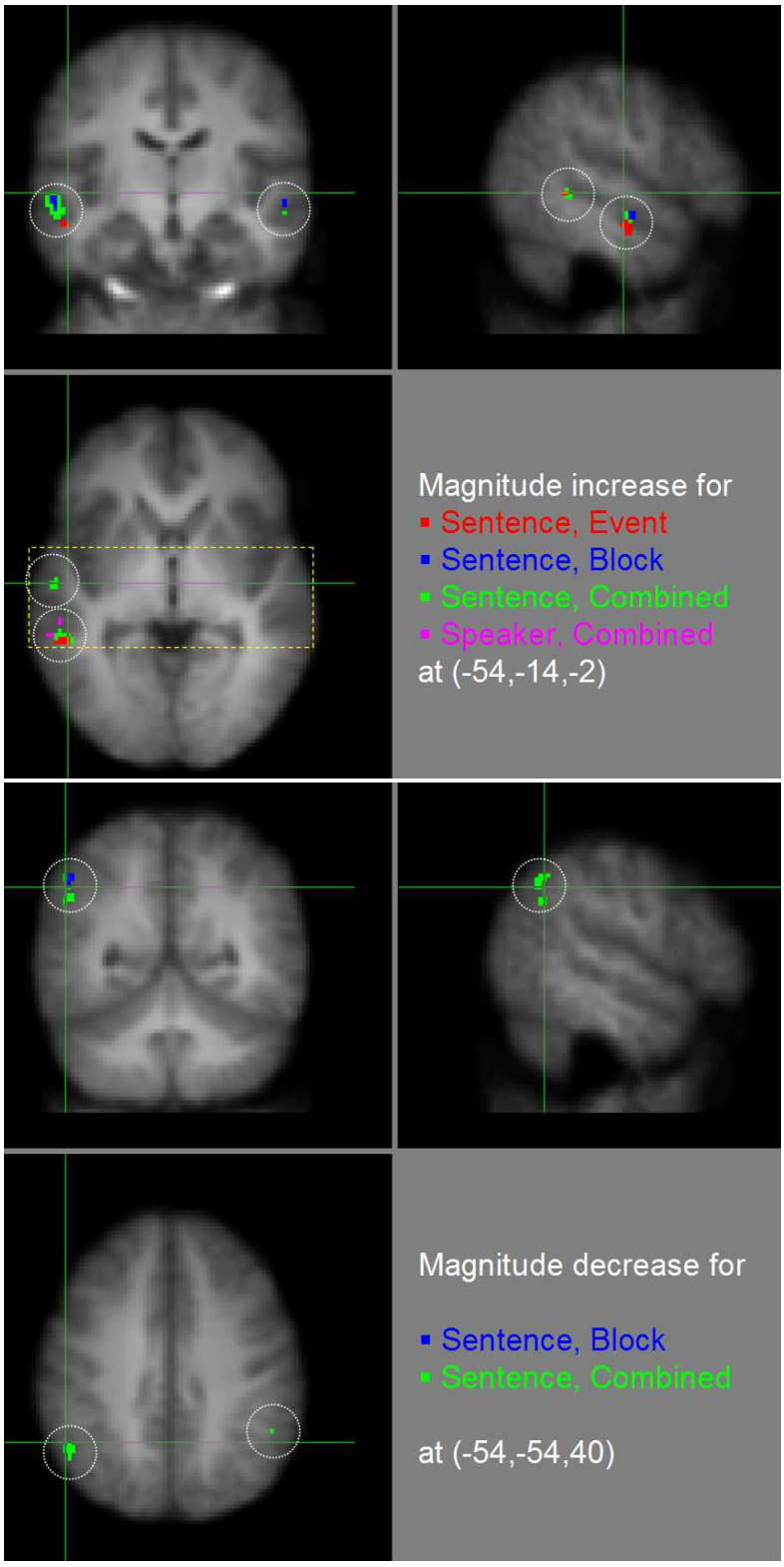


Figure 6: Sentence and speaker magnitude T statistics (40 Df) for event superimposed on block superimposed on combined data sets, thresholded at $P < 0.05$ (corrected) and superimposed on the average anatomy of the 14 subjects. The portion of the slice used in Figures 4 and 5 is outlined in yellow dashes.

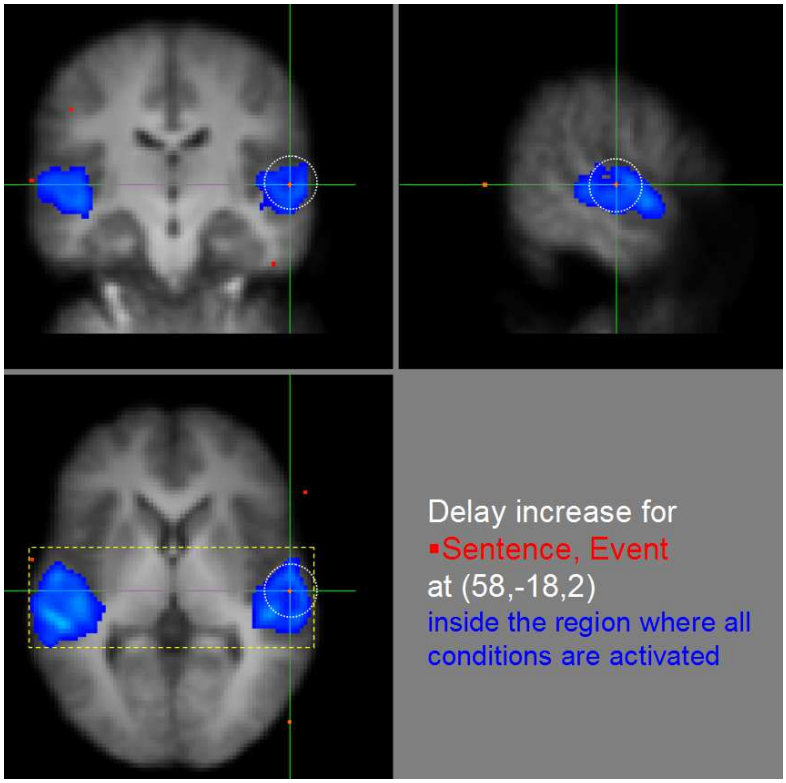


Figure 7: Sentence delay T statistics (40 Df) for the event data set, thresholded at $P < 0.05$ (corrected), superimposed on the search region where all conditions are activated, superimposed on the average anatomy of the 14 subjects. The portion of the slice used in Figures 4 and 5 is 4mm below the dashed yellow outline.