

Baseline Conditions and Subtractive Logic in Neuroimaging

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Abstract: Discrepancies in the patterns of cortical activation across studies may be attributable, in part, to differences in baseline tasks, and hence, reflect the limits of the subtractive logic underlying much of neuroimaging. To assess the extent of these effects, three of the most commonly used baseline conditions (rest, tone monitoring, and passive listening) were compared using phoneme discrimination as the experimental task. Eight participants were studied in a fMRI study with a 4.1 T system. The three baseline conditions systematically affected the amount of activation observed in the identical phoneme task with major effects in Broca's area, the left posterior superior temporal gyrus, and the left and right inferior parietal regions. Two central findings were: 1) a differential effect of baseline within each region, with the rest baseline condition producing the greatest amount of activation and the passive listening condition producing the least, and 2) systematic baseline task activation in the inferior parietal regions. These results emphasize the relativity of activation patterns observed in functional neuroimaging, and the necessity to specify the baseline processes in context to the experimental task processes. *Hum. Brain Mapping* 14: 228–235, 2001. © 2001 Wiley-Liss, Inc.

Key words: functional imaging; brain mapping; baselines

INTRODUCTION

Discrepancies are not infrequent across neuroimaging studies that examine the same process even when using similar tasks. One example is phonological perception, in which “five studies generated five different

findings” [Demonet et al., 1992; Paulesu et al., 1993; Petersen et al., 1989; Poeppel, 1996; Sergent et al., 1992; Zatorre et al., 1992]. Poeppel [1996] suggested that one possible reason is a lack of explicit task decomposition of both the experimental and the control tasks. The baseline condition is used to quantify or visualize brain activity, and researchers have noted possible limitations in the common procedures [Binder et al., 1996, Binder et al., 1999; Mellet et al., 1999; Sergent et al., 1992; Wise et al., 1999]. The contribution of the current study is that it empirically demonstrates differences in activation patterns for the identical phonological perception task by contrasting the effects of three commonly used baselines (rest, passive, and task-related). The more general argument is that neuroimaging results are dependent on both the baseline

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and experimental tasks, which has implications for how neuroimaging data are conceptualized and summarized.

The simplest baseline, the resting baseline, may be used with the implicit assumption that at “rest” the brain provides no modulated activation. But such an assumption is false, and recent studies have found evidence of episodic memory retrieval [Andreasen et al., 1999], linguistic processing [Binder et al., 1996] and conceptual processing [Binder et al., 1999]. Unfortunately, the investigator has no measure of the processes executed when the participant is not formally engaged in a task [Binder et al., 1996, 1999; Demonet et al., 1993; Liotti et al., 1994; Roland, 1993].

A similar limitation arises with passive baseline tasks, in which participants listen to or view stimuli with instructions not to process them [Menard et al., 1996; Zatorre et al., 1992]. The goal is to equate stimulus presentation and response with the experimental task, without the intervening perceptual and cognitive processes. If participants passively listen to or view stimuli, it is difficult to determine exactly what they are attending to, whether it is irrelevant or conversely, whether they are deeply processing the stimuli [Demonet et al., 1993; Sergent et al., 1992]. Therefore, the effect that the passive baseline has on an activation map may be unpredictable.

The task-related baseline is intended to isolate specific mental operations to relate them to brain activation [Petersen et al., 1988]. The hierarchical baseline procedure eliminates the uncontrolled processing associated with the rest baseline by providing the participant with a well-specified task. As several investigators have noted, however, the hierarchical baseline procedure is based on the logic of “pure insertion,” namely, that it is possible to insert or delete processes without affecting other processes. This logic has been disproved in neuroimaging studies [Friston et al., 1996; Jennings et al., 1997; Sidtis et al., 1999] and behavioral studies [Sternberg, 1969].

The current study examines how three types of baseline conditions (rest, passive listening to phonemes, and monitoring tones) affect the activation in the same experimental task, a phoneme-discrimination task in which participants heard pairs of consonant-vowel-consonant (CVC) non-words and judged whether or not the two non-words ended with the same sound. This task involves stimulus encoding, short-term memory, segmenting the final phonemes, comparing, and responding.

Such task decompositions can be applied to baseline tasks to give a better understanding of their processing overlap with the phoneme discrimination task. For

example, during the tone discrimination baseline, triplets of high and low pitch tones were presented, and the participants judged whether or not the final tone was a high pitch tone. This task requires processes similar to those in the experimental task, namely, stimulus encoding, short-term memory, segmenting the final tone, comparing and responding, although the stimuli are tones rather than phonemes. The overlap implies that there should be less activation detected with the tone discrimination baseline than with either the rest or the passive conditions.

In the passive-listening baseline, the stimuli were presented as in the experimental phoneme discrimination task, but participants were asked not to respond and to avoid thinking about the stimuli. Activation associated with the auditory processing of the stimuli should be observed. On the other hand, if the stimuli automatically elicit cognitive processes similar to those of the phoneme discrimination task, the activation would be less observable than in the rest-baseline task.

During the rest baseline, it has been argued that conceptual and linguistic thoughts occur [Binder et al., 1999; Mellet et al., 1999], although these processes are likely to be less patterned and more semantic than the processes in phoneme discrimination. There should be less overlap in processing between the experimental task and rest baseline condition, leading to the prediction that activation should be more detectable with this baseline than with either the tone discrimination or passive-listening conditions. The general prediction is that the three baselines will lead to differences in activation with the same experimental task. This hypothesis was tested by examining the activation in three main areas that have been associated with phoneme perception: 1) the inferior frontal gyrus (IFG), which on the left is associated with phonological and linguistic production and comprehension; 2) the posterior superior temporal gyrus (lpSTG), which is often associated with linguistic comprehension; and 3) the inferior parietal region, which has been associated with the maintenance of phonological information [Demonet et al., 1992, 1994; Zatorre et al., 1992, 1996].

MATERIALS AND METHODS

Participants

Eight right-handed volunteers between the ages of 21 and 35 years (3 men, 5 women), with no history of neurological or auditory symptoms, were scanned. Each gave informed written consent approved by the University of Alabama at Birmingham (UAB) IRB.

Image Acquisition

Scanning was performed at 4.1 Tesla on a system with a Bruker magnetic resonance spectrometer and console and Magnex magnet and gradients, located at the Center for Nuclear Imaging Research at UAB. Two imaging protocols were used because of a system upgrade mid-way through data collection. No significant differences in the amount of activation was observed in any of the ROIs when comparing the two protocols ($P > 0.1$ for each ROI). The first protocol consisted of eight 128×128 gradient echo axial scout images and six interleaved spiral functional images; 120 sequential images of each slice using a TR = 4,200 msec and a TE = 25 msec (six of the eight participants). The second protocol consisted of 20 256×256 gradient echo anatomical scout images and 18–20 64×64 EPI functional images; 120 sequential images of each slice using a TR = 2,500 msec and a TE = 38.5 msec (two of eight participants). The slice thickness was 5 mm with a 5 mm slice gap for both protocols.

An imaging session consisted of three separate imaging series, one with each of the three baselines, presented in counterbalanced orders across sessions. An image series included five epochs of the discrimination task and five epochs of the baseline task resulting in a total of 120 repetitions of each slice. The total imaging session was approximately 2 hr in duration.

Image Analysis and Task Comparisons

Data analysis was performed with the STIMULATE [Strupp, 1996] analysis package. A cine loop of the 120 frames was used to detect gross subject motion; data sets with observable motion were not analyzed further. Activation maps were obtained using correlational analysis with a trapezoidal reference function. A stringent r threshold ($r > 0.3$, using an F-statistic with $\alpha = 0.005$) and a cluster-size constraint (three contiguous voxels) reduced the possibility of a Type II error. To minimize effects of changes in the blood-flow rate of larger vessels, voxels that had a large percentage change in signal intensity (greater than 10%) were excluded from the analyses.

The ROIs were defined by using the parcellation method originally described by Rademacher et al. [1992]. For each participant, the limiting sulci and cerebral landmarks were identified by viewing the structural images in the three orthogonal planes of a 3-D rendering of the axial slices. The major analysis focused on three ROIs: IFG, the inferior parietal region (supramarginal/angular gyrus), and the left posterior superior temporal gyrus (lpSTG). The primary audi-

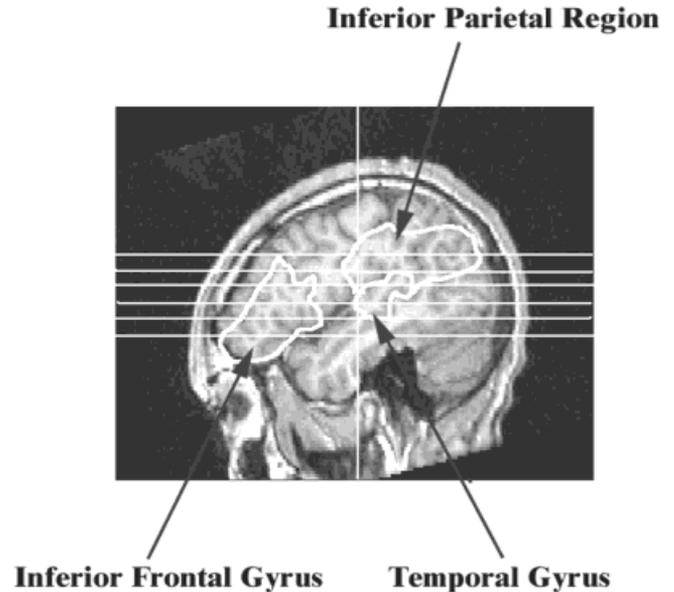


Figure 1.

A typical slice prescription and the ROIs, which include the inferior frontal gyrus (IFG), the posterior superior temporal gyrus (pSTG), and the inferior parietal region (IP).

tory cortex was excluded from the lpSTG ROI. Figure 1 depicts the ROIs overlaid on a single participant along with the slice orientation. As shown, the six slices covers the majority of IFG and pSTG, as well as a significant portion of the inferior parietal region. For the two participants with a different slice prescription, only slices that corresponded to the ROIs were used in the analysis.

The data analysis focuses on quantifying the volume of fMRI-measured activation using the number of voxels that have an activation level that is significantly above the baseline within each of the anatomically defined ROIs for each participant. Because the main prediction was that activation in the ROIs would be modulated by baseline condition, the activation was examined using an analysis of variance with ROI (IFG, lpSTG and IPL), laterality (right vs. left) and baseline (rest, passive vs. tone) as within-subject factors. In addition, we quantified the number of voxels that were significantly more activated in the baseline task than in the phoneme discrimination task. In the current study the error term was defined as the square root of MS_e/n , where MS_e is the pooled error term for both of the independent variables [Loftus and Masson, 1994].

Stimuli

The stimuli were 16-bit digital recordings of 50, 500 msec CVC non-words of a male voice. The amplitude

of the initial and final consonants was amplified to compensate for the losses due to transmission. In each trial two CVC syllables were presented with a 500 msec inter trial interval. Half of the CVC pairs ended in the same sound. The low pitch tones had a frequency of 500 Hz and the high pitch tones 750 Hz [Binder et al., 1995]. The tones were 300 msec in duration and 500 msec separated each tone in the triplet.

Procedure

Participants had a practice session before imaging. During this session, ear molds were made and questionnaires were completed. One of the questionnaires was a handedness inventory [modified from Annett, 1967; Briggs and Nebes, 1975]. All participants scored as right handed with a mean of 21 ± 2.7 , where +24 is extremely right-handed and -24 is extremely left-handed. The practice session also included an over-

TABLE I. Baseline difference statistics

ROI	t(7)		
	Rest vs. passive	Rest vs. tone	Tone vs. passive
Left IFG	2.8*	1.81	1.1
Left IP	3.95**	1.7	1.1
Left pSTG	3.54**	2.78*	<1
Right IFG	<1	<1	<1
Right IP	2.6*	1.26	1.25
Right pSTG	1.75	1.89*	0.088

* $P < 0.05$.

** $P < 0.005$.

view and practice of the tasks to be performed during the imaging session.

During the phoneme discrimination task, participants heard pairs of CVC non-words and were instructed to respond “yes” with the left push button if the non-word pair ended in the same sound and “no” with the right push button if the non-word pair did not end in the same sound.

During the rest baseline, participants were not presented with any stimuli, and they were asked to “relax and refrain from thinking of anything.”

During the passive listening-baseline task, participants were presented with the same stimuli that were used in the discrimination task but were told, “please, do not respond to the stimuli during this period, just try to relax and refrain from thinking about anything.”

During the tone monitoring-baseline task, participants heard tone triplets and were instructed to respond “yes” with the left push button if the triplet ended in a high pitched tone and “no” with the right push button if the tone triplet did not.

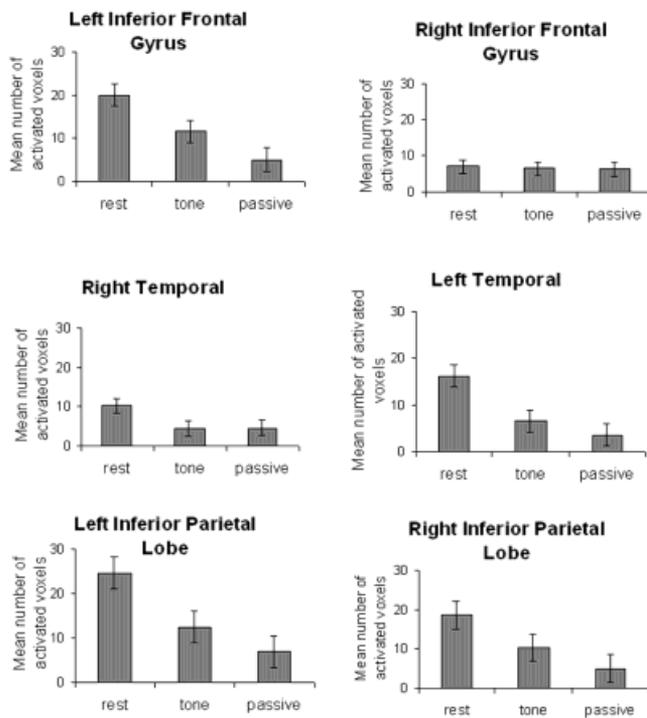


Figure 2.

Each graph depicts the amount of activation in a given ROI as a function of baseline condition. The graphs are all on the same scale. Error bars represent the square root of MS_e/n , where MS_e is the pooled error term for both of the independent variables [Loftus and Mason, 1994]. The left IFG, left temporal and left and right IP regions all show a monotonic decrease in the amount of activation as a function of baseline condition. In addition, the right homologue patterns are similar to those for the corresponding left region, with the exception of the right IFG.

RESULTS AND DISCUSSION

As predicted, the three baselines resulted in systematically different levels of activation in all ROIs [$F(2,12) = 11.69, P < 0.002$]. As shown in Figure 2, the rest condition produced the greatest number of activated voxels in most regions. The passive-listening condition produced the least number of activated voxels (Table I). Because phonemes are linguistic stimuli, there was predictably more activation in the left hemisphere than the right, resulting in a marginally significant effect of laterality, as well as a significant interaction between the baseline condition and laterality [$F(1,7) = 4.16, P < 0.08; F(2,12) = 4.11, P < 0.044$].

Inferior Frontal Gyral ROI

Left IFG has been implicated by several studies in phonological processing. As shown in Figure 2, the activation within IFG was significantly affected by the baseline condition and the laterality was marginally significant [$F(2,12) = 4.21, P < 0.04$; $F(1,7) = 4.58, P < 0.07$]. In addition, there was a significant interaction between the baseline condition and laterality [$F(2,12) = 5.86, P < 0.02$]; the left IFG revealed significant baseline differences, right IFG did not [$F(2,12) = 6.11, P < 0.02$; $F < 1$]. This asymmetry in the two hemispheres indicates that the baseline conditions have specific effects, not global increases or decreases in the amount of activation. For the left IFG, planned contrasts revealed that the rest condition resulted in significantly more activation than the tone or passive-listening conditions. The decreased activation for the tone and the passive-listening conditions is consistent with the hypothesis that processes in those conditions are more similar to those in the phoneme discrimination task.

The activation in this region when contrasted with the rest condition was concentrated around the ascending ramus and extended into BA 44, the same area cited in a review of other phonological processing tasks [Poldrack et al., 1999]. The locations of the activation for the other two baselines were subsets of that observed with the rest baseline, but they were not the same subset, suggesting some processing differences. The passive-listening baseline showed activation within BA 44 near the inferior frontal sulcus, whereas the tone discrimination baseline revealed activation located around the ascending ramus. The modulation caused by the passive-listening condition may be more related to the similarity of the sound structure of the phoneme stimuli, whereas the modulation caused by the tone-discrimination task may be related to segmentation or verbal working-memory processes.

Posterior Superior Temporal ROI

The lpSTG, like IFG, has been implicated in phonological processing [Burton et al., 2000; Demonet et al., 1994; Fiez et al., 1996; Price et al., 1992; Zatorre et al., 1996]. As predicted and shown in Figure 2, significant activation was observed for all three baseline conditions. In addition, although there was a significant difference among the baselines [$F(2,12) = 9.48, P < 0.004$], there was no effect of laterality, $F < 1$, and a marginally significant interaction between the baseline condition and laterality [$F(2,12) = 3.41, P < 0.07$]. Additional analysis revealed that although left pSTG

revealed significant effects of baseline, the differences in right pSTG were similar but attenuated and not statistically significant [$F(2,12) = 14.05, P < 0.0007$; $F(2,12) = 2.91, P < 0.1$]. Planned contrasts showed that the rest condition resulted in more activation than both the tone and passive-listening conditions.

Activation in pSTG was expected because auditory linguistic stimuli are associated with activation not only in primary auditory cortex but also in auditory association cortex, particularly left pSTG [Michael et al., 2001]. Also, the activation is more left lateralized for the tone baseline than the passive-listening baseline, suggesting less effect of the non-linguistic tones on the linguistically associated left pSTG compared to the linguistic stimuli presented in the passive-listening condition. Therefore, the differential laterality suggests that the stimuli have differential effects, even though the tone monitoring task was structured to overlap with the experimental task.

Inferior Parietal ROI

The left inferior parietal lobe has been associated with phonological processing and working memory [Awh et al., 1996; Demonet et al., 1996; Paulesu et al., 1993]. As predicted and shown in Figure 2, significant differences in activation was observed in this region among the three baselines, but there was no significant effect of laterality, nor was there a significant interaction between the two factors [$F(2,12) = 5.43, P < 0.02$; $F(1,7) = 2.18, P > 0.18$; $F < 1$]. Additional tests revealed that the left IPL revealed a significant effect of baseline whereas the effect in the right IPL was only marginally significant [$F(2,12) = 4.76, P < 0.03$; $F(2,12) = 3.31, P < 0.07$].

The tone baseline task and the phoneme discrimination task both require the short-term maintenance of stimuli, and it may be this overlap in processing that is responsible for the activation modulation observed. The passive condition, on the other hand, is not expected to need such buffering because no response is required. The inferior parietal region has not only been associated with verbal working-memory, but it has also been associated with an interface system between auditory and articulatory representations [Hickok and Poeppel, 2000]. Because both the experimental phoneme discrimination task and the passive listening baseline may be expected to access this interface system, the modulation of activation in the inferior parietal region by the passive baseline condition may be due to the automatic triggering of articulatory representations when presented with an auditory stimulus.

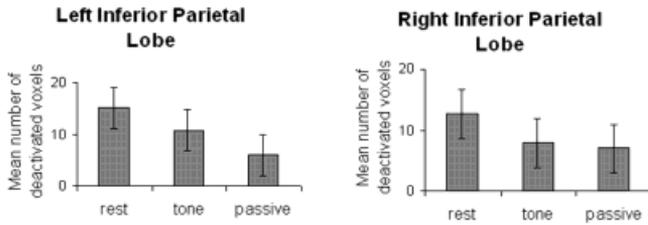


Figure 3.

The graphs depict the amount of baseline task activation in a given ROI. The amount of activation is defined as the mean number of deactivated voxels. Note that the graphs are on the same scale. Error bars represent the square root of MS_e/n , where MS_e is the pooled error term for both of the independent variables [Loftus and Masson, 1994].

Baseline Task Activation

We also examined the activation when the experimental task was subtracted from the baseline tasks. Whereas the rest condition produced significant activation within left IFG, lpSTG, left and right inferior parietal regions, and posterior cingulate, only the left and right inferior parietal regions revealed consistent baseline task activation across participants for the passive and tone baseline conditions as well. An ANOVA with baseline as a within subject factor revealed that there were no significant differences across baselines for the left and right inferior parietal lobe [$F(2,12) = 1.96, P > 0.18; F < 1$]. Paired contrasts did reveal, however, that the rest condition activated significantly more voxels in left IPL than the passive condition (see Fig. 3 and Table II). Despite the rest condition being associated with left IPL activation, there was still considerably more activation in this region compared to both the tone and the passive conditions. This suggests that there is minimal overlap of the processes of the rest baseline and the phoneme discrimination task.

Although there was a greater amount of baseline task activation in left IPL for the rest baseline compared to the passive baseline, this effect is not observed in right IPL. This again shows that the effect of

baseline is not a global increase or decrease in the amount of activation.

DISCUSSION

This is the first study that empirically demonstrates differences in activation patterns for an identical task by contrasting the effects of three commonly used baselines (rest, passive and task-related). The results support what has been previously hypothesized, namely, that the choice of baseline differentially affects the observed activation pattern and hence, may be responsible for some of the discrepancies in activation patterns noted by Poeppel [1996].

Several new analytical approaches have been adopted that eliminate the necessity of an absolute zero baseline point. These approaches include the graded design [Carpenter et al., 1999; Grasby et al., 1994; Just et al., 1996] and co-variance approaches [Clark et al., 1984; Fletcher et al., 1999; Friston et al., 1997; Horwitz et al., 1984, 1998], which represent significant advances over the standard subtraction technique. The results produced by these techniques, however, are still usually relative to a baseline, although in more subtle ways. In the graded designs, the baseline may affect the absolute levels of activation; specifically, the absolute level will be lower if the baseline shares more processes with the experimental tasks. The baseline can also affect the detection of differences between the graded conditions if it plays a role in identifying the relevant (i.e., significantly activated) voxels. The covariance approach typically involves determining whether the covariance pattern changes between tasks, which appears to make the choice baseline somewhat irrelevant. The choice of baseline, however, can still affect the results if a baseline task is used in the identification of the voxels that are used in the covariance calculation; indeed, this procedure is used [Horwitz et al., 1998]. Thus, we suggest that the influence of the baseline task is not eliminated even by these more sophisticated designs, although this does

TABLE II. Baseline task activation

ROI	Mean number of active voxels			t(7)		
	Rest	Tone	Passive	Rest vs. passive	Rest vs. tone	Tone vs. passive
Left IP	15.0	10.7	6.8	2.14*	<1	1.16
Right IP	11.6	7.9	6.6	1.37	<1	0.39

* $P < 0.05$.

not negate the considerable value and power of these new approaches.

With the explosive growth of neuroimaging studies, there have been attempts to pool neuroimaging data and synthesize the results across studies to develop cortical maps that associate particular processes to particular cortical regions. The current results warn against any simple association between experimental tasks and cortical areas. It complicates the interpretation of both single studies as well as meta-analyses because it suggests that, in general, results cannot be associated accurately with single processes, but rather with contrasts between processes, such as between the processes in two conditions or tasks. As shown here, different activation patterns emerge from the same experimental condition when measured with different baselines. These data suggest that the conceptual interpretation of studies will be limited by differences in baseline tasks; a similar point may extend also to differences in experimental tasks or in data acquisition procedures. Although pooling data may provide some insights, accuracy will be sacrificed if we ignore the existence of such effects either quantitatively or conceptually.

Functional neuroimaging has enabled advances in our understanding of the neuronal networks involved in cognition. There is a tendency in the field, however, to focus on the experimental task and ignore or give less attention to the baseline task. The current results demonstrate that such a bias or assumption is inaccurate, and may account for some of the discrepancies that arise across studies that ostensibly study the same or similar task. That results are relative to the baseline is not new nor is this quality specific to neuroimaging, even data in behavioral studies are interpreted with reference to various control measures and the same point is true of other types of neuroscience data, such as single cell recording. The relativity of the data poses a challenge to how researchers think about the relation of particular experimental designs to the results.

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