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Subtractions, Conjunctions, and Interactions in Experimental Design of Activation Studies

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Abstract: This paper contrasts different experimental designs for revealing the neural correlates of phonological retrieval (i.e., naming). Cognitive subtraction designs require a minimum of one task pair and the comparison between tasks reveals the differing functional task components. Conjunction analysis requires a minimum of two task pairs, each differing by the same component, and this component is revealed as the difference which is common to both task pairs. Two different limitations of cognitive subtraction are highlighted: 1) the difficulty of finding baseline tasks that activate all but the process of interest, and 2) activation differences (between the two tasks of a pair) include the interaction term, i.e., the effect that the added component in the activation task has on preexisting components. The problem of baseline selection can be overcome by conjunction analysis, for which there may be many processing differences for each task pair, providing that the only common difference between pairs is the component of interest. The problem of interactions can be overcome when the experimental design is factorial. This permits the effect that an added component has on the expression of preexisting components (i.e., the interaction term) to be evaluated explicitly. We demonstrate that when the design is factorial, conjunction analysis reveals commonalities in activation, while the interactions reveal task-specific effects. *Hum. Brain Mapping 5:264–272, 1997.* © 1997 Wiley-Liss, Inc.

Key words: PET; subtractions; conjunctions; interactions; reading; phonology

INTRODUCTION

Neuroimaging studies reveal the functional neuroanatomy of cognitive processes by contrasting the hemodynamic responses elicited by different experimental conditions. All categorical activation studies are therefore subtractive in nature. In this paper, we present and discuss three variations of experimental paradigms: cognitive subtraction, conjunction analysis, and analysis of interaction terms. The results of the different approaches are illustrated with experiments which aim to identify the neural correlates of phonological retrieval during reading (i.e., assigning a verbal name to visually presented words). The merits of each approach are assessed in relation to lesion studies that demonstrate that reading and naming deficits primarily result from damage to left posterior temporal and inferior frontal cortices [Mesulum, 1990; McCarthy and Warrington, 1990].

All the imaging experiments reported involved PET scans using bolus infusion of H_2O^{15}. Experiments 1 and 3 were acquired on an ECAT EXACT HR+ scanning system (CTI, Siemens, Knoxville, TN), and experiments 2, 4, and 5 were acquired with a Siemans 953B (CTI, Siemens) dedicated head scanner [Spinks et al., 1992]. There were 6 subjects in each experiment, and data were analyzed using statistical parametric map-

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ping (Wellcome Department of Cognitive Neurology) and standard procedures [Friston et al., 1995, 1996a].

COGNITIVE SUBTRACTION

In designs based on cognitive subtraction, there are a minimum of two tasks: an activation task that engages the cognitive component of interest (CCI), and a baseline task that engages all the processes engaged by the activation task with the exception of the CCI. The neural correlates of the CCI are simply revealed by subtracting activity during the baseline task from that during the activation task. Cognitive subtraction designs are hierarchical when the baseline task involves one more component than a third task. A good example of this is the three-level hierarchical design of Petersen et al. [1990] in which 1) word generation was contrasted to reading aloud, 2) reading aloud was contrasted to passive word viewing, and 3) passive word viewing was contrasted to visual fixation. The psychological processing differences between cognitive levels (i.e., 1) semantic processing, 2) phonological output processing, and 3) visual word forms) were then be linked to pairwise activation differences.

Interpreting the results of cognitive subtraction studies relies on two assumptions. The first assumption is that there will be more neuronal activity in a functionally specialized area when a task demands the explicit involvement of the function than when it does not. The second assumption is that of ''pure insertion,'' which asserts that an extra cognitive component can be purely inserted without affecting the expression of preexisting components [Sternberg, 1969]. This second assumption implies that the activations associated with the comparison of two tasks only reflect the cognitive component added in the activation task, leaving unchanged the implementation of components shared by activation and baseline tasks [see Friston et al., 1996b]. Experiments 1 and 2 investigate the validity of these assumptions with studies of phonological retrieval.

Experiment 1: Explicit vs. implicit reading

The assumption that there will be more neuronal activity in a functionally specialized area when a task demands the explicit involvement of a function than when it does not, predicts that reading words aloud will activate phonology more strongly than when subjects view the same words silently. This comparison has previously been reported by Petersen et al. [1990] and Bookheimer et al. [1995]. Both studies reported differences in motor and premotor areas and, in addition, Bookheimer et al. [1995] reported strong differences in bilateral superior temporal cortices and the left supramarginal gyrus. However, neither study controlled for articulation or the differences in auditory processing that ensue from hearing/monitoring the sound of the spoken response [see Price et al., 1996a]. Further, association of bilateral superior temporal and left supramarginal activation with generating and monitoring the sound of the spoken response has been demonstrated by contrasting reading aloud to a condition where subjects ''mouth'' the words without generating any noise [Price et al., 1996b]. In this case, phonological retrieval and articulation are controlled in the baseline condition and activity differences must relate to the remaining cognitive difference, i.e., generating and monitoring the sound of the spoken response. Such an effect has obscured the identification of the neural correlates of phonological retrieval during reading aloud relative to silent reading.

In experiment 1, we pursue the comparison between explicit and implicit reading by attempting to control for articulation and processing of the sound of the spoken response in a comparison of reading aloud with viewing the same words and saying ''Okay'' in response to each word. Subjects articulated the responses silently in both conditions in order to ensure that activity differences did not relate to any enhancement of auditory monitoring (of the spoken response) in the reading condition. The activation task (reading with silent articulation) involves visual, orthographic, semantic, phonological, and motor output processing. The baseline task (viewing the same words and articulating ''Okay'') should control for all these processes, with the exception of explicit phonological retrieval. We hoped that instructing the subjects to say ''Okay'' in response to the words would distract them from explicit reading. The activation differences between the tasks should then, according to the assumption of pure insertion, primarily relate to phonological retrieval.

The results identified increased activation for explicit reading in the left extrastriate visual cortex, the right cerebellum, and the left precentral cortex (see Fig. 1), but no activation differences in areas that are classically associated with phonological retrieval. The right cerebellum and left precentral activity relates to differences in articulatory requirements when subjects say a different word to each stimulus compared to saying the same words repeatedly in the control condition [Price et al., 1996a]. The left extrastriate

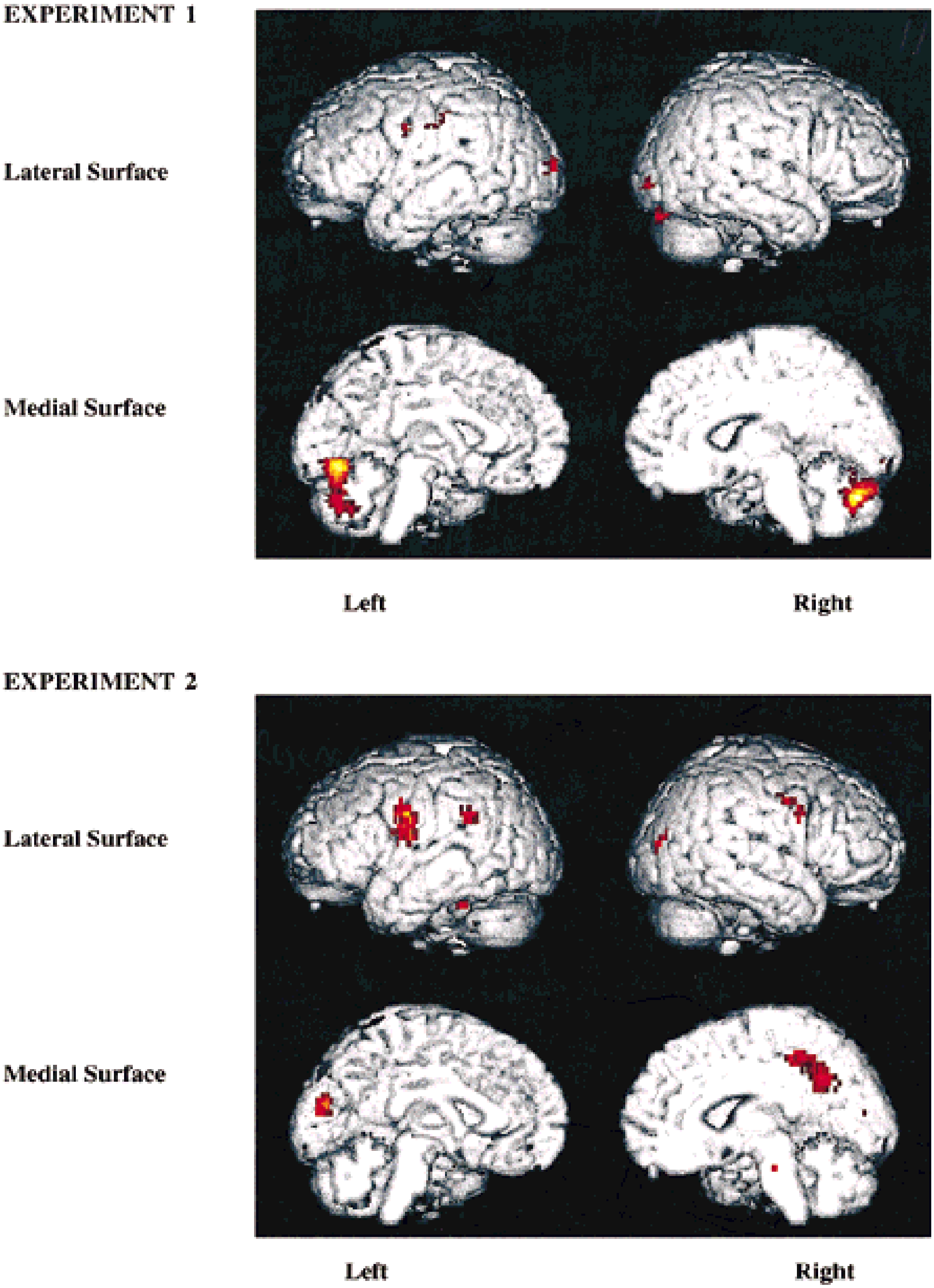

Figure 1.

Cognitive subtraction result. Coordinates of peak activation according to Talaraich and Tournoux [1988]. Areas activated by experiment 1 include the left extrastriate cortex (−8, −72, −12: z-score = 4.3), the right cerebellum (+14, −76, −26: z-score = 3.5), and the left precentral (−64, −18, +34: z-score = 3.1). Areas activated by experiment 2 include bilateral supramarginal gyrus (−40, −46, +32: z-score = 3.9; +34, −50, +36: z-score = 3.5; +40, −34, +40: z-score = 3.3), the left precentral gyrus (−52, −2, +24: z-score = 3.4), and the left cuneus (−14, −80, +20: z-score = 3.5).

cortex is a visual processing area[1] but is not a region associated with phonology. Since visual and orthographic input was the same in both conditions, we suggest that extrastriate activity resulted from top-down modulation of visual processing during the naming task. In other words, it was specific to the integration of visual processing and naming. This sort of modularity effect is a good example of an interaction effect which could be demonstrated explicitly if the design were factorial (see below and Friston et al. [1996b]).

Our interpretation for the lack of activity in any classical phonological processing regions is that phonology was activated implicitly in the baseline task. We also considered the possibility that saying ''Okay'' in the baseline condition enhances activity in phonological retrieval regions relative to silent viewing, thereby obscuring any differences between explicit and implicit phonology. However, this explanation cannot fully account for the results, because in another study [Price et al., 1996c], we detected activity in phonological regions when subjects explicitly named objects and colors relative to saying ''Yes'' to the same stimuli.

Although activity in phonological processing areas is difficult to detect when explicit reading is contrasted to implicit reading, it is readily detected when reading is contrasted to a low-level nonword baseline that does not activate phonology implicitly [Price et al., 1994, 1996d; Bookheimer et al., 1995], i.e., the cognitive distance between activation and baseline tasks is increased. In this circumstance, however, identification of regions specialized for phonological retrieval is precluded by the concurrent activation of orthographic and semantic processing. In the section on conjunction analysis below, we describe how the cognitive component of interest can be segregated from other related processes, thereby facilitating a chose of baseline that increases the cognitive distance between tasks.

Experiment 2: Monitoring for phonological vs. semantic features

One approach for maximizing activity of a particular cognitive function is to engage subjects in complex monitoring tasks [see Corbetta et al., 1991]. In experiment 2, phonological involvement was maximized in the activation task by engaging subjects in phonological judgments and contrasting activity to that when subjects were engaged in semantic judgments. The phonological judgments involved deciding whether visually presented words had two syllables or not. The baseline task involved deciding whether the visually presented words represented living items or not, which should have controlled for the visual, orthographic, semantic, and decision processes involved in the activation task.

The results identified increased activity for the phonological task in the bilateral supramarginal gyri, the left precentral sulcus, and the left cuneus (see Fig. 1). The cuneus is in the extrastriate visual cortex, and activity here suggests that visual processing during the syllable judgment task was enhanced relative to the semantic task. Concurrent activation in the supramarginal and precentral gyri has previously been associated with rhyming [Paulesu et al., 1993], phonological recoding [Démonet et al., 1994], and generating words in response to phonological cues vs. semantic cues [Mummery et al., 1996]. The supramarginal gyrus has also been shown to be more active for word processing than object processing [Vandenberghe et al., 1996; Bookheimer et al., 1995]. These studies are consistent with a role for the supramarginal gyrus in sublexical phonological processing (which is not available for object processing). However, another argument might be that the supramarginal gyri are involved in short-term memory [Paulesu et al., 1993] and in counting, which are engaged more by the phonological task than the semantic task. In summary, activation in the cuneus suggests that there was enhancement of visual processing during the syllable judgment task; activity in the bilateral supramarginal and left precentral gyri may relate to relative differences in short-term memory and counting strategies in the respective tasks. Complex monitoring tasks are therefore not exempt from the limitations of cognitive subtraction paradigms. To the contrary, selection of the appropriate baseline is confounded by the necessity to equate conditions for cognitive strategy.

Experiments 1 and 2 highlight the limitations of cognitive subtraction. Top-down modulation of visual processing during activation tasks undermines the assumption of pure insertion, and the lack of activation differences in any areas that could be associated with phonological retrieval (experiment 1) provides no evidence for the assumption that there is more phonological activity during tasks that explicitly engage phonology relative to tasks where phonology is activated implicitly.

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[1] The left extrastriate cortex may also be involved in orthographic processing [Petersen et al., 1990], but since the same region is activated by objects and colors (experiments 3 and 5), our evidence does not support orthographic specificity.

CONJUNCTION ANALYSIS

Conjunctions are an extension to the cognitive subtraction paradigm. While cognitive subtractions involve a minimum of two tasks (one task pair) with the presence or absence of the CCI as the only difference between tasks, conjunction analysis involves a minimum of two task pairs (four tasks) and there may be many processing differences between each task pair, providing that the only difference that is common to both task pairs is the CCI. The neural correlates of the CCI in a conjunction analysis are defined by the activation differences common to task pair I and task pair II [see Price and Friston, 1997]. In other words, cognitive subtraction identifies the activation differences between two task pairs that differ only by the CCI, and conjunctions reveal the commonalities in activation differences between two pairs of tasks that share only the CCI.

There are two main advantages of conjunction analysis relative to cognitive subtractions. The first is that it provides a greater latitude for selecting baseline tasks because it is not necessary to control for all but the component of interest. The activation and baseline could be very similar or very different depending on the experimental question. For example, baseline tasks could differ substantially from activation tasks when there is a possibility of implicit processing in the former. Alternatively, the analysis can capitalize on the initial subtraction by incorporating baselines that remove stimulus-specific processes such as sensory input or output. The only constraint on selecting the baseline task is that the CCI is the only common processing difference across task pairs. The second advantage of conjunction analysis is that interactions that are not common to both task pairs will be discounted in the conjunction, whether they exist or not. There may be occasions, however, when the site of interactions is common to both task pairs, and in this case, a factorial design (see below) is required to segregate interactions from main effects. A disadvantage of conjunction analysis is that, like cognitive subtraction, it cannot distinguish when an area is responding equally to two different components (e.g., phonological retrieval and semantic processing). The likelihood of revealing an area that is coincidentally activated by two different functions will, of course, increase when the "cognitive distance" between the activation and baseline tasks is wide (i.e., there is a low-level baseline task).

Experiments 3–5 were designed to identify the neural correlates of phonological retrieval using conjunction analysis. Each of these experiments comprised two task pairs (I and II) and each pair comprised an activation task (A) and a baseline task (B); see Figure 2. Statistical analysis involved two stages. In the first stage, the areas of activation for each task pair were identified by cognitive subtraction. These activations can be thought of as two simple main effects. In the second conjunction stage, areas of common activation between the two task pairs were identified by creating a statistical parametric map (SPM) of the sum of both simple main effects and eliminating voxels where there were significant differences between activation in task pair I and task pair II [see Price and Friston, 1997].

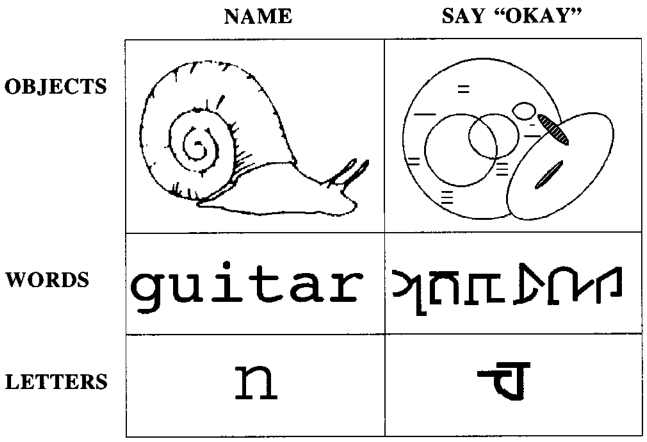


Figure 2.
Stimuli. Examples of the stimuli used in the conjunction studies. Objects were compared to nonobjects, words to falsefont strings, and letters to single falsefonts. In experiment 5, objects and nonobjects were presented in color.

Experiment 3: The conjunction of word and object naming

Task pair I involved (A) reading words and (B) saying "Okay" in response to strings of falsefont matched in length and size to the words. Presentation of falsefont does not involve implicit word processing and therefore activation differences between these two tasks include word recognition, semantic processing, and phonological retrieval. Similarly, the tasks for pair II were (A) naming objects and (B) saying "Okay" in response to false objects with silent responses to each condition (see experiment 1). The processing differences between the tasks of pair II include object recognition, semantic processing, and phonological retrieval. The processing differences common to both task pairs should therefore be semantic and phonological processing. Areas of common activation (see Fig. 3) included the left visual extrastriate cortex, right cerebellum, and left precentral cortex as in experiment 1, but in addition there was activity in the left posterior temporal lobe and the left inferior frontal cortex—regions known to be crucial to naming—and the right inferior frontal cortex (BA47). By increasing the cognitive distance between activation and baseline tasks, areas involved in explicit phonological retrieval and implicit semantic processing were revealed. This particular conjunction, however, did not segregate the CCI from visual processing (in the left visual extrastriate cortex) which was common to both task pairs.

Experiment 4: The conjunction of word and letter naming

Task pair I comprised reading words and viewing falsefont as in experiment 3, but task pair II involved (A) naming single letters and (B) saying "Yes" in response to single falsefonts. The processing differences for task pair I included orthographic, semantic, and phonological retrieval. The processing differences shared by task pair II were letter processing and phonological retrieval.

The areas that were identified by the conjunction analysis were the left posterior basal temporal lobe, the left inferior frontal cortex (BA47), the left middle frontal cortex (BA46), and the right middle temporal cortex (see Fig. 3). Activation in the left posterior basal temporal lobe and the left inferior frontal cortex corresponded to the areas activated in experiment 3. They can be linked to phonological retrieval because patients become anomic if either of these areas is damaged. In this conjunction, there was no activation in the left visual extrastriate cortex. Top-down modulation of visual processing does not appear, therefore, to be common to reading and letter naming.

Experiment 5: The conjunction of object and color naming

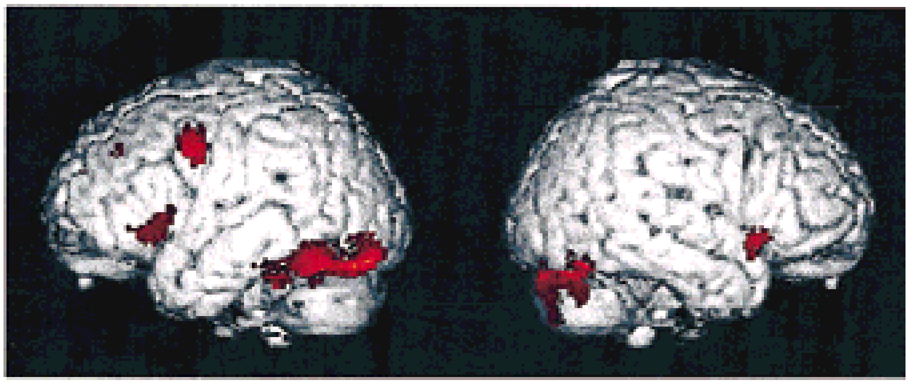
Task pair I involved (A) object naming and (B) viewing the same objects and saying "Yes." Task pair II involved (A) color naming and (B) viewing the same colored shapes and saying "Yes." The tasks of each pair had identical inputs, and phonological retrieval was the only cognitive difference common to both task pairs. The conjunction of activation differences was almost identical to that of experiment 3 in the left posterior basal temporal lobe. There was also activation in the left middle frontal cortex (BA46), the left frontal operculum, the left extrastriate cortex, and the right cerebellum (see Fig. 3). Further, activation in the left posterior basal temporal lobe and the left inferior/middle prefrontal cortices was common to all three experiments (3–5), even though each experiment comprised three different groups of subjects. This replication provides convincing evidence that the left posterior basal temporal lobe and the left prefrontal frontal cortex underlie the retrieval of phonology and that these regions are involved in word, letter, object, and color naming.

The scanning conditions for experiments 3–5 were identical to those used for experiments 1 and 2, and yet the first two experiments failed to identify the areas involved in phonological retrieval. The reason for the lack of phonological activity in the first two experiments, we believe, reflects implicit phonological processing during the baseline tasks (saying "Okay" to words in experiment 1 and performing semantic judgments in experiment 2). Implicit phonological processing was avoided in experiment 3 by selecting baseline tasks that were not closely matched to the phonological activation tasks. Since the left visual extrastriate activation in experiments 1–3 and 5 was not present in the conjunction of reading and letter naming (experiment 4), this region is not implemented as a modality-independent phonological processing area. We have suggested that it reflects top-down modulation of visual processing during reading, picture, and color naming (experiments 3 and 5), but confirmation of this hypothesis would require a factorial design and an analysis of the interaction between visual processing and naming.

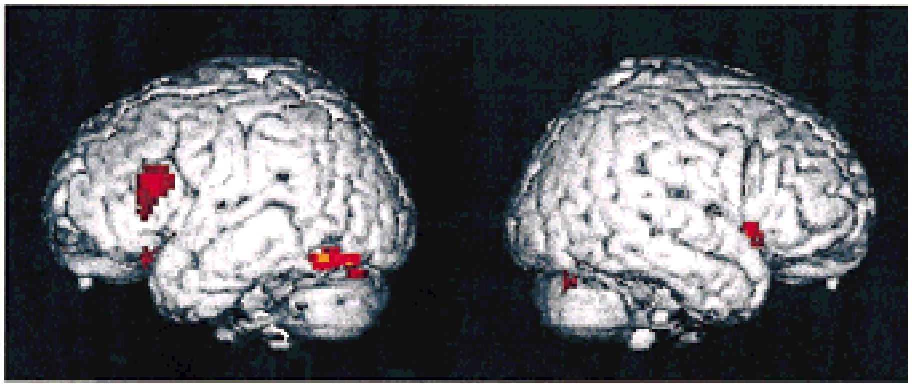
FACTORIAL DESIGNS AND THE ANALYSIS OF INTERACTION TERMS

In designs based purely on cognitive subtraction, there is only one variable (or factor) that has several different levels. Conjunction designs can also have one factor if the baseline tasks for each pair are replications of the same condition (replicated for each activation task). In the conjunction designs of experiments 3–5, however, each baseline was specific to each activation task. This is a form of factorial design. In factorial designs, there are two or more variables (or factors), and the different levels of each factor are equated. For instance, experiment 4 had two factors (stimulus type and task) with two levels of stimulus type (words and letters) and two levels of task (naming and baseline). Factorial designs allow the effect that one variable has on the expression of the other variable to be measured explicitly. By convention, the analysis of factorial designs involves calculating the main effects of each variable and the interaction between these variables. In cognitive activation studies, the main effects identify

a. Words and Objects



b. Words and Letters



c. Objects and Colours

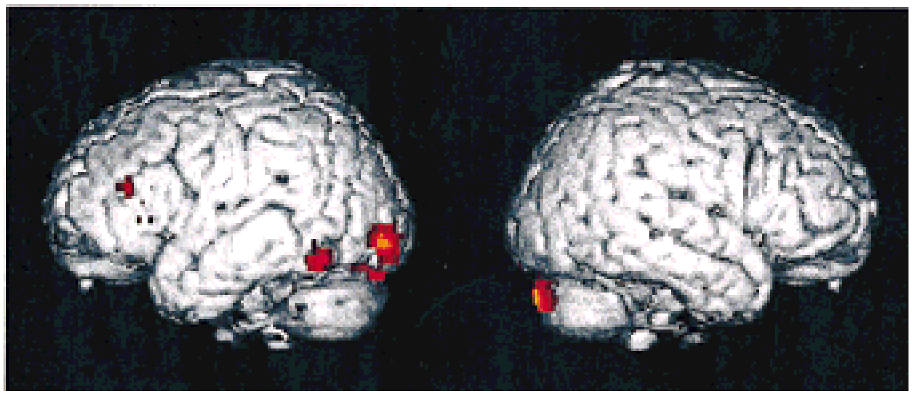


Figure 3.

Conjunction results. Coordinates of peak activation according to Talaraich and Tournoux [1988]. **a:** Conjoint areas activated by experiment 3, including the left extrastriate cortex (−4, −76, −12: z-score = 4.2), the bilateral cerebellum (+18, −72, −28: z-score = 4.7; −28, −82, −18: z-score = 3.8; −16, −74, −30: z-score = 3.5), the left precentral (−52, +2, +38: z-score = 4.1), the left posterior basal temporal lobe (−44, −50, −12: z = 3.3; −42, −36, −24: z = 3.4), and bilateral inferior frontal cortex, BA47 (−40, +26, −4: z-score = 3.1; +42, +18, −10: z-score = 3.5), with a subthreshold activation in left Broca's area, BA44 (−48, +16, +22 z-score = 2.5). **b:** Conjoint areas activated by experiment 4, included the left posterior basal temporal lobe (−38, −66, −16: z-score = 3.8), the left inferior frontal cortex, BA47 (−24, +24, −16: z-score = 3.8; −30, +26, −16: z-score = 3.0), the left middle frontal cortex, BA9/46 (−44, +28, +28: z-score = 3.5; −26, +20, +20: z-score = 5.1), the right middle temporal cortex (+46, +14, −4: z-score = 3.9), and the bilateral cerebellum (−44, −72, −20: z-score = 3.9; −6, −76, −24: z-score = 3.2; +30, −70, −28: z-score = 3.6; +28, −96, −16: z-score = 3.5). **c:** Conjoint areas activated by experiment 5, included the left posterior basal temporal lobe (−42, −60, −16: z-score = 3.4), the left inferior frontal cortex, BA46 (−34, +34, +20: z-score = 3.2), the left frontal operculum (−32, +26, +8: z-score = 3.0), the left extrastriate cortex (−32, −92, −8: z-score = 4.1; −14, −72, +4: z-score = 3.9), and the right cerebellum (+12, −86, −36: z-score = 4.4).

the brain areas where there is more activity in the sum of the activation tasks than in the sum of the baseline tasks. For experiment 4, the main effect of naming is the sum of activity from the naming tasks (words and letters) minus the sum of activity in the baseline tasks. Similarly, the main effect of modality is the sum of activity for word-like stimuli minus the sum of activity for letter-like stimuli. The interaction between these factors identifies areas where the effect of one variable varies depending on the presence or absence of the other variable. Analysis of the interaction term in experiment 4 involves contrasting activations for task pair I (reading-baseline) with activations for task pair II (letter naming-baseline). This contrast revealed activations specific for word naming in the left extrastriate cortex and a midportion of the left inferior temporal cortex (BA20) which is associated with semantic processing [Vandenberghe et al., 1996].

Factorial designs have several important advantages over one-factor subtraction designs. First, they allow greater generalizability of the results because the level effects can be specified for each factor (as in pure subtraction) or generalized for all factors. Second, and most importantly, when the effect of one factor level varies according to the level of another factor, factorial designs allow us to verify the significance of this difference with the interaction term. A third advantage of factorial designs is economy of subjects because, for the same degree of power, fewer subjects are required for one ''two-variable factorial design'' than for two ''one-way designs'' (since the effects of one variable across the levels of the other variable can be averaged in a factorial design). See Friston et al. [1996b] for further discussion.

The limitations of conventional factorial analysis for functional imaging studies are: 1) it is sometimes difficult to equate the different levels of the factors precisely, and 2) main effects include the interaction term and the areas common to both task pairs. Both of these limitations can be overcome using conjunction analyses which 1) do not require the levels of the two tasks pairs to be matched for level, and 2) segregate the areas of common activation from the interactions.

CONCLUSIONS

Cognitive subtraction is the basis of all activation experiments, but as demonstrated in experiments 1 and 2, it is limited by the difficulty of selecting tasks that differ by only the CCI. Further, the difference between two tasks includes not only the process added in the activation task but also the effect that the added component has on the expression of baseline processes (i.e., the interaction between new and preexisting components). Conjunction analysis involve two task pairs, and the common difference across task pairs identifies the CCI. The latitude of task selection is increased by conjunction designs because, providing that there is only one shared difference between pairs, there can be many cognitive differences for each pair. Conjunction designs can therefore eschew the problems associated with implicit processing and will exclude activation from top-down modulation when it is not common to both task pairs.

Conjunction designs resemble factorial designs insofar as each activation task has its own independent baseline task. However, when the experimental design is factorial, the different levels of each variable must be matched across task pairs (see above). In contrast, the baselines for each task pair in a conjunction design could, theoretically, all involve replications of the same condition (e.g., rest or visual fixation), providing that the only difference shared by both task pairs is the CCI. Conjunction and factorial designs allow the identification of common processing differences to be revealed. Interactions between task differences identify the processes that are specific to one or the other task pair. We conclude that when the task includes cognitive subtraction of at least two task pairs, each differing by the same CCI, common differences can be identified by conjunction analysis, and task-specific differences can be revealed by the interaction term.

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