A taxonomy of study design

Karl J Friston, Cathy J Price, Christian Buechel and Richard J Frackowiak

Contents

I. Introduction

This chapter is concerned with the way in which methods presented in previous chapters are implemented in terms of experimental design; and the sort of questions they are used to address. In this chapter we review different sorts of experimental design and examine some of the assumptions about the relationship between cognitive function and neurobiology. We start with a simple taxonomy of experimental design that includes (i) categorical, (ii) parametric and (iii) factorial designs. Each of these designs is discussed from a conceptual

viewpoint and illustrated using an exemplar activation study. The remaining sections of the chapter focus on parametric and factorial designs by considering specific examples of their use. For parametric designs we have chosen nonlinear regression and show how curvilinear relationships between task parameters and evoked hemodynamic responses can be characterized. The example of factorial designs was chosen to address problems with cognitive subtraction and the validity of pure insertion.

II. A taxonomy of experimental design

II.A Categorical designs

The tenet of the categorical approach is that the difference between two tasks can be formulated as a separable cognitive or sensorimotor component and that the regionally specific differences in brain activity identify a corresponding functionally specialized area. Early applications of subtraction range from the functional anatomy of word processing [1] to functional specialization in extrastriate cortex [2]. The latter studies involved presenting visual stimuli with and without some specific sensory attribute (e.g. colour, motion *etc*). The areas highlighted by subtraction were identified with homologous areas in monkeys that showed selective electrophysiological responses to equivalent visual stimuli. Cognitive subtraction is conceptually simple and is a very effective device for mapping functional anatomy. When used in the context of serial subtraction however it depends on the assumption that cognitive states differ in components that can be *purely inserted* or removed with no interaction between them, both at the level of a function and its neural implementation. The possible fallibility of this assumption (see below) has prompted the exploration of other experimental designs.

II.B. Parametric designs

The premise with parametric designs is that regional physiology will vary monotonically and systematically with the amount of cognitive or sensorimotor processing. Examples of this approach include the experiments of Grafton *et al* [3] who demonstrated significant correlations between rCBF and the performance of a visually guided motor tracking task (using a pursuit rotor device) in the primary motor area, supplementary motor area and pulvinar thalamus. The authors associated this distributed network with early procedural learning. On the sensory side we [4] have demonstrated a remarkable linear relationship between rCBF in periauditory regions and frequency of aural word presentation. Significantly this correlation was not observed in Wernicke's area, where rCBF appeared to correlate, not with the discriminative attributes of the stimulus, but with the presence or absence of semantics. This nonlinear relationship between stimulus presentation frequency and evoked response speaks to the importance of modelling nonlinear associations explicitly in an analysis. This theme will taken up again below.

Time dependant changes in physiology are clearly central to studies of learning and memory. Many animal models of procedural learning depend on habituation and adaptation, either at a behaviourial or electrophysiological level. In the context of functional imaging, physiological adaptation to a challenge is simply the change in rCBF activation with time. This is an interaction of the effect with time.

II.C. Factorial designs

At its simplest an interaction is basically a change in a change. Interactions are associated with *factorial* designs where two *factors* are combined in the same experiment. The effect of one factor on the effect of another, is assessed by an interaction term (two factors interact if the level of one factor affects the effect of another). Factorial designs have a wide range of applications. The first PET experiment of this sort was perhaps the simplest imaginable and examined the interaction between motor activation (sequential finger opposition paced by a metronome) and time (rest - performance pairs repeated 3 times) [5]. Significant adaptation was seen in the cerebellar cortex (ipsilateral to the hand moved) and cerebellar nuclei. These results are consistent with the electrophysiological studies of Gilbert and Thach [6], who demonstrated a reduction in simple and complex spike activity of Purkinje cells in the cerebellum during motor learning in monkeys. Psychopharmacological activation studies are examples of a factorial design [7]. In these studies subjects

perform a series of baseline-activation task pairs before and after the administration of a centrally acting drug. The interaction term reflects a modulatory drug effect on the task-dependent physiological response. Such studies are providing an exciting insight into the relationship between cognition and neurotransmitter function in man [8]. A further example of factorial designs includes experiments designed to examine the interaction between cognitive processes, for example dual task interference paradigms. An early example of this approach involved an analysis of encoding of episodic verbal material (using paired associates). Memory and control tasks were performed under two conditions, an easy and a difficult manual distracter task. Encoding is generally confounded with priming. However, due to the differential impact of the distracter task on encoding and priming, we were able to make inferences about encoding *per se* using the interaction effects [9].

The examples cited above all involve the use of factorial designs where each factor has a number of discrete or categorical levels. These designs have facilitated studies of adaptation, neuromodulation and interference at a cognitive level. It is, of course, possible to combine parametric and factorial designs, wherein a task or stimulus parameter is varied under two or more conditions. For example, the frequency of stimuli can be manipulated under different forms of attentional set [10]. Interaction effects in this context can be thought of as a change in the slope of a regression of hemodynamic response on the task parameter under different conditions. This sort of design has clear applications for examining changes of sensitivity of a particular area to stimulation under different conditions. We will return to factorial designs and their relationship to 'cognitive interactions' below.

All the examples cited above use SPMs in conjunction with the general linear model. The following section provides a illustration of the basic differences between categorical, parametric and factorial approaches to the same data.

III An illustrative example using PET data

III.A The data

The data were obtained from five subjects scanned 12 times whilst performing one of two verbal tasks in alternation. One task involved repeating a letter presented aurally at one per two seconds (*word shadowing*). The other was a paced verbal fluency task, in which the subjects responded with a word that began with a presented letter (*intrinsic word generation*). To facilitate intersubject pooling, data were realigned spatially normalized and smoothed with an isotropic Gaussian kernel (FWHM of 16mm). In this case there are five subjects and 12 conditions. We removed the confounding effect of global activity by designating global activities as covariates of no interest. This example is equivalent to a one way AnCova with a blocked design [11]. There are thus 12 condition specific effects, five subject effects and a covariate effect. By specifying appropriate contrasts we tested for different effects of a categorical, parametric or factorial nature.

III B Categorical or subtractive approach

In this example we address the effects of activations due to intrinsic word generation or, equivalently, deactivations due to word repetition (extrinsic word generation). Following the philosophy of cognitive subtraction this comparison is effected by subtracting the word shadowing from the verbal fluency conditions to assess activations associated with cognitive components in word generation that are not present in word shadowing (e.g. the intrinsic generation of word representations and the 'working memory' for words already produced). Having estimated the 12 condition-specific (and all other) effects using the general linear model the effect of verbal fluency *vs* word shadowing was assessed using a contrast that was 1 in all the verbal fluency conditions, -1 in the word generation conditions and 0 elsewhere [1 -1 1 -1 ... -1 0 0 0 0....]. The results of this analysis are presented in Figure 1 which shows the design matrix, the contrast and the resulting SPM{Z}. The results demonstrate significant activations of the left anterior cingulate, left dorsolateral prefrontal cortex, operculum and related insula, thalamus and extrastriate areas (among others).

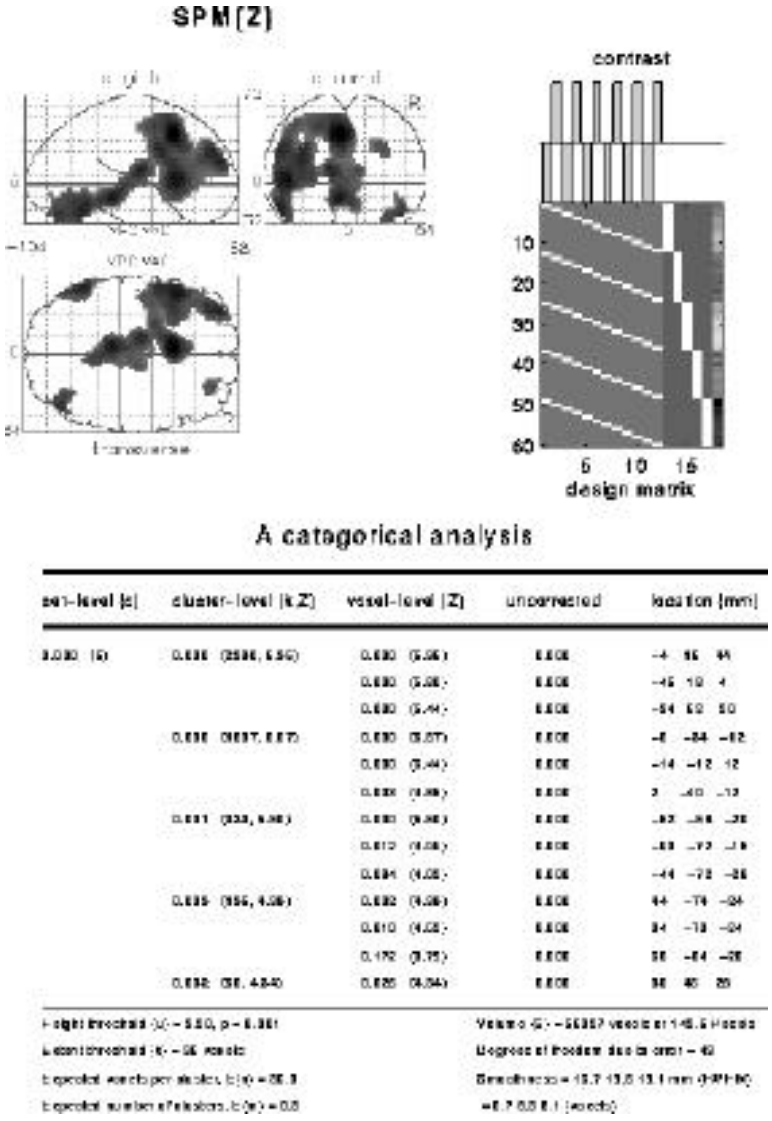
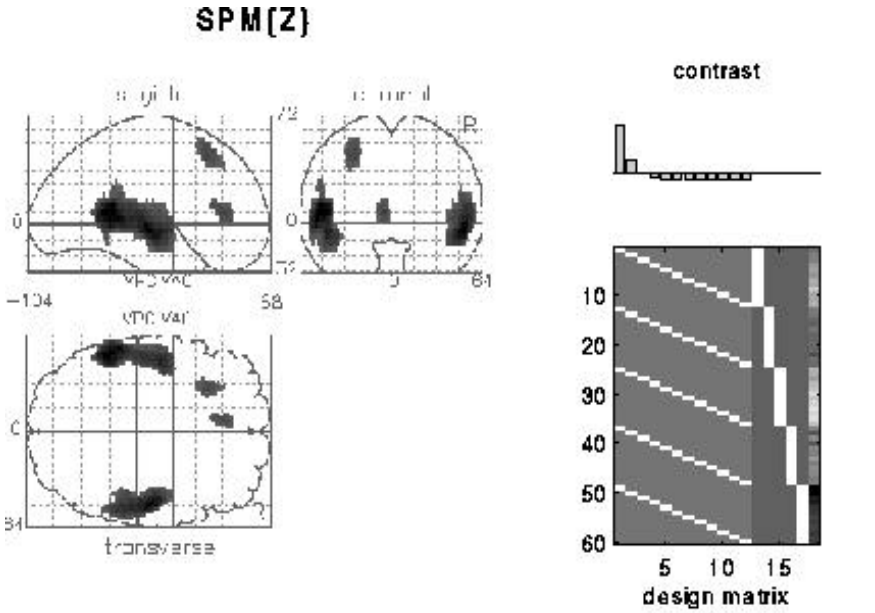


Figure 1
A subtraction analysis: Top right: Design matrix: This is an image representation of the design matrix. Contrast: This is the contrast or vector defining the linear compound of parameters tested. The contrast is displayed over the column of the design matrix that corresponds to the effect[s] in question. The design matrix here includes condition, subject (block) and one confounding covariate (global activity) effects. The contrast can be seen to test for differences between the verbal fluency (even) and word shadowing (odd) conditions. Top left: SPM{Z}: This is a maximum intensity projection of the SPM{t} following transformation to the Z score. Lower panel: Tabular data are presented of 'significant' regions (in terms of set, cluster and voxel level inferences).

III.C A parametric approach

In this example we tested for monotonic, nonlinear (exponential) time effects using the contrast depicted in Figure 2. The results of this analysis identify bilateral foci in the temporal regions and prefrontal cortices that show monotonic decreases of rCBF. These decreases are task-independent. This example is trivial in its conception but is used here to introduce the notion of a parametric approach to the data. Parametric approaches test for systematic relationships between neurophysiology and sensorimotor, psychophysical, pharmacological or cognitive parameters. These systematic relationships are not constrained to be linear or additive and may

show very nonlinear behaviour, reflecting complex interactions at a physiological or cognitive level.



A parametric analysis

set-level {c}	cluster-level {k,Z}	voxel-level {Z}	uncorrected	location {mm}
0.000 (4)	0.000 (361, 5.60)	0.000 (5.60)	0.000	-48 -48 8
		0.000 (5.26)	0.000	-54 -40 4
		0.000 (4.74)	0.000	-44 -10 -4
	0.001 (253, 5.36)	0.000 (5.36)	0.000	60 -16 -4
		0.006 (4.72)	0.000	62 -32 4
		0.027 (4.33)	0.000	62 -40 0
	0.110 (55, 3.96)	0.101 (3.96)	0.000	-6 34 8
		0.260 (3.60)	0.000	-8 26 12
	0.092 (105, 3.88)	0.133 (3.88)	0.000	-26 22 44
		0.422 (3.46)	0.000	-28 34 40

Height threshold (u) = 3.20, p = 0.001 — Volume (S) = 66027 voxels or 148.6 Hessels

Extent threshold (k) = 36 voxels — Degrees of freedom due to error = 48

Expected voxels per cluster, E(n) = 36.3 — Smoothness = 10.7 10.6 10.1 mm (FWHM)

Expected number of clusters, E(m) = 0.3 — = 5.7 5.3 5.1 (voxels)

Figure 2
A parametric analysis: The format of this figure is the same as for Figure 1 and shows the results of testing for a nonlinear (exponential) decreasing monotonic time effect using a contrast of the condition effect estimates.

III.D. A factorial approach

This example looks at regionally specific interactions, in this instance between an activation effect due to intrinsic word generation and time. The contrast used is depicted in Figure 3 and shows a typical mirror

symmetry. This contrast highlights those regions that de-activate early in the experiment and activate towards the end. In other words, those areas that show a time-dependent augmentation of their activation. The areas implicated include left frontal operculum, insula, thalamus and left temporal cortex. Note that these regional results suggest a true physiological 'adaptation' in the sense that it is the physiological *response* (to a task component) that shows a time-dependent change (contrast this with the task-independent changes of the previous section). In this example we have described a time-dependent reorganisation of physiological responses to the same task. It is tempting to call this plasticity, however the term plasticity means many things to many people and hence it should be used carefully [12].

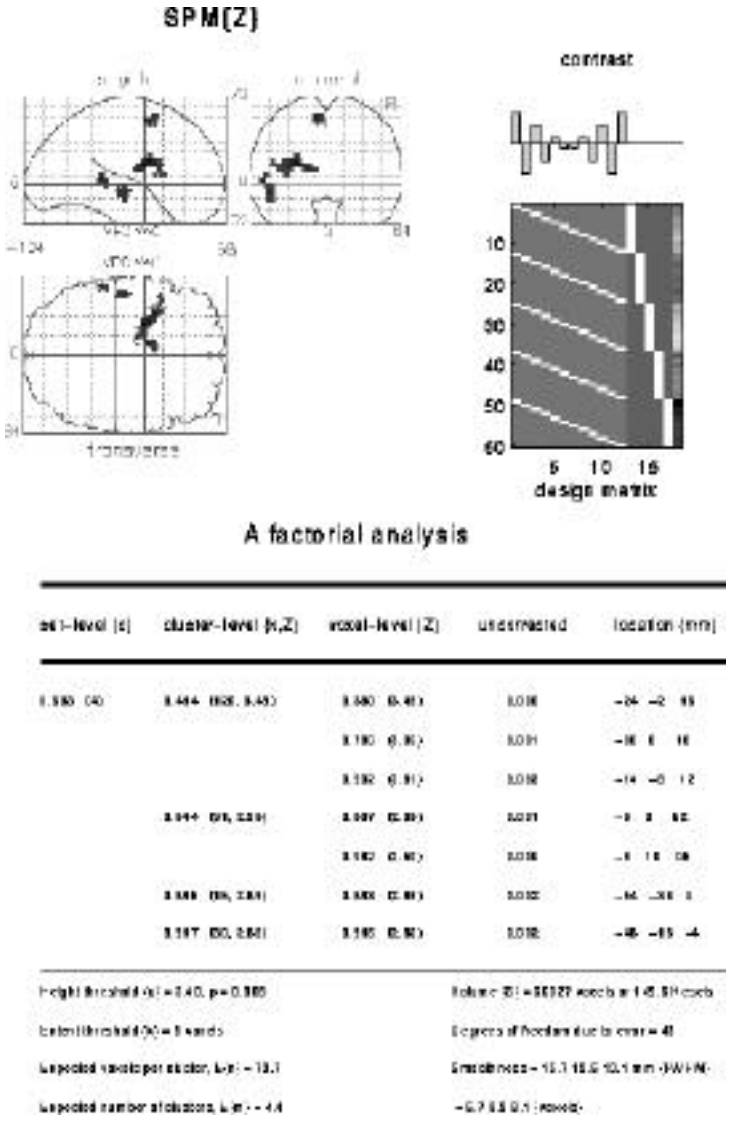


Figure 3
A factorial analysis: The format of this figure is the same as for Figure 2 and shows the results of testing for an interaction between activations due to verbal fluency and time. The contrast used detects regions whose response to verbal fluency increases with time. The results of this analysis can only be reported descriptively because the p values do not survive a correction for the volume analyzed.

III.E Summary

Experimental design has been briefly reviewed using a taxonomy of activation studies that distinguishes between categorical (subtractive), parametric (dimensional) and factorial (interaction) designs. Subtraction designs are well established in functional mapping but are predicated on possibly untenable assumptions about the relationship between brain dynamics and the functional processes that ensue. For example, even if, from a functionalist perspective, a cognitive component can be added without interaction among pre-existing components the brain's implementation of these processes will almost certainly show profound interactions. This conclusion follows from the observation that neural dynamics are nonlinear. Parametric approaches avoid many of the shortcomings of 'cognitive subtraction' by testing for systematic relationships between neurophysiology and sensorimotor, psychophysical, pharmacological or cognitive parameters. These systematic relationships are not constrained to be linear or additive and may show very nonlinear behaviour. The fundamental difference between subtractive and parametric approaches lies in treating a cognitive process, not as a categorical invariant, but as a dimension or attribute that can be expressed to a greater or lesser extent. It is anticipated that parametric designs of this type will find an increasing role in psychological and psychophysical activation experiments. Finally factorial experiments provide a rich way of assessing the affect of one manipulation on the effects of another. The designs can be used to examine a variety of effects; we have mentioned adaptation, neuromodulation and dual task interference as three compelling examples. The assessment of differences in activations between two or more groups represents a further question about regionally specific interactions. The limiting case of this example is where one group contains only one subject. This may be one way to proceed with single subject analyses; in that the interesting things about an individual's activation profile are how it relates to some normal profile or a profile obtained from the same subject in different situations or at a different time. These differences in activations are interactions.

IV Nonlinear parametric approaches

Parametric study designs can reveal information about the relationship between a study parameter (e.g. word presentation rate) and regional perfusion. The brain’s responses in relation to study parameters may be non-linear, therefore linear regressions, as often used in the analysis of parametric studies, might characterise them properly. We describe here a method that fits nonlinear functions of stimulus or task parameters to rCBF responses, using second order polynomials. This technique is implemented in the context of the general linear model and SPM. We consider the usefulness of statistical inferences, based on SPM{F}, about differences between non-linear responses as an example of a factorial approach to paramteric designs. We will illustrate these poitns with a PET activation study using an auditory paradigm of increasing word presentation rate.

IV.A. Theoretical background

Digital signal processing utilises many different techniques to characterise discrete signals by a combination of a number of basis functions. Well known examples are the Fourier expansion and the polynomial expansion. We adapt this technique to characterise activations in terms of a set of basis functions of a given parameter (e.g. study parameter or response) and show how such responses can be approximated by a small number of such basis functions. In what follows we use a second order polynomial expansion of the task paramters. Recall the basic equation of the general linear model:

$$\mathbf{X} = \mathbf{G}\,\boldsymbol{\beta} + \mathbf{e} \qquad 1$$

G is the design matrix, which has one row for every scan and one column for every modelled (i.e. “designed”) effect, **ß** is the parameter matrix which has one row for each column of **G** and one column for every voxel in the volume and **e** is the matrix of error terms. In this case the polynomial basis functions are the explanatory variables used to model the rCBF responses **X** and comprise the first two column of **G**. The first two rows of **b** (the least squares estimates of **ß**) are the coefficients of the second order polynomial that best model the relationship between rCBF and the variable in question. To test the overall significance of the polynomial regression we test the null hypothesis in the uaual way using the F statistic (see the Chapter on statistical models). The ensuing SPM{F} can be interpreted as an image of the significance of the variance explained by the effects of interest (i.e. the polynomials in **G**) relative to error.

The probability of getting one or more voxels with a certain F value in a given SPM{F} is the same as the probability that the largest F value of the SPM{F} is greater than this F value. At high thresholds this probability equals the expected number of maxima. Therefore the problem of calculating a corrected p value can be reduced to finding the expected number of maxima at or above this threshold. Worsley *et al* [13] derived an equation for the probability that the largest F value of the SPM{F} is greater than a threshold *f* given the smoothness of the underlying Gaussian component processes.

$$P(F_{\max} \geq f) \rightarrow \frac{\lambda(C)\det(\Lambda)^{\frac{1}{2}}\Gamma\left(\frac{1}{2}(m+n-N)\right)(m-1)!}{(2\pi)^{\frac{1}{2}N}2^{\frac{1}{2}(N-2)}\Gamma\left(\frac{1}{2}m\right)\Gamma\left(\frac{1}{2}n\right)(m-N)!}\left(\frac{mf}{n}\right)^{\frac{1}{2}(m-N)}$$

where n and m are the degrees of freedom of the F statistic, N is the dimension and λ(C) is the Lebesgue measure of C (the number of voxels in the volume) and Λ is the variance-covariance matrix of the first derivate of the underlying Gaussian component processes. P(Fmax > F) corresponds to the corrected p value.

This general approach to parametric studies can also be extended to compare the non-linear responses of different groups. To test for differences, the polynomials appear twice in the design matrix. First the functions are replicated in both groups; in the second partition the polynomials are inverted for the second group. This partition models differential responses and, effectively, represents the interactions. These nonlinear interactions can be designated as the effects of interest and the resulting SPM{F} depicts the significance of the differential response.

IV.B. An example

A patient, who had recovered from severe aphasia after an infarction largely confined to the left temporal lobe and involving the whole of the superior temporal gyrus, was scanned 12 times while listening to words persented at different rates. To illustrate a comparison of regressions between different subjects, a normal subject was studied using the same paradigm. The SPM{F} refelcting the significance of a nonlinear relationship between word presetnation rate and evoked repsonse in the patient is shown in Figure 4 (upper panel). As an example, of one of the many forms of such as nonlinear relationship, the adjsuted and fitted repsonses from a voxel (at -34, 40, 24 mm) are shown in the lower left panel. This region shows a highly non-linear (inverted U) rCBF response in relation to word presentation rate.

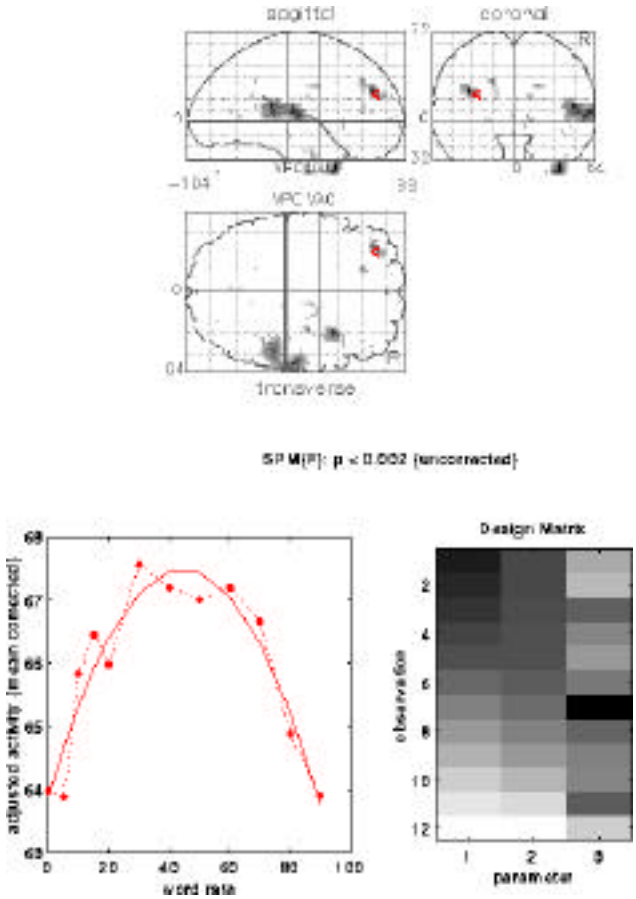


Figure 4
SPM{F} for polynomial regression in the patient who had recovered from an ischaemic infarction in the territory of the left middle cerebral artery. Voxels over a threshold of F = 15 are shown. The regression for a voxel in a left frontal region (x=-34, y=40 and z=24 mm). F=20, df 2, 8, p<0.001 (uncorrected).

Figure 5 demonstrates statistical inferences about nonlinear differences in rCBF responses between the two subjects. The first two columns of the design matrix are the effects of interest (i.e. differences). Confounding effects are the commonalities (columns 3 and 4), subject or block effects (column 5 and 6) and global acitvity (column 7). There are two maxima apparent in the SPM{F}. To demonstrate a non-linear interaction we have chosen a voxel in the left hippocampus (-18, -26, -12 mm). Note the decrease of rCBF in relation to increasing word presentation rate in the normal subject compared to the patient who shows an increasing rCBF.

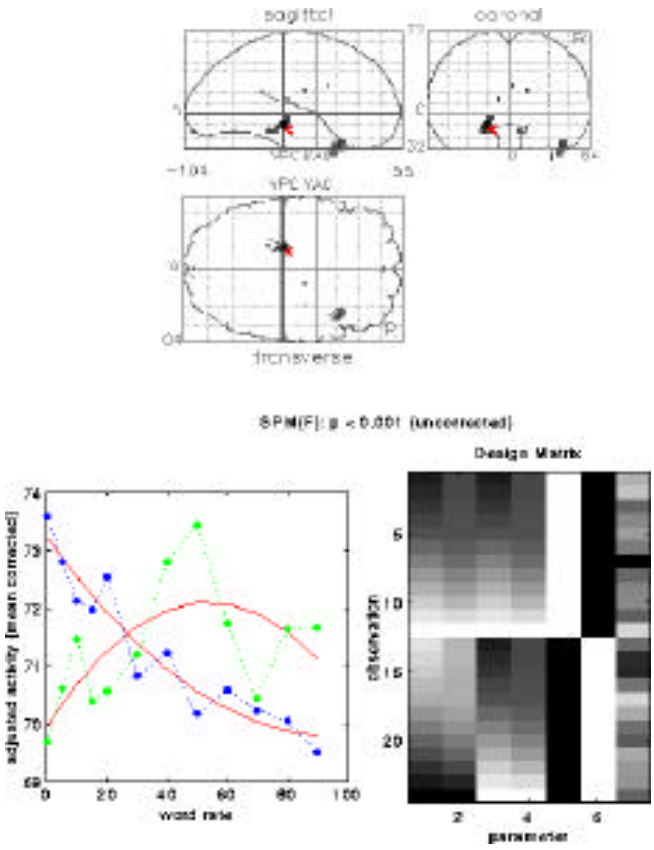


Figure 5
SPM{F}, regression plot and design matrix for the differences of rCBF responses in the patient and the control subject. Voxels over a threshold of F = 10 are shown. Regression for differential rCBF responses at a voxel x:-18, y:-26 and z:-12 mm are shown. F=17, df 2,17, p<0.0005 (uncorrected).

IV.C. Summary

Non-linear fitting techniques allow detection of activations in brain regions that might not be so evident using simple (i.e. linear) regression. The general approach using polynomial expansions avoids predefined fit-functions and can model a family of nonlinear rCBF responses, without specifying the exact form of the relationship. Different brain areas can show differential responses to a study parameter that can then be used to characterise each area involved in a task. Although we have restricted our model to a second order polynomial regression, other basis functions could be used. The use of cosine basis functions has some advantages in modelling ceiling or floor effects, however the interpretation of polynomial coefficients (i.e. a decomposition into linear and non-linear effects) is more intuitive than interpreting the coefficients of cosine basis functions. This fact may be important in experimental analysis where the introduction of nonlinearity (the second order term) considerably improves a fit. In general, questions pertaining to the number and type of basis functions are questoins of model selection.

V Subtraction, factorial designs and pure insertion

V.A Introduction

This section represents a critique of *cognitive subtraction* as a conceptual framework for the design of brain activation experiments and allows us to demonstrate the potential usefulness of factorial designs. Subtraction designs are well established and powerful devices in mapping cognitive neuroanatomy [1] but are predicated on

possibly untenable assumptions about the relationship between brain dynamics and the functional processes that ensue (and where these assumptions may be tenable they are seldom demonstrated to be so). Concerns with cognitive subtraction can be formulated in terms of the relationship between cognitive processes and their neuronal implementation. We suggest that nonlinear systems like the brain do not behave in a fashion this is consistent with pure insertion. We illustrate our point with a simple example - the functional anatomy of phonological retrieval during object naming.

V.B Cognitive subtraction, pure insertion and additive factors

Cognitive subtraction involves the successive elaboration of a task by adding separable cognitive components and measuring the resulting increases of neuronal activity elicited by these tasks. The physiological activations that obtain on serial subtraction of such measurements are then identified with the added cognitive components. The approach, predicated on *pure insertion*, assumes that each cognitive component evokes an 'extra' physiological activation that is the same irrespective of the cognitive or physiological context. Pure insertion is an idea that underlies the original Donders subtractive method and has proven itself in many situations; for example in the psychophysics of reaction time measurements during the detection of visual targets embedded in a background of distracters. The linear (additive) relationship between reaction time and the number of distracters has been used to infer a 'serial search' of the visual field [14]. Compelling examples of pure insertion usually involve an empirical demonstration of this additive relationship between a perceptual or cognitive process and a phenomenal brain measure (e.g. reaction time). However, pure insertion in the context of brain activation experiments is an *a priori* assumption that has not been validated in any physiological sense. We present here an evaluation, in physiological terms, of cognitive subtraction by focusing on pure insertion. This evaluation follows Sternberg's proposal [15] to use additivity and *interaction* within factorial designs (the additive factor method) to address the issue.

Pure insertion is implicit in serial subtraction. The idea is that as a new cognitive component (A) is added to a task, the implementation of pre-existing components (e.g. B) remains unaffected. If this were not the case the difference between tasks that did, and did not, include component B would depend on the presence of component A. In other words pure insertion requires that one cognitive component does not affect the effect of another. In factorial designs pure insertion is another way of saying that the interaction terms are negligible. The fact that interactions can be measured, using functional imaging [5], means that the validity of pure insertion can now be addressed empirically. In this paper we use a simple factorial design to demonstrate that the physiological brain does not conform to pure insertion.

V.C. The nonlinear brain and interactions

Even if, from a functionalist perspective, a cognitive component can be added without interacting with pre-existing components, the brain's implementation of these processes will almost certainly show profound interactions. This conclusion follows from the observation that neural dynamics are nonlinear [16]. Nearly all theoretical and computational neurobiology is based on this observation. The point is that although a cognitive science model describing functions may include serial and additive elements, the implementation of those functions is not. Consequently, the structure of the cognitive components (functional model) and the brain's physiological implementation are not isomorphic and the mapping of one onto the other is problematic. Put boldly, cognitive science may be an internally consistent discipline, but it has no necessary or defined relation to measurements of brain function. Cognitive subtraction makes some strong assumptions about this relationship which are difficult to reconcile with basic neurobiology.

One of the innumerable examples of nonlinear brain dynamics that confound cognitive subtraction is modulation; from classical neuromodulation to large-scale modulatory interactions between different cortical areas. A particularly relevant example is the modulatory role of attention on perceptual processing; for example the responsiveness of V5 to motion in the visual field [17]. It is likely that responsiveness is enhanced by selectively attending to motion [18]. V5 activation therefore represents an interaction between visual motion and selective attention. Consider now an experiment in which visual motion is presented with and without selective attention for motion. The resulting difference in physiological activation of V5 would, in terms of

cognitive subtraction, be attributed to selective attention for motion. This would be a fallacious conclusion because the differential responses of V5 represent an interaction between visual analysis of a particular attribute and selective attention to that attribute. In neuronal terms this interaction might be described in terms of a modulation of V5 responsiveness to motion in the visual field, mediated by afferents from some higher order area. The fallacy would be revealed by repeating the experiment in the absence of visual motion. In this instance 'selective attention for motion' should not activate V5 because there are no motion-dependent responses to modulate. This second experiment would demonstrate an interaction between 'selective attention for motion' and 'visual motion' using a factorial experimental design. The V5 example highlights the close relationship between functional interactions (between different cognitive or sensorimotor components) and statistical interactions that can be inferred using factorial designs. It should be said that we do not consider 'attention' a cognitive component (although the 'control' of attention can be) but our point is clearly illustrated by this example. Furthermore, a motion stimulus may not be necessary to demonstrate a modulatory effect of attention. For example, 'imagined' motion could interact with selective attention in an analogous way. This sort of experiment would speak to an intimate relationship between imagery and attention.

Similar conclusions have been reached in neuropsychology. A patient with acquired dyslexia without dysgraphia was found to have a deficit in accessing phonology from semantics and a mild deficit in attending selectively to components of compound visual stimuli. These deficits interacted to severely disrupt her ability to name the components of visual arrays, despite the fact that she could name each component when presented it in isolation (a symptom of attentional dyslexia). This example "highlights the importance of interactions between deficits as being a major contributory factor to some neuropsychological syndromes" [19]. In summary, pure insertion discounts both functional and physiological interactions and therefore represents a very restrictive precondition for cognitive subtraction.

V.D. Cognitive subtraction vs. Factorial designs

We suggest that a more powerful approach to cognitive neuroanatomy is to consider interactions explicitly, both in terms of a cognitive model and in terms of experimental design and analysis. This suggestion acknowledges that the conjunction or integration of two or more cognitive processes may require an active physical implementation. For example, naming an object involves object recognition, phonological retrieval and the integration of the two, where that integration calls upon separable brain processes. Put more simply, phonological retrieval influences object recognition, and *vice versa*, and these effects are physiologically measurable. This perspective requires a factorial design in which the interaction term represents non-additive (i.e. nonlinear) physiological concomitants of naming a recognised object, that is independent of the activations produced by recognising or naming alone. This is the example we use to illustrate our ideas below.

V.E. An empirical example

The example chosen uses the same data to address the question, "is the inferotemporal region implicated in phonological retrieval during object naming?" from a subtraction perspective and from a factorial perspective. Considerable evidence from neuroanatomy and unit-electrode recordings suggests that neurons in the inferotemporal cortex of animals respond selectively to specific objects in the visual field, or have the appropriate responses to do so [20, 21, 22]. On the basis of this and other evidence it might be hypothesised that inferotemporal regions are functionally specialised for object recognition in man. Furthermore, lesion studies in man have shown that the ability to name objects is impaired when the inferotemporal regions are damaged. For example De Renzi *et al.* [23] studied the neuropsychological correlates of inferior temporal ischaemic damage. As well as alexic subjects were impaired on naming objects and photographs. This evidence suggests that the integrity of the inferotemporal cortex may be necessary for phonological retrieval (among other things) in object naming.

Consider the problem of designing an experiment to identify brain areas selectively activated by phonological retrieval during object naming. The cognitive processes involved in such a task include visual analysis, object recognition, phonological retrieval and speech. Suppose that we are not concerned with the sensorimotor aspects

of the task but wish to test a hypothesis that the inferotemporal regions are involved in both object recognition and phonological retrieval. In this case we need a series of tasks that, on successive subtraction, isolate these two cognitive components (i.e. three tasks). The tasks used were:

A Saying 'yes' when presented with a coloured shape (**visual analysis, and speech**)
B Saying 'yes' when presented with a coloured object (**visual analysis, speech and object recognition**).
C Naming a visually presented coloured object (**visual analysis, speech, object recognition and phonological retrieval**).

Subtraction of task A from task B should identify brain regions associated with object recognition and subtraction of task B from task C should identify regions implicated in phonological retrieval. The hypothesis is that both subtractions should activate the left inferotemporal regions (among other regions). The data were obtained from six subjects scanned 12 times (every eight minutes) whilst performing one of four different tasks (the three tasks A, B, C and a further task D to be described below). The subjects were instructed to respond with either 'yes' (tasks A and B) or a name (tasks C and D). In the analysis we are only concerned with differential responses in the left inferotemporal region. Therefore, we make no correction for multiple non-independent comparisons in other brain regions.

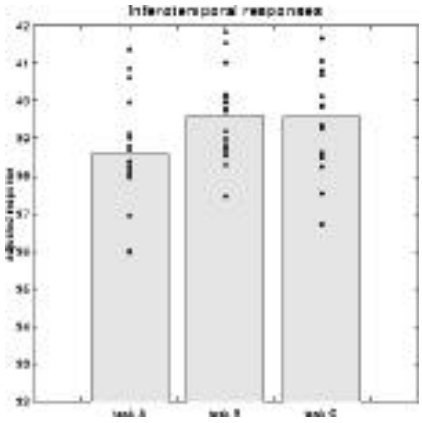


Figure 6
Task-dependent activities: Adjusted (for the confounding effects of global activity and the subject or block effect) rCBF equivalents for the three tasks (A, B and C). The bars represent mean activity and the dots are the individual data points from each scan. Note that there are activation in passing from task A to B but not in going from task B to C. These data were taken from a voxel in the left inferotemporal regions (-48,-18, -24mm according to the atlas of Talairach and Tournoux).

Significantly activated voxels ($p < 0.05$ uncorrected) in the subtraction of task A from task B included, as predicted, a small focus in the left inferotemporal region. No significant activations were detected in the second subtraction, comparing tasks B and C. From our current perspective the key thing to note is that the inferotemporal regions showed no further activation due to phonological retrieval. Figure 6 shows the activity of a voxel in the inferotemporal region [-48, -24, -32mm BA 20 - according to the atlas of Talairach and Tournoux [24]] during the three tasks (A, B and C). On the basis of these results one might conclude that the inferotemporal regions are specialised for (implicit) object recognition and that this cognitive component is sufficient to explain the activations even in the context of naming the objects. In other words there is no evidence for differential responses in the inferotemporal regions due to phonological retrieval. These results show that phonological retrieval does not, in itself, activate the infero-temporal region. The conclusion is that the inferotemporal regions cannot be implicated in phonological retrieval (as far as can be measured with functional imaging).

The forgoing conclusion is wrong because it assumes pure insertion and hence has to lead to the influence that activation due to object recognition is the same, irrespective of whether phonological retrieval is present or not. In order to say that phonological retrieval does not activate the inferotemporal region (as found in the second subtraction) one has to assume that the activation due to object recognition is the same as in the first subtraction (i.e. object recognition in the absence of phonological retrieval). To validate this assumption we need to measure activations due to object recognition in the presence of phonological retrieval. This can be effected by comparing tasks that involve phonological retrieval with and without object recognition. This comparison required a fourth condition:

D Name the colour of a presented shape (**visual analysis, speech, and phonological retrieval**).

Subtraction of task A from task B gives the activations due to object recognition in the absence of phonological retrieval and subtraction of task D from task C gives recognition-dependent activation in the context of phonological retrieval. Pure insertion requires these activations to be the same and this is not the case. Figure 7 (upper panel) shows that activation in the context of phonological retrieval is far greater than under conditions without phonological retrieval. In other words phonological retrieval can be thought of as modulating the recognition-dependant responses of the inferotemporal region and in this sense the inferotemporal regions clearly contribute to phonological retrieval.

There is an alternative and equivalent perspective on this interaction that considers the inferotemporal activations induced by phonological retrieval with and without object recognition. Figure 7 (lower panel) shows that, in the absence of object recognition, phonological retrieval *deactivates* the inferotemporal regions, whereas in the context of object recognition, this effect is nullified if not reversed. These data come from a voxel in BA 20 (-48, -18, -24mm). In summary inferotemporal responses do discriminate between situations where phonological retrieval is present or not and can be directly implicated in this cognitive process. These differential responses are expressed at the level of interactions and are revealed only with a factorial experimental design.

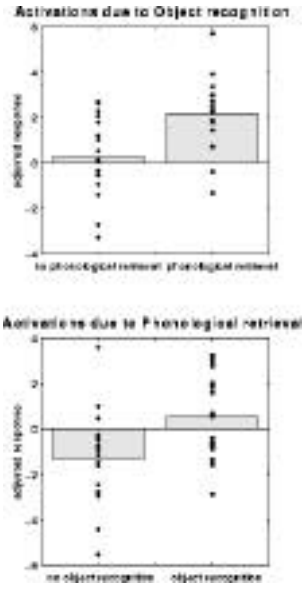


Figure 7
Modulation of task-dependent activations: Upper panel: The activations due to object recognition with (right) and without (left) phonological retrieval. For this graph the difference were obtained by subtracting the adjusted activities in the first second and third occurrence of the two tasks in each subject. Lower panel: The same but comparing the activation due to phonological retrieval with (right) and without (left) object recognition. As in the previous Figure the bars represent mean activity and the dots are the individual data points from each scan.

Using the same statistical model as in the previous analysis we tested for the main effect of object recognition, the main effect of phonological retrieval and the interaction between them, by using the appropriate contrasts. The SPM reflecting the interaction effects is shown in Figure 8 where significant voxels are rendered onto an MRI scan (white areas are significant at $p < 0.05$ uncorrected). This interaction effect depicts augmented activation due to a conjunction of phonological retrieval and object recognition and allows us to confirm that the inferotemporal region is implicated in phonological retrieval during object naming.

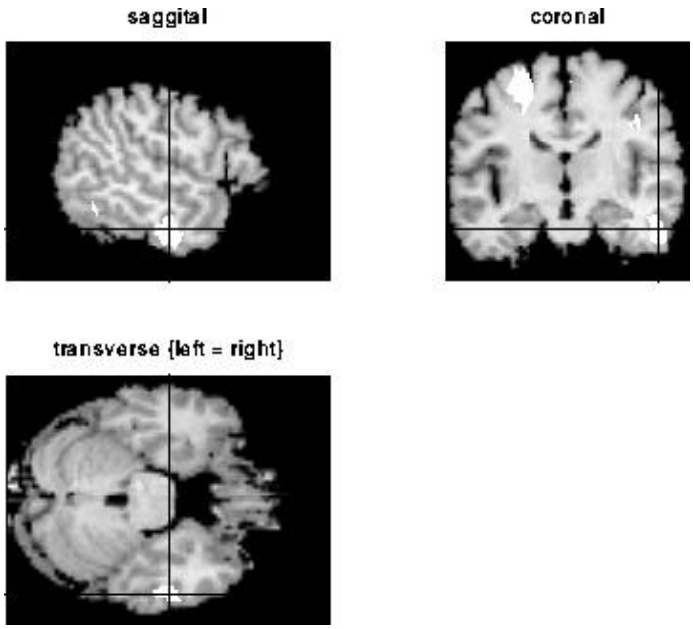


Figure 8
Factorial SPM White areas correspond to voxels that showed a significant interaction [i.e. (C - D) - (B - A)] at $p < 0.05$ (uncorrected) rendered onto a MRI scan in standard space (Talairach and Tournoux 1988).

V.G Psychophysiological Interactions and other parametric factorial deisgns

There are many interesting aspects of parametric designs: For example does the sensitivity of hippocampal responses, to increasing word-list length, in a free recall memory task, change with strategic differences in memory processing when the number of words exceeds the capacity of short-term systems? In other words is there a strategy-dependent change in slope, at some critical value, when we plot brain activity against the experimental parameter? How does one disambiguate the effects of increased 'effort' and processing effects specific to the parameter in question (e.g.are prefrontal responses attributable to increased processing incurred by the number of distracters, in a target detection task, or would these responses be seen with any task involving increases in effort?). One approach to this issue is to repeat the experiment using a different parameter, whilst matching the levels of 'effort', and looking for differences in the regression of prefrontal responses on the two parameters. This brings us to interactions and factorial designs, but now in a parametric context. A simple example of these designs would be examining the brain responses to increasing frequency of stimulus presentation under different [attentional] conditions. A further example is shown in Figure 9, where subjects were asked to produce words at different frequencies. In one context, the subject simply repeated a heard word and in the second they generated a word beginning with a heard letter. In this case the interaction corresponds to a differential sensitivity to word-production rate depending upon whether the words were extrinsically or intrinsically generated. A profound interaction is shown in the right posterior temporal region where, for extrinsically generated words, activity increases gently with word production rate, whereas for intrinsically generated words it decreases. The observation that activity systematically decreases with the increasing frequency of a neuronal event (in this case the intrinsic generation of a word) is of fundamental importance, and speaks to

true deactivation or reduction in the activity evoked by each word.

In the next section we look at factorial designs, of a parametric nature, from a rather different perspective that allows one to make some inferences about functional integration in the brain in terms of top down modulatory interactions.

Parametric factorial designs

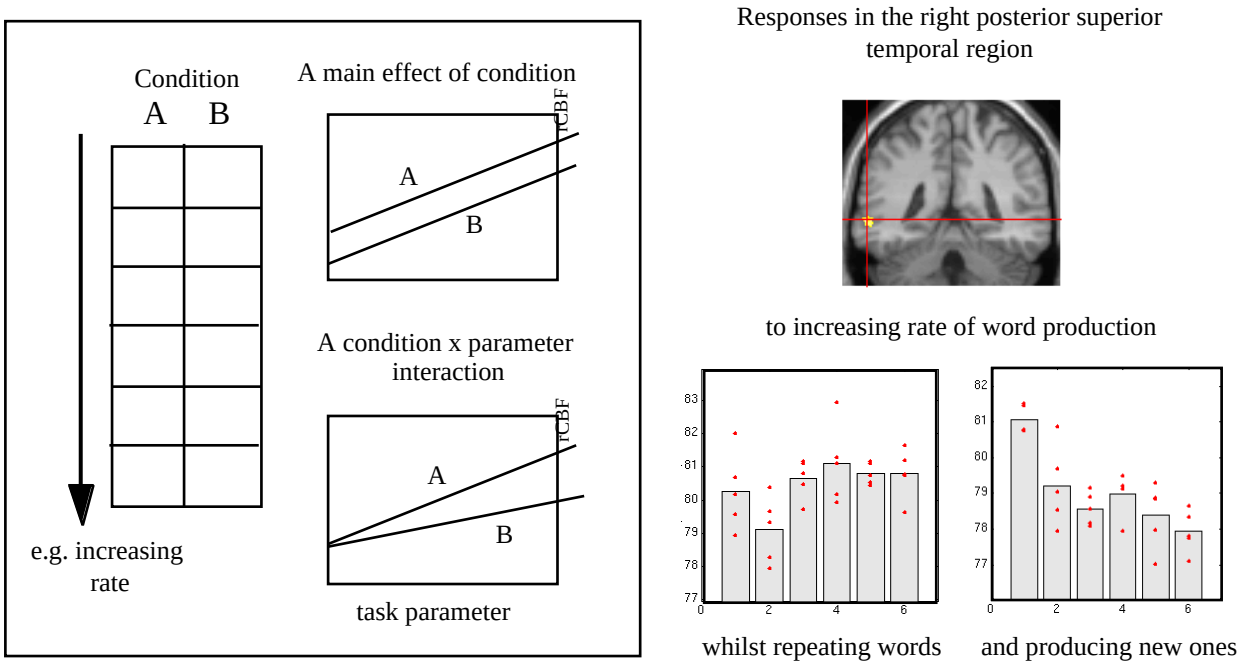


Figure 9
Left: Schematic detailing the experimental layout and the possible effects of changing from condition **A** to **B**. These include a main effect of condition or an interaction with the parameter reflecting the levels of the second factor. An interaction is equivalent to a condition-dependent change in the sensitivity of brain responses to the parameter in question (i.e. slope of the regressions above). An empirical example of this sort of effect is shown on the right. Adjusted activity from a voxel in the posterior superior temporal region is shown as a function of word-production rate under the two conditions of extrinsic and intrinsic word generation. The change in slope is obvious. The voxel from which these data derived is shown on the SPM{t} (upper right). These data come from a PET study of 6 normal subjects.

A new concept is introduced here, dubbed psychophysiological interactions by analogy with psychopharmacological interactions. In psychopharmacological experiments we are interested in the interaction between the sensorimotor or cognitive evoked responses and some pharmacological or neurotransmitter manipulation. In psychophysiological interactions we are trying to explain the physiological response in one part of the brain in terms of an interaction between the presence of a sensorimotor or cognitive process and activity in another part of the brain. For example by combining information about activity in the parietal region, mediating attention to a particular stimulus, and information about the stimulus, can we identify regions that respond to that stimulus when, and only when, activity in the parietal region is high?. If such an interaction exists, then one might infer that the parietal area is modulating responses to the stimulus for which the area is selective. This has clear ramifications in terms of the top-down modulation of specialized cortical areas by higher brain regions. This is an interesting analysis from two points of view. Firstly, the explanatory

variables used to predict activity (i.e. the response variable) in any brain region comprises a standard predictor variable based on the experimental design (e.g. the presence or absence of a particular stimulus attribute) and a response variable from another part of the brain. The second reason that this analysis is interesting is that it uses techniques usually used to make inferences about functional specialization to infer something about functional integration; in this instance, effective connectivity of a modulatory sort. Figure 10 illustrates a specific application of the approach. Subjects were asked to view [degraded] faces and non-face (object) controls.

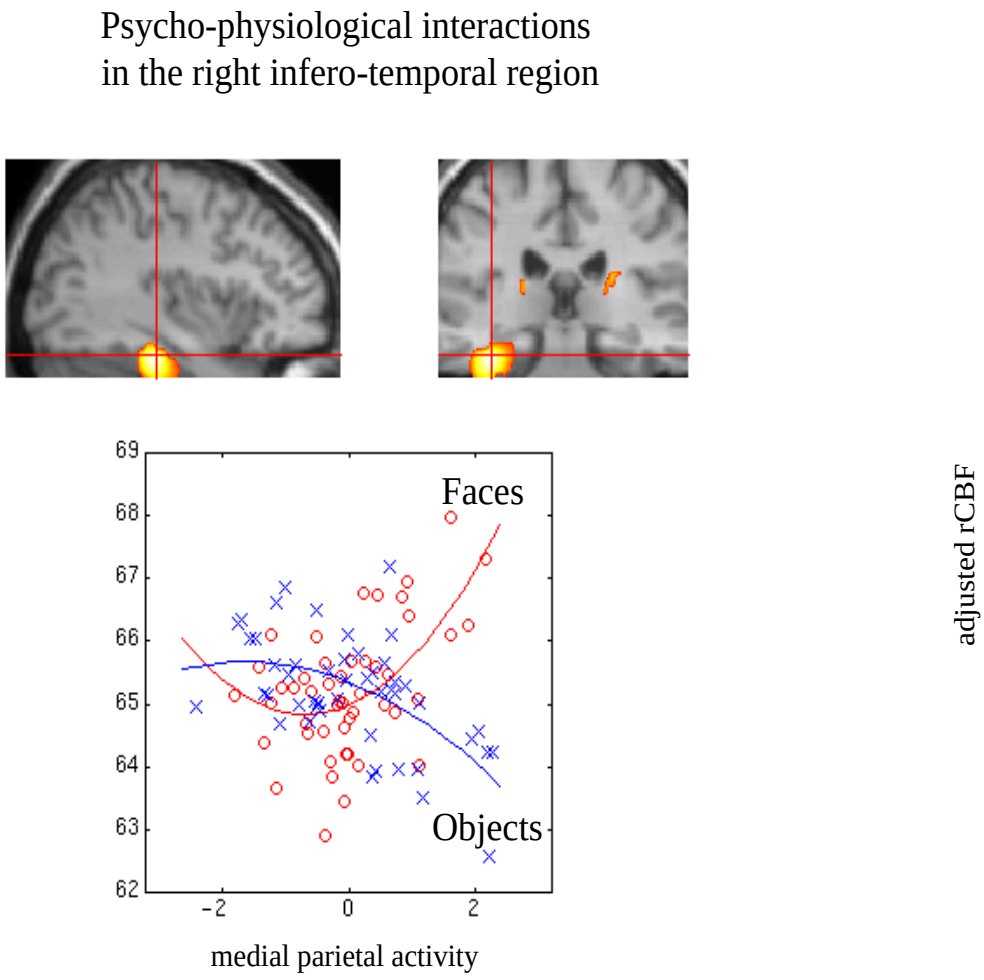


Figure 10
Top: SPM{t} that identifies areas whose activity can be explained on the basis of an interaction between the presence of faces in visually presented stimuli and activity in a reference location in the medial parietal cortex. This analysis can be thought of as finding those areas that are subject to top-down modulation of face-specific responses by medial parietal activity. The largest effect was observed in the right infero-temporal region. The corresponding activity is displayed as a function of [mean corrected] activity in a medial parietal voxel. The crosses correspond to activity whilst viewing non-face stimuli and the circles to faces. The essence of this effect can be seen by noting that this region differentiates between faces and non-faces when, and only when, medial parietal activity is high. The lines correspond to the best second-order polynomial fit. These data were acquired from six subjects using PET.

The interaction between activity in the medial parietal region and the presence of faces was most significantly expressed in the right infero-temporal region. Changes in medial parietal activity, were introduced experimentally by pre-exposure of the stimuli before some scans. These results can be interpreted as a priming-dependent instantiation of attentional, memory or learning differences in face-specific responses, in inferotemporal regions that are mediated by interactions with medial parietal cortex. Note that we could have

modelled the priming effect explicitly in our design matrix but chose to substitute medial parietal activity in its place, enabling us to make a more mechanistic inference: Namely, not only do infero-temporal responses show a priming-dependent effect but this effect is mediated by modulatory influences from a higher (parietal) area.

VI. Cognitive conjunctions

V!.A Concept

Cognitive conjunctions can be thought of as an extension of the subtraction technique, in the sense that they combine a series of subtractions. In subtraction we test a hypothesis pertaining to the activation in one task relative to another. In cognitive conjunctions several hypotheses are tested, asking whether all the activations, in a series of task pairs, are jointly significant. Consider the problem of identifying regionally specific activations due to a particular cognitive component (e.g. object recognition). If one can identify a series of task pairs whose differences have only that component in common, then the region which activates in all the corresponding subtractions can be uniquely associated with the component in question. This is tenable even if interactions are prevalent because the interactions will (by design) be specific to each pair. In this way cognitive conjunctions can be used to discount interactions and render the inference less sensitive to the context in which a particular cognitive component is expressed. To make this argument clear consider the object naming experiment described above Subjects either viewed coloured shapes or coloured objects (and said "yes") or they named coloured shapes or coloured objects (naming either the object or the colour). The differences between naming an object or the colour of a shape include object recognition and the interaction between recognition and explicit phonological retrieval. The difference between simply viewing an object and a coloured shape is object recognition (for simplicity we ignore interactions with visual processing). The common difference is object recognition and this conjunction discounts the interaction between recognition and phonological retrieval of the name of the recognized object. Regionally specific activations that are significant in both comparisons (and are not significantly different) will identify areas that are specialized for object recognition *per se*.

Figure 11 presents this a approach in a more schematic format: While cognitive subtraction looks for activation differences between a pair of tasks, cognitive conjunction looks for the commonality in activation differences (i.e. subtractions) between two or more pairs of tasks that share only the component of interest. Figure 11a represents a cognitive subtraction hierarchy. The process of interest (PI) is revealed by subtracting activity during the baseline task (B) from that during the activation task (A). Figure 11b_represents a cognitive conjunction design which has two task pairs (IA,IB and IIA,IIB) designed such that the cognitive differences between the tasks of each pair both contain the process of interest (PI). Regional activation associated with PI is revealed by finding areas activated in both independent subtractions (IA - IB and IIA - IIB). For IA - IB, the differences are {P2 P4} and for IIA - IIB the differences are {P3, P4}. P4 (= PI) is activated in both comparisons, P2 and P3 are distinct but arbitrary task components which could, of course, represent interaction effects.

11a: Cognitive Subtraction

		Task A	Task B
Process	1		
	2		
	3		
	4 (PI)		
	5		

11b: Cognitive Conjunction

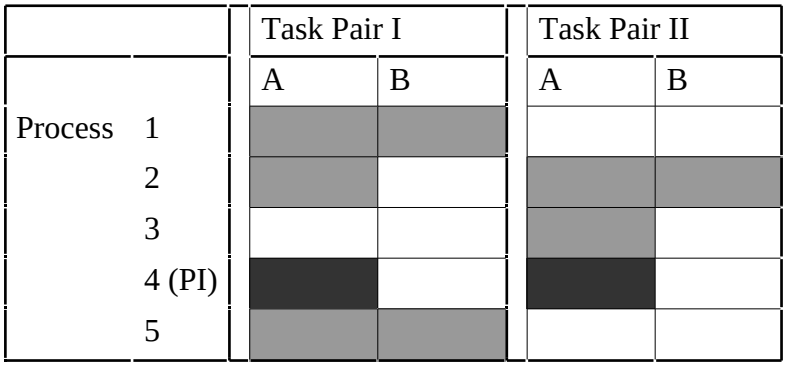


Figure 11
Figure 10a represents a cognitive subtraction hierarchy. PI is the process of interest, A is the activation task and B is the baseline task. Figure 10b represents a cognitive conjunction design which has two task pairs (I and II) each with an activation (A) and baseline (B) task. P1, P2, P3 and P4 are distinct but arbitrary task components.

VI.B Implementation

In this sections we present the details of how we construct SPMs to test for the conjunction of two or more hypotheses. Although there are a number of ways in which one could test for the conjoint expression of two or more effects, we have the special problem of formulating such a test so that can be used in the context of statistical parametric mapping (and implicitly the theory of Gaussian fields). In brief the solution we have adopted consists of creating a SPM that reflects the sum of all the effects one is interested in and then eliminate regions where there are significant differences among these effects. In this approach a conjunction corresponds to a significant sum of all the effects if, and only if, there are no significant differences among them. This second condition confers the essence of a conjunction: For example; consider two effects evidenced by high values of some statistic, say z_1 and z_2. The sum of these numbers would be an appropriate statistic for the assessment of the first *or* second hypothesis because either a large z_1 or z_2 can give a high value of $z_1 + z_2$. However a conjunction requires the first *and* second hypotheses to be true. This is the case if z_1 and z_2 are high and are not significantly different. For readers familiar with factorial designs this can construed as identifying main effects in the absence of an interaction. It should be noted that conjunctions discount activations that are significantly different even if they are all significant in their own right.

A more general formulation of conjunctions can be framed in terms of main effects and interactions. In this formulation the *main effect* is the conjoint expression of the series of simple effects one is testing for. A conjunction is defined as a significant main effect in the absence of any differences or *interactions* among the simple effects. The conventional wisdom is that it does not usually make sense, either statistically or scientifically, to test for main effects in the presence of an interaction. A conjunction therefore resolves this problem by discounting main effects when there is evidence for an interaction.

An issue that specific to SPMs is that we want to eliminate voxels that show an interaction in a way that is independent of identifying voxels that show a conjoint or main effect. This is important because the elimination of regions, where significant differences are observed, can be used to reduce the search volume, rendering the correction for multiple comparisons less severe and the analysis more sensitive.

In what follows we present the details of the approach for the general problem of testing for the conjunction of N effects in the context of the linear model:

$$\mathbf{y} = \mathbf{X}.\boldsymbol{\beta} + \mathbf{r}$$

where **y** is the response variable (e.g. rCBF); a column vector with one element for each scan. **X** is the design matrix modelling the effects, with one effect in each column and one row for each scan. The parameter column vector **ß** contains one element for each effect in **X**. **r** is a column vector of identically and independently

distributed Gaussian residuals.

The problem can be formulated as follows: The N hypotheses can be specified in terms of a set of contrasts (e.g. a matrix **C** with one contrast per column i.e $\mathbf{C} = [\mathbf{c}_1\ \mathbf{c}_2\ ...\ \mathbf{c}_N]$) that specify linear compounds of parameter estimates (e.g. task condition means) where the compounds (e.g. activations) are weighted by the elements in the column vectors $\mathbf{c}_1, \mathbf{c}_2$..... We now wish to contract a SPM that reflects the conjoint expression of the effects specified by $\mathbf{c}_1, \mathbf{c}_2$.... and to eliminate regions where there are differences or interactions among these effects. First we note, from linear models theory, that the improvement in sums of squares in a nested sequence of models are independent, even in the non-null case. In particular, suppose we fit the sequence of models:

$$M_0: \quad \mathbf{y} = [\mathbf{X}_r].\boldsymbol{ß}_0 + \mathbf{r}_0$$

$$M_1: \quad \mathbf{y} = [\mathbf{X}_i\ \mathbf{X}_r].\boldsymbol{ß}_1 + \mathbf{r}_1$$

$$M_2: \quad \mathbf{y} = [\mathbf{X}_c\ \mathbf{X}_i\ \mathbf{X}_r].\boldsymbol{ß}_2 + \mathbf{r}_2$$

where the $\mathbf{X}_c$, $\mathbf{X}_i$ and $\mathbf{X}_r$ represent mutually orthogonal partitions of the original design matrix **X**. These partitions embody the conjunction of simple effects specified in **C**, the differences or interactions among these effects and all remaining effects respectively. $\mathbf{X}_r$ is **X** orthogonalised with respect to $\mathbf{X}_s$, where $\mathbf{X}_s$ is the space spanned by the simple effects of interest; $\mathbf{X}_s = \mathbf{X}.\mathbf{C}$. $\mathbf{X}_i$ is $\mathbf{X}_s$, orthogonalised with respect to $\mathbf{X}_c$ and $\mathbf{X}_c$ is the main effect of interest $\sum \mathbf{X}.\mathbf{c}_i$. We can now test for interactions by comparing M_0 with M_1 and for the main effect of interest by comparing M_2 with M_1, in a such a way that these tests are based on independent statistics (under the null hypothesis).

Let R_0, R_1 and R_2 denote the error sums of squares and the degrees of freedom d_0, d_1 and d_2 for the three models respectively. Then $(R_0 - R_1)$, $(R_1 - R_2)$ and R_2 are all independent (non-central) χ^2 random variables with degrees of freedom $(d_0 - d_1)$, $(d_1 - d_2) = 1$ and d_2 respectively. From this it follows that the sequential F statistics:

$$F_i = \frac{(R_0 - R_1)/(d_0 - d_1)}{R_1/d_1}, \quad F_c = \frac{(R_1 - R_2)/(d_1 - d_2)}{R_2/d_2},$$

are independent provided $(R_1 - R_2)$ and R_2 are central, i.e. there is truly no main effect. This is the case under the null hypothesis, which we are trying to protect against. This means that we can eliminate voxels that show an interaction using F_i and then use F_c to construct the SPM testing for the main effect to give us the conjunctions. The advantage of this formulation is that F_c has *exactly* a $F_{1,d2}$ distribution, irrespective of the presence of interactions. The distribution of F_i when there is a main effect, is not a (central) F distribution because the denominator now contains sums of squares due to this main effect. However this does not invalidate the procedure; the elimination step is not a hypothesis test, so there is no false positive rate to control.

The resulting SPM{F} can also be represented as an SPM{t} [or, after transformation, SPM{Z}]. This is because F_c is the corresponding t value squared. The SPM{F} will show conjoint activations and deactivations, whereas the SPM{t} will only show one tail (i.e. common activations). Both the SPM{F} or SPM{t} can now be subject to standard inferential procedures based on the theory of Gaussian random fields.

VII. Conclusion

We have presented a deliberately emphatic critique of cognitive subtraction and in particular the notion of pure insertion upon which serial subtraction relies. The main contention is that pure insertion may, or may not, be a valid cognitive science level description, but it is almost certainly not valid in relation to the brain's implementation of cognitive functions. This conclusion follows from the fact that the brain is a highly nonlinear system and, phenomenologically, does not conform to additive or linear principles. Pure insertion disallows any interactions and yet these interactions are evident, even in the simplest experiments. To illustrate

this point we have used a factorial experiment designed to elucidate the functional anatomy of object recognition and phonological retrieval. We showed that pure insertion can be an inappropriate and misleading assumption. In so doing we were able to demonstrate that inferotemporal activations, due to object recognition, were profoundly modulated by phonological retrieval of the object's name This interaction clearly implicates the inferotemporal regions in phonological retrieval during object naming, despite the absence of a main effect of phonological retrieval in the same region. By avoiding cognitive subtraction and using a factorial design of this sort we were able to reconcile our functional imaging results with lesion deficit studies [23].

It is interesting to speculate that cognitive processes may only express themselves at the level of interactions. For example, the *semantics* (memory or knowledge of meaning) of a word may only be realised by the interaction, or integration, between a particular phonology (word) and an associated percept, intention, affect or action (e.g. for nouns, the interaction between phonology and object recognition). If this is the case, there would be no 'semantic centre' *per se*, but semantics would be subtended by interactions between a set of cortical regions subserving subordinate components (e.g. phonological retrieval and object recognition). In this regard it is noteworthy that in semantic dementia, which is associated with progressive loss of semantic knowledge, the atrophy seen on magnetic resonance images is often maximal in the infero-lateral temporal cortex [25]. Although very conjectural this perspective is consistent with conclusions based on lesion data [26].

In conclusion we suggest that the effect of a cognitive component (this is independent of all other components) is best captured by the main effect of that component and that the integration of various components (i.e. the expression of one cognitive process in the context of another) is embedded in interaction terms. Brain regions can be functionally specialised for integration in the sense that they can demonstrate significant interactions in terms of their physiological responses. If we are right then brain *activations* are only part of the story in mapping cognitive anatomy. Regionally specific *interactions* may hold the key for a more complete and richer characterization. There are many implicit assumptions that underlie experimental design in neuroimaging and ongoing re-evaluation of these assumptions is the spur to adopt new and more cognitively informed approaches (and possibly the refinement of cognitive models).

References

1. S.E. Petersen, P.T. Fox, M.I. Posner, M. Mintun, M.E. Raichle Positron emission tomographic studies of the processing of single words. J Cog. Neurosci 1:153-170 (1989).
2. C.J. Lueck, S. Zeki, K.J. Friston, N.O. Deiber, P. Cope, V.J. Cunningham, A.A. Lammertsma, C. Kennard, R.S.J. Frackowiak. The colour centre in the cerebral cortex of man. Nature 340:386-389 (1989).
3. S. Grafton, J. Mazziotta, S. Presty, K.J. Friston, R.S.J. Frackowiak, M. Phelps. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J. Neuroscience 12:2542-2548 (1992).
4. C.J. Price, R.J.S. Wise, S. Ramsay, K.J. Friston, D. Howard, K. Patterson, R.S.J. Frackowiak. Regional response differences within the human auditory cortex when listening to words. Neurosci. Letters 146:179-182 (1992).
5. K.J. Friston, C. Frith, R.E Passingham, P. Liddle, R.S.J. Frackowiak. Motor Practice and neurophysiological adaptation in the cerebellum: a positron tomography study. Proc. Royal Soc. Lond. Series B. 248:223-228 (1992).
6. P.F.C. Gilbert and W.T. Thach. Purkinje cell activity during motor learning. Brain Res. 128:309-328 (1977).
7. K.J. Friston, P. Grasby, C. Bench, C. Frith, P. Cowen, P. Little, R.S.J. Frackowiak R. Dolan. Measuring the neuromodulatory effects of drugs in man with positron tomography. Neuroscience Letters 141:106-110 (1992).
8. P. Grasby, K.J. Friston, C. Bench, P. Cowen, C. Frith, P Liddle, R.S.J. Frackowiak, R. Dolan. Effect of the 5-HT1_A partial agonist buspirone on regional cerebral blood flow in man. Psychopharmacology 108:380-386 (1992).
9. P.C. Fletcher, C.D. Frith, P.M. Grasby, T. Shallice, R.S.J. Frackowiak, R.J. Dolan. Brain systems for encoding and retrieval of auditory-verbal memory. Brain 118:401-416 (1995).
10. C.D. Frith, K.J. Friston **F** The role of the thalamus in 'top down' modulation of attention to sound NeuroImage 0:0 (1996)
11. K.F. Friston, C.D. Frith, P.F. Liddle, R.J. Dolan, A.A. Lammertsma, R.S.J. Frackowiak. The relationship between global and local changes in PET scans J. Cereb. Blood Flow Metab. 10:458-466 (1990).
12. R.S.J. Frackowiak. Plasticity in the human brain: insights from functional imaging. Neurosci. 2;353-362 (1996).
13. K.J. Worsley. Local Maxima and the expected Euler characteristic of excursion sets of c^2, F and t fields. Advances Appl. Prob. 26;13-42 (1994).
14. A. Treisman and J. Souther. Search asymmetry: A diagnostic for preattentive processing of separable features. J.

Exp. Psychol: Gen, 114:285-310 (1985).
15. S. Sternberg. The discovery of processing stages: Extension of Donders method. Acta Psychologia 30:276-315 (1969).
16. A. Aertsen & H. Preissl. Dynamics of activity and connectivity in physiological neuronal Networks in "Non Linear Dynamics and Neuronal Networks" (H.G.Schuster VCH publishers Inc. eds.), p 281-302, New York NY, USA, 1991.
17. S. Zeki, J.D.G. Watson, C.J. Lueck, K.J. Friston, C. Kennard, R.S.J. Frackowiak. A direct demonstration of functional specialisation in human visual cortex. J Neurosci. 11:641-649 (1991).
18. M. Corbetta, F.M. Miezin, S. Dobmeyer, G.L. Shulman, S.E. Petersen. Selective and divided attention during visual discrimination of shape, color and speed. Functional anatomy by positron emission tomography. J Neurosci 11(8):2383-2402 (1991).
19. C.J. Price and G.W. Humphreys. Attentional dyslexia: The effect of co-occurring deficits. Cog. Neuropsychology 10:569-592 (1993).
20. L.G. Ungerleider and M. Mishkin. Two cortical visual systems in "Analysis of Visual Behaviour" (D.J Ingle, M.A. Goodale, R.J.W. Mansfield eds.), pp549-86, (MA): MIT Press, Cambridge, (1982).
21. R. Desimone, T.D. Albright, C.G. Gross, C. Bruce. Stimulus selective properties of inferior temporal neurons in the macaque. J Neurosci. 4:2051-2062 (1984).
22. D.I. Perret, A.J. Mistlin, D.D. Potter, P.A.J. Smith, A.S. Head, A.J. Chitty, R. Broenimann, A.D. Milner, M.A. Jeeves. Functional organization of visual neurones processing face identity in "Aspects of face processing" (H. Ellis, M.A. Jeeves, F. Newcombe, A.W. Young eds.), pp 187-198 , Dordrecht: Martinus Nijhoff, 1986.
23. E. De Renzi, A. Zambolin, G. Crisi. The pattern of neuropsychological impairment associated with left posterior cerebral artery territory infarcts. Brain 110:1088-1116 (1987).
24. J. Talairach & P. Tournoux. A Co-planar stereotaxic atlas of a human brain. Thieme, Stuttgart, 1988.
25. J.R. Hodges, K. Patterson, S. Oxbury, E. Funnell. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 115:1783-1806 (1992).
26. J.M. Nielsen. Agnosia, apraxia , aphasia: Their value in cerebral localization. 2nd edition New York: Paul B Hoebner, 1946.