Dynamic Changes in Effective Connectivity Characterized by Variable Parameter Regression and Kalman Filtering

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Abstract: Attention to visual motion can increase the responsiveness of the motion-selective cortical area V5 and the posterior parietal cortex. We addressed attentional modulation of effective connectivity using *variable parameter regression* and functional magnetic resonance imaging. We present data from a single subject scanned under identical stimulus conditions (visual motion) while varying only the attentional component of the task. Variable parameter regression of the influence of V5 on PP revealed increased effective connectivity during attention to visual motion. With this dynamic measure of effective connectivity we were able to make inferences about the source of modulation by looking for regions that predicted the observed changes in connectivity. Using an ordinary regression analysis, we showed that activity in the prefrontal cortex could explain these changes and was sufficient to account for these modulatory influences on connections in the dorsal visual pathway. *Hum. Brain Mapping 6:403–408, 1998.* © 1998 Wiley-Liss, Inc.

Key words: effective connectivity; fMRI; attention; Kalman filter; variable parameter regression

INTRODUCTION

Functional neuroimaging has been extremely successful in establishing functional segregation as a principle of organization in the human brain. More recent approaches have addressed the integration of functionally segregated areas through characterizing neurophysiological activations in terms of distributed changes. These approaches have introduced a number of concepts (e.g., functional and effective connectivity), techniques (e.g., structural equation modelling [Büchel and Friston, 1997; McIntosh and Gonzalez-Lima, 1994]) and their application to issues in imaging neuroscience (e.g., changes in effective connectivity as a function of attentional set or time, as seen in learning). Effective connectivity is defined as the influence that one neural system exerts over another [Friston et al., 1995b], either at a synaptic (cf. synaptic efficacy) or a cortical level. A simple way to characterize the effect area x has on y is by standard regression analysis. Since a single regression coefficient obtains, this implicitly assumes that the effective connectivity is constant over all observations. This is clearly a limiting factor, because most experiments aimed at assessing effective connectivity evoke changes in connectivity as a function of time (i.e., learning), related experimental conditions, subjects' responses, or regional brain activity (i.e., activity-dependent changes in connectivity).

Here we demonstrate how an extension of ordinary regression analysis, *variable parameter regression*, can

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overcome this limitation and be used to identify nonlinear changes in effective connectivity. The operational equations used are special cases of Kalman filtering [Garbade, 1977; Kalman, 1960]. To demonstrate the approach, we used fMRI data from a single subject, to assess changes in effective connectivity that were related to attentional set. In the context of attentional modulation, the question of *site* and *source* of modulation is of special interest. In a second step, we will show how variable parameter regression can be used to find the site or origin of afferents that may mediate attentional modulation.

METHODS

Variable parameter regression

Variable parameter regression assumes T ordered scalar observations $(y_1, \ldots y_T)$ generated by the model:

$$y_t = x_t\beta_t + u_t, \quad t = 1, \ldots, T, \tag{1}$$

$$u_t \sim N(0, \sigma^2) \tag{2}$$

where x_t is an n-dimensional row vector of known regressors and β_t is an n-dimensional column vector of unknown coefficients that corresponds to estimates of effective connectivity. u_t is drawn from a Gaussian distribution. All observations are expressed as deviations *from* the mean. The dynamic evolution of β is assumed to follow a random walk with zero drift over time:

$$\beta_t = \beta_{t-1} + p_t, \quad t = 2, \ldots, T, \tag{3}$$

$$p_t \sim N(0, \sigma^2 P) \tag{4}$$

where $\sigma^2 P$ is the stationary covariance matrix of the innovation p_t. If $P = 0$, then variable parameter regression reduces to the ordinary stationary coefficient linear regression problem. The variance term σ^2 of Eq. (4) is the same as that in Eq. (2) and is presented explicitly for clarity. The innovations u_t and p_t are uncorrelated. An innovation is simply an underlying stochastic process or sequence of numbers. Other models than a random walk for β are possible.

Parameter estimation

Given the observations $y_1, \ldots, y_T$, we are interested in the trajectory of the β_t coefficients. Assume P and σ^2 are known. Let $\hat{\beta}_t(s)$ be the estimate of β_t based on the observations $(y_1, \ldots, y_s)$, let $\sigma^2 R_t$ be the estimated covariance matrix of $\hat{\beta}_t(t-1)$, and let $\sigma^2 S_t$ be the estimated covariance matrix of $\hat{\beta}_t(s)$. The first step in Kalman filtering is to obtain the prediction that updates $\hat{\beta}_{t-1}(t-1)$ and its covariance matrix for the passage of time from $t - 1$ to t:

$$\hat{\beta}_t(t-1) = \hat{\beta}_{t-1}(t-1) \tag{5}$$

$$R_t = S_t - 1 + P. \tag{6}$$

The filter step revises this estimate of β_t by adding the new information contained in the observation y_t:

$$\hat{\beta}_t(t) = \hat{\beta}_t(t-1) + K_t e_t \tag{7}$$

$$\text{where } e_t = y_t - x_t\hat{\beta}_t(t-1)$$

$$\text{and } K_t = R_t x'_t E_t^{-1},$$

$$\text{and } E_t = x_t R_t x'_t + 1 \tag{8}$$

$$S_t = R_t - K_t x_t R_t. \tag{9}$$

From Equations (5–7) it is obvious that Kalman filtering is a recursive process, where new information is added as it arrives. Estimates from early time steps are therefore less reliable than those from later ones. To circumvent this problem, a third step, called smoothing, can add the information that arrived after time t to the estimate of β_t. Let $\sigma^2 V_t$ be the estimation covariance of the smoothed estimate $\hat{\beta}_t(T)$. The smoothed estimates are computed as:

$$\hat{\beta}_t(T) = \hat{\beta}_t(t) + G_t[\hat{\beta}_{t+1}(T) - \hat{\beta}_t(t)] \tag{10}$$

$$\text{where } G_t = S_t[S_t + P]^{-1}, \tag{11}$$

$$V_t = S_t + G_t[V_{t+1} - R_{t+1}]G'_t, \tag{12}$$

$$V_T = S_T. \tag{13}$$

So far, we have assumed that covariance matrix P and variance scalar σ^2 are known. However, these are exactly the parameters that we are interested in. In the next step we show how P and σ^2 can be estimated by maximum likelihood. The log-likelihood function of P and σ^2 is

$$L = -\frac{1}{2}\sum_{t=n+1}^{T} \ln(\sigma^2 E_t) - \frac{1}{2}\sum_{t=n+1}^{T}\left\{\frac{e_t^2}{\sigma^2 E_t}\right\}. \tag{14}$$

An estimate of σ^2, for given P, is available by analytic maximization of Eq. (14):

$$\hat{\sigma}^2 = \sum_{t=n+1}^{T} \left\{ \frac{e_t^2}{(T-n)E_t} \right\}. \qquad (15)$$

The concentrated log-likelihood function is then:

$$L^*(P) = -(T-n)\ln(\hat{\sigma}) - \frac{1}{2}\sum_{t=n+1}^{T} \ln(E_t) \qquad (16)$$

where both $\hat{\sigma}$ and E_t are implicit functions of P. L* is thus a complicated nonlinear function of P. Therefore, numerical optimization is necessary to maximize L* as a function of the unknown elements in matrix P. Since estimates of P that are not nonnegative definite are meaningless, maximization of the likelihood function should be restricted to the set of positive definite matrices.

Statistical inference

Whether the maximum likelihood estimate $\hat{P}$ is significantly different from a hypothesized value P_0 can, in some circumstances, be tested with the likelihood statistic:

$$-2\ln(\lambda) = -2[L^*(P_0) - L^*(\hat{P})]. \qquad (17)$$

If the parameter vector has dimension $n = 1$, so that P is a scalar (i.e., variance of the innovation term p_t in Eq. 4), it has been shown that for $P_0 > 0$, the likelihood statistic will (asymptotically) have a chi-square distribution with one degree of freedom under the null hypothesis [Cooley and Prescott, 1976]. However, it has been shown that for the most interesting null hypothesis $P_0 = 0$ (i.e., no change of β_t over time), the likelihood statistic will be biased towards zero [Garbade, 1977]. Hence, using a chi-square distribution to determine the critical value of $-2\ln(\lambda)$ will lead to a conservative test of the stability of the β_t coefficients. However, simulations have shown that this test performs quite well in models where parameter variation was modeled as (1) a random walk with drift, (2) discrete jump, and (3) a stable Markov process. It has also been shown that the power of the variable parameter regression likelihood test in rejecting the null hypothesis increases as a function of sample size and instability of coefficients [Garbade, 1977].

The smoothed estimates of the varying regression coefficient, $\hat{\beta}_t(T)$'s, allow the graphical presentation of the changes of regression coefficients and implicitly effective connectivity. Furthermore, the square roots of the diagonal elements of $\sigma^2 V_t$ provide the standard error of these estimates.

Experimental design

The subject was scanned during three conditions, "fixation," "attention," and "no attention." During the "attention" and "no attention" condition, the subject fixated centrally while white dots emerged radially from the fixation point to the edge of the screen. During "fixation," the screen was dark with only the fixation dot visible. The difference between the optic-flow conditions lay in the explicit instructions given to the subject. In the "attention" condition, the instruction was to "detect changes" in speed, and during the "nonattention" condition, the subject was instructed to "just look." Psychophysical tests prior to scanning induced the anticipation of speed changes during the attention conditions. However, the physical stimulus characteristics for "attention" and "no attention" conditions were identical during scanning (i.e., no speed changes).

Data acquisition and analysis

The experiment was performed on a 2 Tesla Magnetom VISION (Siemens, Erlangen, Germany) whole-body MRI system equipped with a head volume coil. Contiguous multislice T2*-weighted fMRI images (TE = 40 msec; 90 msec/image; 64×64 pixels (19.2×19.2 cm)) were obtained with echo-planar imaging (EPI) using an axial slice orientation. A T2*-weighted sequence was chosen to enhance blood oxygenation level-dependent (BOLD) contrast. The volume acquired covered the whole brain except for the lower half of the cerebellum and the inferiormost part of the temporal lobes (32 slices; slice thickness, 3 mm, giving a 9.6-cm vertical field of view). The effective repetition time was 3.22 sec. All volumes were realigned to the first volume, coregistered with the subject's T_1 structural MRI, normalized to a standard template, and smoothed using an 8-mm FWHM Gaussian kernel using SPM97 [Friston et al., 1995a].

RESULTS

The regions of interest for the analysis of effective connectivity were identified using the maxima in a standard Statistical Parametric Mapping (SPM) analysis of the condition-specific effects [Büchel and Friston, 1997]. We concentrate here on the effect of attention on the connection between the motion-sensitive area V5 and the posterior parietal cortex (PP) in the right hemisphere. In a previous analysis, using structural equation modeling, we demonstrated that it is principally this connection in the dorsal visual stream that is modulated by attention to visual motion. We further demonstrated that nonlinear modulatory effects exerted by the dorsolateral prefrontal cortex could account for this effect. In the current analysis we were interested in whether variable parameter regression was capable of reproducing these findings. We therefore assessed the effective connectivity β_t by regressing PP on V5. An alternate direction search, i.e., numerical optimization, gave a chi-square statistic of 56.4. We therefore had to reject the null hypothesis of no variation at the 5% level. P was estimated to be 0.074 and σ^2 was 0.23. The ordinary regression coefficient β for the model $y = x\beta + u$ was estimated at 0.73. Figure 1a,b shows the trajectories of the smoothed and filtered estimates $\hat{\beta}_t(T)$, together with the associated standard errors. It is clearly evident that $\hat{\beta}_t$ is higher during the "attention" conditions relative to the "no attention" conditions. Figure 1c relates our technique to an ordinary regression. In this analysis, we constrained the variance term P to zero and reestimated β_t. The trajectory of $\hat{\beta}_t$ now converges to β, the ordinary regression coefficient of the model $y = x\beta + u$. As expected, the smoothed estimates are simply a constant (i.e., $\beta = 0.73$).

We interpret $\hat{\beta}_t$ as an index of effective connectivity between area V5 and the posterior parietal cortex. In our example, the connection between V5 and PP resembles the *site* of attention modulation. This leads to an interesting extension, where one might hypothesize that a third region is responsible for the observed variation in effective connectivity indicated by the trajectory of $\hat{\beta}_t(T)$. In other words, after specifying the site and nature of attentional modulation, we now want to know the location of the *source*. We addressed this by using $\hat{\beta}_t(T)$ as an explanatory variable in an ordinary regression analysis to identify voxels that covaried with this measure of effective connectivity. Figure 1d shows the results of this analysis. Among areas with statistically significant ($P < 0.001$, uncorrected) positive covariation was the dorsolateral prefrontal cortex and the anterior cingulate cortex. This confirms the putative modulatory role of the dorsolateral prefrontal cortex in attention to visual motion, as suggested in Büchel and Friston [1997].

DISCUSSION

We have addressed attentional modulation of effective connectivity using variable parameter regression and functional magnetic resonance imaging. Variable parameter regression of the influence of V5 on PP revealed increased effective connectivity during attention to visual motion. Using an ordinary regression analysis, we showed that activity in the prefrontal cortex could explain these changes and was sufficient to account for these modulatory influences on connections in the dorsal visual pathway.

Alternative approaches

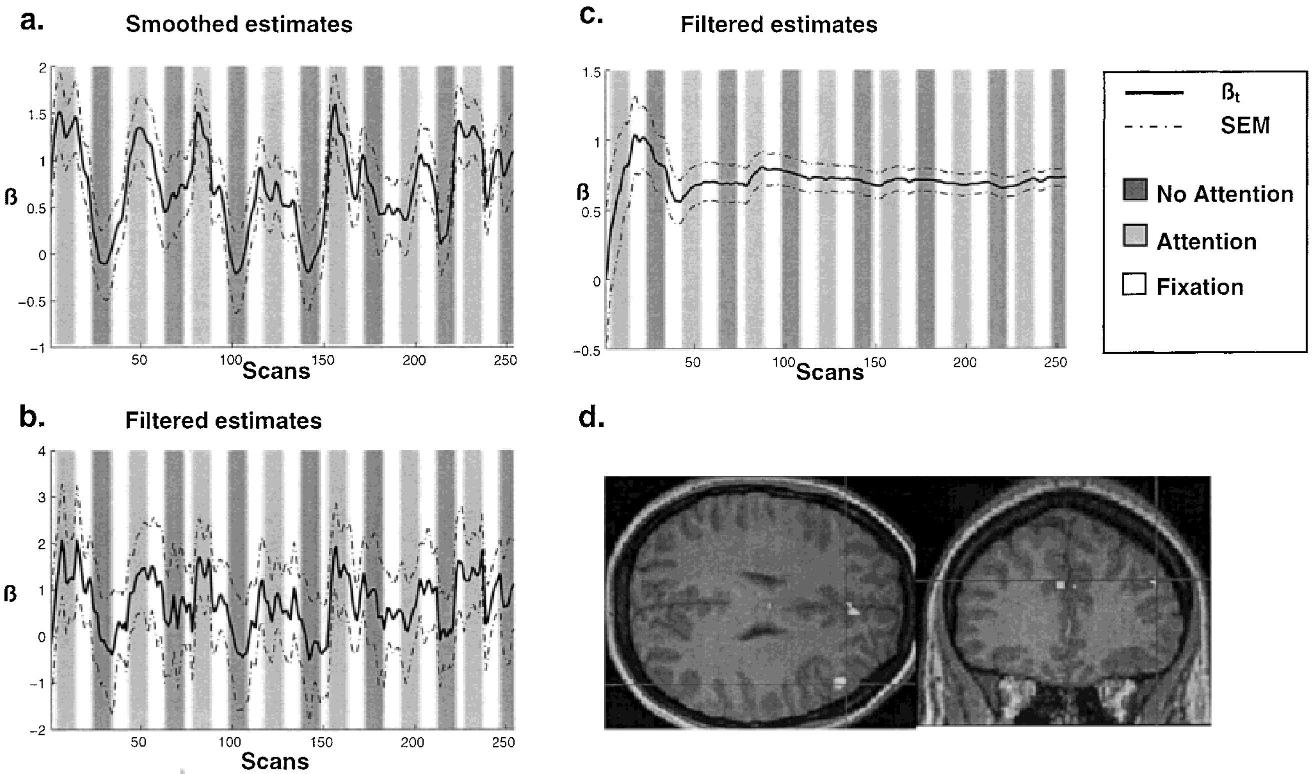
The variable parameter regression employed above used a very simple model for the innovation of β_t. An alternative approach would be to consider β as a function of exogenous variables (i.e., time-dependent explanatory variable). In the experiment above we could treat the task as an exogenous variable. One would simply code attention as a dummy variable, taking the value -1 for "no attention" and $+1$ for "attention," and zero for the baseline scans. Let A be this task variable. The hypothesis concerning attentional modulation of the connection between V5 and PP could then be formulated in a simple model:

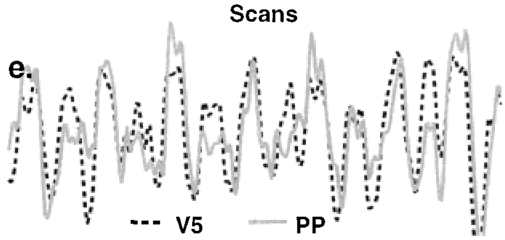
$$y = x\beta_t + \mathrm{diag}\,(x)A\beta_2 + A\beta_3 + u \qquad (18)$$

where diag (x) is a diagonal matrix whose leading diagonal contains the elements of x.

The question of interest is now whether the interaction term diag (x)A can explain a significant amount of variance of y in addition to the two main effects (i.e., x and A). This can be tested using the general linear model in a standard SPM analysis. This approach has been described as testing for a psychophysiological interaction [Friston et al., 1997]. When the form of the changes in effective connectivity can be anticipated, this provides a very powerful tool to assess the site and significance of changes in effective connectivity. In cases where less is known about the expected form of variation of β, one could expand β using a set of basis functions, to model any arbitrary but constrained time-varying β. This would be achieved by A in Eq. (18) with a matrix whose columns contained some suitable basis functions of time (e.g., a discrete cosine set). The ensuing parameter estimates β_2 can then be tested with a SPM{F} in the usual way [Büchel et al., 1996]. We will compare these regression approaches to Kalman filtering in a subsequent paper.

The approach demonstrated in this paper, however, is the least constrained, since the only assumption made is that changes in β are smooth and can be modeled by a random walk. This allowed us to assess





f.

Correlations:

	ac	pfc
vpr	.42	.39
v5	.06	.06
pp	.13	.14

Figure 1.

a and **b:** Trajectory of the smoothed and filtered estimates $\hat{\beta}_t(T)$, together with the associated standard errors for the variable parameter estimation of effective connectivity between V5 and PP. It is evident that $\hat{\beta}_t$ (i.e., the dynamic regression coefficient) is higher during the "attention" conditions relative to the "no attention" conditions. **c:** Relationship between our technique and an ordinary regression analysis. In this analysis, the variance term P was set to zero (i.e., fixed regression model). The trajectory of $\hat{\beta}_t$ now converges to β (=0.73), the regression coefficient of the model $y = x\beta + u$. **d:** Areas that significantly covaried with the time-dependent measure of effective connectivity between V5 and PP (i.e., $\hat{\beta}_t(T)$). SPM{Z} thresholded at $P < 0.001$ (uncorrected) overlaid on coronal and axial slices of the subject's structural MRI. The maximum under the cross-hairs was at 45, 21, and 39 mm, Z = 4.3. **e:** Time courses of V5 and PP as used in the VPR analysis. **f:** Correlation coefficients between regions identified in the SPM (d) (anterior cingulate (ac) and prefrontal cortex (pfc)) and the original variables (v5, pp) and the smoothed estimate of the variable parameter regression (vpr).

changes in effective connectivity with minimal a priori assumptions. Note that a linear combination of basis functions is not, in general, able to model random walks.

CONCLUSIONS

We have demonstrated how variable parameter regression can be used to assess dynamic changes in effective connectivity. We have demonstrated that this technique reliably assessed these changes in effective connectivity as a function of attentional set. Moreover, it allowed us to search for candidate sources of attentional modulation with a standard SPM analysis by treating the time-dependent measure of effective connectivity as an explanatory variable in all other potentially modulatory voxels.

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