Chapter 8

Modelling of fMRI data to probe effective connectivity

In this chapter, we introduce a recent analysis methodology called 'effective connectivity'. The effective connectivity analysis is realized through Dynamic Causal Modelling (DCM) option in the SPM2 package. DCM is a recent option in SPM developed by the Wellcome Department of Imaging Neuroscience, University College London. In this chapter, we demonstrate the analysis methodology of effective connectivity on a few models.

Historically, neuroimaging has been concerned predominantly with the localization of brain function, i.e. where in the brain certain types of cognitive processes is being implemented. The questions are addressed by the 'General Linear Model' for example implemented in SPM (Friston et al., 1995c). In addition, rather than just looking at the localization of areas involved in certain cognitive processes, one can ask the question of how this neural implementation works in terms of functional principles of the system i.e., through functional integration. One way to address this question of functional integration is through temporal correlation between spatially segregated remote neurophysiological events. This is called functional connectivity. The nature of functional coupling such as modulation are not dealt in these kind of models. The other way is to use the models of effective connectivity, where one can model the influence one neuronal system exerts over another system through causal statements (Friston et al., 2003). The basic idea of effective connectivity is to construct a reasonably realistic neuronal model of interacting cortical regions using neuroimaging data. The effective connectivity for the fMRI data is introduced recently by Karl Friston through the
8.1. Dynamic Causal Modelling (DCM)

DCM treats the brain as a deterministic nonlinear dynamical system that is subjected to inputs and produces outputs (Friston et al., 2003). The effective connectivity is parameterized in terms of coupling among unobserved brain states i.e., neuronal activity in different regions. The general idea behind DCM is to construct a neuronal model of interacting cortical regions with neurophysiologically meaningful parameters. These parameters are estimated such that the predicted BOLD series, which results from converting the neural dynamics into haemodynamics, corresponds as closely as possible to the observed BOLD series. In DCM, neural dynamics in several regions represented by a neuronal state vector \( z \) with one state per region are driven by experimental inputs. These inputs enter into the model in two ways: (1) by eliciting responses through direct, influences on specific anatomical nodes, (2) by modulating the coupling among nodes. DCM models the change in neural states as non-linear function of states \( z \), the inputs \( u \) and neural parameters \( \theta^n \):

\[
\dot{z} = F(z, u, \theta^n) \tag{8.1}
\]

where \( F \) is some non-linear function describing the neurophysiological influences. \( \theta \) are the parameters of the model whose posterior density we require for inference. The parameters are the connectivity matrices \((\theta^n \sim A, B, C)\) that define the functional architecture among brain regions at the neuronal level. The bilinear approximation of the Equation 8.1 suggested by Friston et al. (2003) is as follows:

\[
\dot{z} \approx Az + \sum u_jB^jz + Cu = (A + \sum u_jB^j)z + Cu \tag{8.2}
\]

in which the coupling parameters correspond to partial derivatives of \( F \):
The Jacobian or effective connectivity matrix $A$ represents the first-order connectivity among the regions in the absence of modulatory input. The matrix $B^j$ encodes the change in effective connectivity induced by the $j^{th}$ input $u_j$. The $C$ matrix embodies the extrinsic influences of inputs on neural activity. DCM combines this neural model with the biophysical forward model of Friston (20021) which describes how neuronal activity translates into a BOLD response. This enables the parameters and time constants of the neuronal model to be estimated from the measured data, using a fully Bayesian approach with empirical priors for the biophysical parameters and conservative shrinkage priors for the coupling parameters. The posterior distributions of the parameter estimates can then be used to test hypotheses about the size and nature of modelled effects. Usually, these hypotheses concern context-dependent changes in coupling which are represented by the bilinear terms of the model. Thus dynamic causal modelling is a way of modelling the effect one hypothesizes. The nature of effect is represented in terms of parameters $\theta^n$.

The important points to be noted while designing DCM-compatible fMRI studies are as follows. The experiment should be designed in a multi-factorial fashion with at least one factor being effected by sensori input, while others vary with contextual inputs. The slice time TR of the scanner should be as short, as possible (typically it should be less than 1.5—2 seconds) to estimate the DCM parameters perfectly. In general it can also works with higher TRs but one should localize the anatomical hypothesis over nearby brain regions. The specification of a priori hypothesis is also an important point while working with DCM. To make inference over a group, one should evaluate DCM models for each subject/experiment/session and the parameters obtained are taken to the second level to perform statistical tests like $t$-test.

Though our experimental paradigm does not satisfy all the prerequisites for DCM analysis, in this chapter we try to bring out some results based on the

$$A = \frac{\partial F}{\partial z} = \frac{\partial z}{\partial z}$$

$$B^j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j} \frac{\partial z}{\partial z}$$

$$C = \frac{\partial F}{\partial u}$$  (8.3)
brain areas we obtained from the SPM analysis of the complexity experiment. The results will be presented on one representative subject to demonstrate the procedure. The procedure for the DCM analysis is adopted from the SPM website (http://www.fil.ion.ucl.ac.uk/spm/).

8.2 Results

The idea of doing the DCM analysis is to study the effective connectivity among some of the areas that were activated in the comparisons of complex sequence conditions with the 2x6 task. As the current study investigates motor sequence learning, we selected few motor circuits such as dorsal premotor (PMd)—primary motor (MI), PMd—anterior cerebellum, caudate—PMd, dorsolateral prefrontal cortex (DLPFC)—caudate and posterior cerebellum—superior parietal cortex for investigating effective connectivity between them during the task. Anatomical connections between most of these areas is well known (Alexander et al., 1986; Middleton and Strick, 1998b,a; Picard and Strick, 2001)

8.2.1 Testing the model of dorsal premotor cortex, primary motor cortex

We tested a model consisting of ipsilateral (right) dorsal premotor and ipsilateral (right) primary motor cortex on one representative subject. For the early and the consolidation stages we performed DCM analysis for these; two areas, which were found to be active in the RFX analysis of Early 4x6>2x6 contrast. In the absence of modulatory inputs the intrinsic connections (matrix A and its probability values shown in the brackets of Figure 8.1) showed significant connection strength from right dorsal premotor to the right primary motor cortex. Figure 8.2 shows the modulatory effects (matrix B and its posterior probability values) of the early and the consolidation conditions on the reciprocal connections between the these two areas. The results suggest that, in the early stage of 4x6 the connection between right dorsal premotor and right primary motor cortex is significant in strength and displayed high probability value.
8.2. Results

Figure 8.1: The intrinsic connections strengths between ipsilateral dorsal premotor and ipsilateral primary motor area.

Figure 8.2: The modulatory connections for (a) Early and (b) Consolidation stages related to the 4x6 task. This graph shows in the early stage the connections between right dorsal premotor and right primary motor are strong but became weak by the consolidation stage.
Note that the intrinsic and extrinsic connection strength units are generally defined in Hz. Hence, the strength of a coupling can be thought of as a rate constant or the reciprocal of the time constant (the speed with which one area can affect another one). The modulatory parameters quantify how experimental manipulations change the values of intrinsic connections.

8.2.2 Testing the model of dorsal premotor cortex, anterior cerebellum

We tested another model consisting of ipsilateral (right) dorsal premotor cortex and ipsilateral anterior cerebellum on one representative subject. We performed DCM analysis separately for the early and the consolidation stages on those areas which got activated in the 4x6x2xG contrasts. In the absence of modulatory inputs the intrinsic connection showed significant connection strength from right dorsal premotor to the right anterior cerebellum (Figure 8.3). Figure 8.4 shows the modulatory effects of the early and the consolidation conditions on the reciprocal connections between the these two areas. This suggests that, in the early stage of 4x6 the connection between right dorsal premotor and right, anterior cerebellum is more in the strength and showed significant probability value.

![Intrinsic connections](image)

Figure 8.3: The intrinsic connections strengths between ipsilateral dorsal premotor and ipsilateral anterior cerebellum.
8.2. Results

8.2.3 Testing the model of caudate, dorsal premotor cortex

We tested another model consisting of contralateral caudate and ipsilateral (right) dorsal premotor cortex on one representative subject. We performed DCM analysis separately for the early and the consolidation stages on those areas which got activated in the 4x6>2x6 contrasts. In the absence of modulatory inputs the intrinsic connection showed significant connection strength from left caudate to the right dorsal premotor (Figure 8.5). Figure 8.6 shows the modulatory effects of the early and the consolidation conditions on the reciprocal connections between the these two areas. This demonstrates that in the consolidation stage of 4x6 the connection between left caudate and right dorsal premotor is significant in the strength and displayed more confidence value (greater than 92% as evidenced by the posterior probability value).
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8.2.4 Testing the model of dorsolateral prefrontal cortex, caudate

We tested another model consisting of contralateral (left) dorsolateral prefrontal cortex (DLPFC) and contralateral caudate on one representative subject. We performed DCM analysis separately for the early and the consolidation stages on those areas which got activated in the consolidation 4xG>2x6 contrast. In the absence of modulatory inputs the intrinsic connection showed significant connection strength from left dorsolateral prefrontal cortex to the left caudate (Figure 8.7). Figure 8.8 shows the modulatory effects of the early and the consolidation conditions on the reciprocal connections between these two areas. This demonstrates that in the consolidation stage of 4x6 the connection between left DLPFC and left caudate is significant in the strength and displayed more than confidence value (greater than 95% as evidenced by the posterior probability value).

8.2.5 Testing the model of posterior cerebellum, superior parietal cortex

We tested another model consisting of ipsilateral (right) posterior cerebellum and ipsilateral (right) superior parietal cortex on one representative subject. We
8.2. Results

Figure 8.6: The modulatory connections for (a) Early and (b) Consolidation stages related to the 4x6 task. This graph shows in the consolidation stage the connections between left caudate and right dorsal premotor is strong but found to be non-significant in the early stage.

performed DCM analysis separately for the early and the consolidation stages on those areas which got activated in the consolidation 2x12>2x6 contrast. In the absence of modulatory inputs the intrinsic connection showed significant connection but negative valued strength from right posterior cerebellum to right superior parietal cortex (Figure 8.9). Figure 8.10 shows the modulatory effects of the early and the consolidation conditions on the reciprocal connections between the these two areas. This demonstrates that in the consolidation stage of 2x12 the connection between posterior cerebellum and posterior superior parietal cortex is significant in the strength and displayed more probability value.

The modulatory connections (matrix B and their corresponding probability values) for 2x6 task on all the five models did not yield any significant connections either in the early or the consolidation stages. This further validates the complexity related effects (i.e., areas of activation in the complex tasks and their
8.3 Summary and Conclusions

In this chapter we presented results from DCM analysis to demonstrate the effect of learning on some connections. The results suggest that in the 4x0 task the modulatory connections from right dorsal premotor to right primary motor and from the right dorsal premotor to the right anterior cerebellum are significantly high as compared to their connections in the consolidation stage. The modulatory connections from left caudate to right dorsal premotor and left dorsolateral prefrontal cortex and left caudate displayed significant connections in the consolidation stage of the 4x6 task. In the 2x12 task we probed in the modulatory connection between right posterior cerebellum and right superior parietal cortex. The DCM analysis yielded their connectivity was strong in the consolidation stage. The results also point out the importance of DCM analysis to probe into the effective connectivity as effected by the experimental/modulatory inputs.
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Figure 8.8: The modulatory connections for (a) Early and (b) Consolidation stages related to the 4x6 task. This graphs shows in the consolidation stage the connections between left dorsolateral prefrontal cortex and left caudate is strong but found to be non-significant in the early stage.

Figure 8.9: The intrinsic connections strengths between right posterior cerebellum and right superior parietal cortex.
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Figure 8.10: The modulatory connections for (a) Early and (b) Consolidation stages related to the 2x12 task. This graphs shows in the consolidation stage the connections between right posterior cerebellum and right superior parietal cortex is strong but found to be weak in the early stage.