Connectivity of Complex Networks: A Monte Carlo-Based Approach for Dynamic Causal Modeling

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INTRODUCTION: Understanding the complex connectivity of the brain is important because dysfunctional connectivity might be involved in neuropsychiatric diseases. Dynamic causal modeling (DCM)[1] is the emerging fMRI tool to study brain connectivity because it treats the brain as a deterministic input-output system, assumes neuronal interactions among regions, and accommodates arbitrary complex connectivity patterns. However, the hypothesis-driven DCM is not an efficient exploratory technique because it is computationally highly demanding and the number of possible interconnection models increases exponentially with the number of nodes, N, in the network as $2^{N(N-1)}$. To overcome these limitations, we propose a data-driven method, which does not require a priori hypotheses, for connectivity studies in complex networks. We hypothesized that stochastic methods commonly used in physics to solve complex many-body problems, and parallel computers can be used to find the optimal connectivity models of activated networks without a priori assumptions.

METHODS: We developed a Monte Carlo-based DCM method (MC-DCM) that stochastically optimizes the network's interconnections step by step, starting from an arbitrary seed model and using the Bayesian and Akaike information criteria[2] (Fig 1). This automated algorithm uses all DCM subroutines in SPM5 and runs in parallel in multiple-processor computers. Sixteen healthy non-smoking and right-handed men participated in fMRI studies (4-Tesla field) of an n-back sequential letter (verbal) working memory paradigm that has graded levels of difficulty (0-, 1- and 2-back) and blocked design[3]. SPM5 was used for standard statistical analyses of brain activation. Eight volume-of-interest (10-mm spherical) were defined at the location of major activation clusters (fixed across subjects) in the prefrontal [SMA (ventral) and DLPFC (L&R)], and superior parietal (SPC; L&R) cortices, cerebellum (L&R), and the thalamus (Fig 2). The left and right networks, which shared the SMA and the thalamus VOIs, were optimized independently. The thalamus was set as the input region. Two initial seed models were tested: "disconnected" (all connections "OFF") and "fully connected" (all connections "ON"). The status (ON or OFF) of each connection was randomly changed with 20% probability; thus at each MC-step only few connections of the current best model were subject to changes. Three comparison criteria were tested: 1) Bayesian, 2) Akaike and 3) Bayesian & Akaike.

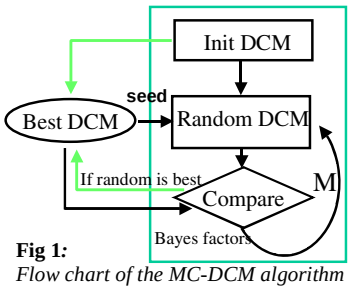

Fig 1: *Flow chart of the MC-DCM algorithm*

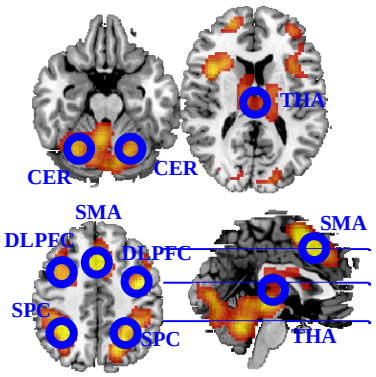

Fig 2: *BOLD-fMRI activation during the n-back verbal WM task and selected VOIs in the brain. Sample: 16 healthy men. One-way within-subjects ANOVA.*

RESULTS: Evaluation of best models suggests that the initial disconnected seed and the comparison criteria #3 are the optimal connectivity searching conditions. The optimal connectivity models for the group of subjects were sorted automatically from 2000 different and randomly selected interconnection models (see example in Fig 3) without a priori hypotheses (CPU time: 500 hours in a Dual Quad Core Xeon PC with 8 processors). The MC-DCM algorithm converges to unique connectivity solutions. The optimal connectivity models for the left and right sides of the WM network resulted identical (Fig 4); the strength coefficients for the latent (**A**; in absence of inputs) and induced (**B**; induced by inputs) connectivity matrices, however, were different for each brain side (as an example, Fig 4 shows the connectivity strengths for the left hemisphere only). The SMA was the most interconnected brain region (it had interconnections with all other nodes the WM network) while the cerebellum only had a reciprocal latent connection with the SMA. All cortical and thalamic-cortical connections were unidirectional.

CONCLUSIONS: The proposed approach is based on stochastic methods commonly used in physics, chemistry, biology, economics and other sciences to solve complex many-body problems, allows for exploratory neuroscience research in brain connectivity using fMRI data, and does not require a priori interconnection hypotheses. Using this extremely computing-demanding approach we were able to demonstrate that the optimal WM-connectivity is identical for the left and right hemispheres. The optimal connectivity model has an SPC-DLPFC-SMA connection loop suggesting an important role of the prefrontal-parietal network in WM processing and of a separate but parallel processing by cerebellum.

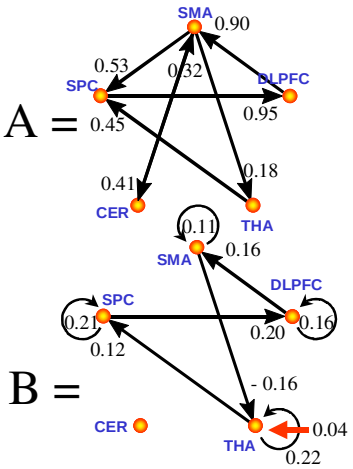

Fig 4: *optimal connectivity model for the WM network in the left hemisphere. The strengths of the latent (**A**) and induced (**B**) connectivity matrices are given in Hz. All connections have probability > 99%*

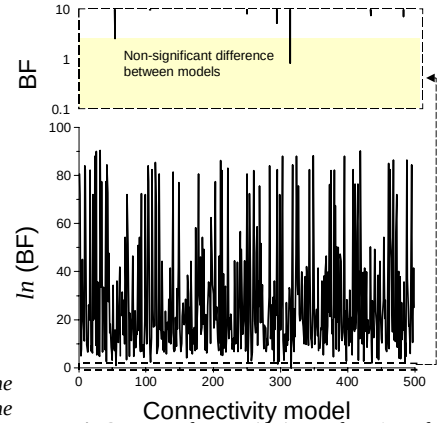

Fig 3: *Bayes factors (BF) as a function of randomly selected DCM models (bottom) and statistical significance (top)*

REFERENCES: 1-Friston et al (2003) Neuroimage **19**: 1273; 2-Penny et al (2004) Neuroimage **22**: 1157; 3- Tomasi et al (2006) Hum Brain Mapp **27**: 694.

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