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ABSTRACT

The description of specific circuits in networks should allow a more realistic definition of dynamic functioning of the central nervous system which underlies various brain functions. After introducing the programmed and acquired networks and recalling the concepts of functional and effective connectivity, we presented biophysical and physiological aspects of the BOLD signal. Then, we briefly presented a few data-driven and hypothesis-driven methods; in particular we described structural equation modeling (SEM), a hypothesis-driven approach used to explore circuits within networks and model spatially and anatomically interconnected regions. We compared the SEM method with an alternative hypothesis-driven method, dynamic causal modeling (DCM). Finally, we presented independent components analysis (ICA), an exploratory data-driven approach which could be used to complete the directed brain interactivity studies. ICA combined with SEM/DCM may allow extension of the statistical and explanatory power of fMRI data.

1. Introduction

1.1. Programmed networks

Our brain is subject to a genetically programmed framework. During intrauterine life, neurons develop into a random and prolific network according to an identical sequence that is determined genetically but already regulated by the local internal environment (embryogenesis and induction phenomena). During postnatal development (Edelman, 1992), a reorganization occurs with elimination of some connections, and reinforcement or weakening of others in response to stimuli derived from the environment (epigenesis), or even creation of new connections (dendritic spines and duplicated synapses observed on brain imaging). New connections create preferential circuits for transmission of information (Nelson et al., 1989). This plasticity allows our cerebral circuits, especially those of the neocortex, to be organized in a way which corresponds and adapts to the world in which each individual lives and develops. Our common genome consists of 30,000 genes, which are translated into thousands of different proteins (Fields and Burnstock, 2006). The mechanism of formation of synapses depends on maturation of the central nervous system, but elimination and selection depend on experience. Signals derived from the environment act on genes via transcription factors that act like switches (Lee et al., 2005). The basis of this centralized system corresponds to primary functions of survival, also called autonomic functions, which are governed by three general systems that control information and regulate vital functions: the endocrine system, the nervous system, and the immune system which ensures maintenance of specific, individual integrity. The endocrine system controls biological functions via slow chemical pathways (minutes, hours, days) via hormones (chemical messengers transported in the blood). Many other non-hormonal "chemical mediators" are also involved in cellular communication; the nervous system controls the relationship functions between organs via rapid pathways (m/s). Nerve fibers constitute the "physical" pathways of communication. Fibers grouped in bundles form nerves; nerve impulses are frequency-coded electrical signals; the immune system controls the integrity of self according to two cooperative and complementary pathways: a cell-mediated pathway (circulating or bound immune cells) and a humoral pathway.

Neurons are subjected to a combination of input signals derived from the presynaptic axons and dendrites connected to it. Some connections are excitatory, others are inhibitory. Each neuron is a very simple automat that receives impulses from its neighbors, and which transmits an impulse according to whether the weighted sum of inputs (weights with a positive sign for an excitatory junction and a negative sign for an inhibitory junction) are greater than a certain excitation threshold. Neuronal networks range from a simple network (two neurons, one sensory, one motor for a simple reflex) to extremely complex networks (thousands of

neurons for a single network). Communication between neurons can correspond to an almost unlimited variety of specific combinations. Several hundreds of different messages can reach the same neuron simultaneously or successively, resulting in a great potential for modulation of the global output message, especially as various types of agents can act on each biochemical step in the synapse. This gives an idea of the enormous number of possible combinations. Astrocytes of the neuroglia also provide an additional level of regulation. According to Casado et al. (2002), several types of neurotransmitters or chemical mediators have been identified, the best known being acetylcholine, noradrenaline, dopamine (central activator involved in motivation, interaction with many drugs, Parkinson's disease), glutamate (major excitatory neurotransmitter associated with learning and memory), serotonin (depression), etc. Chemical synapses play several roles: valve functions (direction of the message), amplifier, modulator of action and efficacy by neurotransmitters. Neurotransmitters can induce either depolarization of the membrane, in which case they are excitatory (such as glutamate), or hyperpolarization, in which case they are inhibitors of neurotransmission (such as GABA). After acting at the synapse, the neurotransmitter released into the synaptic cleft is taken up by a protein transport mechanism to be recycled.

1.2. Acquired networks

The brain continuously adapts to variations of the environment. This capacity is derived from its anatomical and functional organization, an adaptive inheritance from a long evolutionary history which, as a result of mutations, selections, and conservations, has produced a tool able to model itself to the environment and the reality with which it faced and then permanently adjust this model in the light of acquired experience, in which each subject's "frame of reference" corresponds to individually acquired preferential circuits (Darwin, 1871). This acquired experience colors our thoughts, our abstract creations and our consciousness, which is characteristic of our humanity. Acquired experience cannot exert its influence without the functional support of neuronal networks, as illustrated by the clinical effects of brain lesions and in contrast to the theories of Aristotle and Descartes, who placed "reason" because of its rigorous logic above "passions" that they considered to lead us away from the truth (Damasio, 1994). Neither thoughts nor emotions are entities without a material support. Our brain manages all instinctive and innate knowledge which constitutes our species memory. This knowledge is the result of a biologically integrated accumulation of adaptive knowledge, knowledge adapted to living conditions encountered by generations of our ancestors. The knowledge gradually assimilated by the neural structures of our species corresponds to the most important knowledge, at a given point in time, for the survival or reproduction of these ancestors according to Darwin's theory of evolution. In order to survive, we must establish 90% of the effective synaptic connections of our neocortex after birth, as, in order to be really functional, our brain which remains immature at birth must acquire non-innate complementary data about the real environment.

The central nervous system receives information from the external environment and information derived from the internal environment. Emotions are also perceptions that must be taken into account by the CNS. The subsystems responsible for the control of these functions are topographically well defined in the body. All these data are processed and integrated by nerve centers: cortical grey matter, spinal cord and grey nuclei scattered in the white matter. The hierarchical organization has developed during vertebrate evolution to ensure global integration of all metabolic and physiologic data necessary for physiologic, psychosocial and spiritual survival (Nederbragt, 1997). During postnatal development, a reorganization occurs with elimination of some connections, and reinforcement or weakening of others in response to stimuli derived from the environment (epigenesis), or even creation of new connections (dendritic spines and duplicated synapses). New connections create preferential circuits for transmission of information. This plasticity allows our cerebral circuits, especially those of the neocortex, to be organized in a way which corresponds and adapts to the world in which each individual lives and develops (Jacquard, 1982). The mechanism of formation of synapses depends on maturation of the central nervous system, but elimination and selection depend on experience.

2. Functional and effective connectivity

The dichotomy between local and large-scale networks serves as a neural basis for the key assumption that brain functional architecture abides by two principles: functional segregation and functional integration (Horwitz et al., 1999; Varela et al., 2001). A large-scale brain network can be defined as a set of segregated and integrated regions that share strong anatomical connections and functional interactions. Whether top-down or bottom-up, connections and interactions are quintessential aspects of networks (Bressler, 1995; Mesulam, 1998). Cognitive and sensorimotor processes depend on complex dynamics of temporally and spatially segregated brain activities. While the segregation principle states that some functional processes specifically engage well-localized and specialized brain regions, it is now thought that brain functions are most likely to emerge through integration of information flows across widely distributed regions (Tononi et al., 1998; Sporns et al., 2004). In this approach, it is not only isolated brain areas that are presumed to process information but rather a large-scale network, i.e., a set of brain regions interacting in a coherent and dynamic way. Hence, according to the functional integration concept, cortical areas and therefore functions are integrated within specific dynamic networks.

This concept supposes the existence of a dynamic interaction between interconnected, active areas and thus that the brain areas are expressed as networks within integrated systems. In such a system, localized areas are included in networks which become dynamic according to the cognitive task. Brain areas underlie several functions and can belong successively to several different functional networks. In other words, a given brain area does not have a single function; its resources can be exploited in several different cognitive strategies. The principle of functional integration which is also known in the field of electrophysiology was used to analyze the event potentials obtained from multielectrode recordings (Gerstein and Perkel, 1969). Thus, based on the functional integration principle, the relationships between several brain areas may be examined.

Neuroimaging first allowed researchers to describe the cortical and sub-cortical activity of regionally segregated functional regions during a variety of experimental or cognitive tasks. More recently, functional integration studies have described how these functionally specialized areas, i.e., areas whose activity is temporally modified, interact within a highly distributed neural network. By using fMRI which has become the most commonly used method for investigating human brain functions and defining neural populations as distributed local networks which are transiently linked by large-scale reciprocal dynamical connections (Varela et al., 2001), we may study in the brain specific circuits in networks which allow defining in a more realistic way the dynamic of the central nervous system, which underlies various cerebral functions, both in physiological and pathological conditions.

Effective connectivity, closer to the intuitive notion of a connection, can be defined as the influence that one neural system exerts over another, either at a synaptic level (synaptic efficacy) or a cortical level (Friston, 1994; McIntosh and Gonzalez-Lima, 1994). This approach emphasizes that determining effective connectivity requires a causal model of the interactions between the elements of the neural system of interest. In electrophysiology, there is a close relationship between effective connectivity and synaptic efficacy (Aersten and Preissl, 1991). Effective connectivity can be estimated from linear models to test whether a theoretical model seeking to explain a network of relationships can actually fit the relationships estimated from the observed data. In the case of fMRI, the theoretical model is an anatomical constrained model and the data are interregional covariances of activity (Buchel and Friston, 2000). Consequently, effective connectivity represents the dynamic influence that cortical and sub-cortical regions exert on each other via a putative network of interdependent areas (Gerstein and Perkel, 1969; Friston et al., 1993a). This approach might be based on linear time-invariant models that relate the time-course of experimentally controlled manipulations to BOLD signals in a voxel-specific fashion. Although various statistical models have been proposed (Henson, 2004), these standard models treat the voxels throughout the brain as isolated black boxes, whose input output functions are characterized by BOLD responses evoked by various experimental conditions (Stephan et al., 2004). fMRI provides simultaneous recordings of activity throughout the brain evoked by cognitive and sensorimotor challenges, but at the expense of ignoring temporal information, i.e., the history of the experimental task (input) or physiologic variable (signal). This is important as interactions within the brain, whether over short or long distances, take time and are not instantaneous which is implicit within regression models.

3. Physiological and biophysical aspects of the BOLD signal

3.1. Latency of BOLD response

Most functional imaging studies use task-induced hemodynamic responses to infer underlying changes in neuronal activity, although the BOLD responses and their relationship to neural activity remain poorly understood (Arthurs and Boniface, 2002; Buckner, 2003). Some recent studies have found a good correlation between evoked field potentials and hemodynamic response (Mathiesen et al., 1998; Ngai et al., 1999; Logothetis et al., 2001; Leopold et al., 2003; Sheth et al., 2004). We want to describe a dynamic network at the neuronal level by legitimately assuming that the hemodynamic responses measured using fMRI reflect an underlying synaptic activity. It has been clearly established that the temporal latency of the BOLD signal cannot be used to dissociate events occurring at the neuronal level (Aguirre et al., 1998; Saad et al., 2003; Handwerker et al., 2004). Temporal differences between regions cannot be used to infer the dynamics of functional connectivity using fMRI because there are region-specific differences in the coupling of neuronal activity to BOLD response that obscure any differences due to latency (Huettel and McCarthy, 2000, 2001). fMRI temporal precedence therefore cannot be used to infer causality. The only situation in which hemodynamic differences can be interpreted in relation to neuronal activities is when the biophysical mechanisms are the same (Liao et al., 2002). So, in connectivity studies, a model comparison approach is feasible provided the same regions included in the network are compared, which explains why hemodynamic differences within regions but between conditions/groups are meaningful.

3.2. Physiological noise

In the majority of fMRI studies, multivariate statistical methods based on the correlation or covariance matrix of the data are used to characterize dependencies between regionally distinct activated regions. The covariance measure is defined as the degree to which the activities of two regions are related to each other, or how they vary together. In particular, these multivariate methods have been used to characterize in the brain interregional dependencies in the temporal domain where the interregional variability of the hemodynamic response function may introduce an additional variance unexplained by the shared information between many correlated regions. As emphasized by various authors (Lai et al., 1993; Lee et al., 1995; Aguirre et al., 1998; Huettel and McCarthy, 2001; Saad et al., 2001; Handwerker et al., 2004), this type of spatial variability in the fMRI data may be attributed to the brain vascular system which presents regional geometrical (Harrison et al., 2002) and biophysical (Buxton et al., 1998; Obata et al., 2004) differences. The large veins draining activated areas may explain even more variations between correlated BOLD responses independently of synaptic activity (Duyn et al., 1994; Frahm et al., 1994; Kim et al., 1997; Kansaku et al., 1998), and, in certain areas, physiologic noise may intensely contaminate the BOLD response resulting in aliasing effects on fMRI signals (Biswal et al., 1996; Birn et al., 2006). A prominent confounding factor in connectivity measurements is the physiologic noise contained in the BOLD signal, which can influence correlation measurements. This noise mainly originates from fluctuations in vasomotricity, cardiac and respiratory pulsatilities (Windischberger et al., 2002; Wise et al., 2004; Birn et al., 2006; Shmueli et al., 2007). Therefore, fMRI signals would be temporally correlated. Regional differences in hemodynamic filter sensitivity can produce a loss of temporal correlation between the regions. Additionally, neither method can properly model the temporal correlation of the observed fMRI data. Consequently, the correlation calculated in the time domain between BOLD signals may not correctly reflect the structure of correlations between underlying neuronal connectivity since all frequencies in the BOLD signal are considered.

4. Methods of analysis of the brain connectivity

A distinction may be made between methods that consider only correlation and ignore issues of causality and influence and methods that attempt to describe or make inferences about the direction of influence between regions. These two categories of analysis are referred, as evoked above, as functional connectivity and effective connectivity respectively (Friston et al., 1993b; Horwitz et al., 2005). Techniques in the first group that consider only correlations between regions include mapping using seed–voxel correlations. Techniques in the second group use more elaborate models and additional assumptions applied to calculate correlations or covariances to address questions about directional influences and include mapping based on modeling. Methodological approaches to the study of connectivity using BOLD data may be broadly divided into those that are more data-driven and attempt to map connectivity in the whole-brain and those that use prior knowledge or hypotheses-driven to limit to a restricted set of regions.

4.1. Data-driven methods

The first category of methods includes seed–voxel correlations, Granger causality derived autoregressive models (Goebel et al., 2003), fuzzy clustering which assumes that brain voxels can be grouped into clusters sharing similar activity patterns (Baumgartner et al., 1998), hierarchical clustering (Goutte et al., 1999),

psychophysiological interactions which test for changes in the regression slope of activity, at every voxel on a seed voxel, that are induced by an experimental manipulation (Friston et al., 1997), coherence coefficients (Fall and de Marco, 2008). Other techniques such as principal components analysis (Andersen et al., 1999) and independent components analysis (ICA) which suppose that fMRI data are a linear mixing of a given number of temporal factors with an associated factor-specific spatial distribution (Correa et al., 2007).

4.2. Hypotheses-driven methods

The alternative to these mapping techniques is to use a model that attempts to describe the relationships between a set of selected regions, wherein region-specific measurements such as BOLD time series are extracted from whole-brain data prior to the connectivity modeling stage. This category includes structural equation modeling (SEM) (de Marco et al., 2009) multivariate autoregressive modeling (MAR) (Harrison et al., 2003; Kim et al., 2007), dynamic causal modeling (Friston et al., 2003; Penny et al., 2004), generative models including neural mass models (David et al., 2004) and large-scale neural models (Horwitz, 2004). SEM is the most widespread method used to model effective connectivity (McIntosh and Gonzalez-Lima, 1994; Gonzalez-Lima and McIntosh, 1995b; Bullmore et al., 2000). Firstly, we propose to describe the structural equation modeling that we have already applied on fMRI data to the study of specific circuits in networks of emotional (de Marco et al., 2006), language (Quaglino et al., 2008) and attentional (Querne et al., 2008) tasks. Secondly, we compare the SEM with the DCM. Finally, we propose to describe the ICA that is an interesting data-driven method to spatially identify circuits within brain networks. We show that ICA can be used in conjunction with hypothesis-driven methods.

Path analysis, also referred to as structural equation modeling, was originally developed in the early 1970s by Jöreskog, Keesling, and Wiley, when they combined factor analysis with econometric simultaneous equation models (Bollen, 1989; Bollen and Long, 1993; Loehlin, 1998; Jöreskog and Sörbom, 2000). In the early 1990s, McIntosh introduced SEM to neuroimaging (McIntosh and Gonzalez-Lima, 1994) for modeling, testing, and comparison of directional effective connectivity of the brain. SEM has quickly become popular in this field. Structural models make possible to analyze linear relationships between variables from the analysis of the covariance among the variables. Structural models evolved from two principal methods of analyses: factorial analysis (for a review: Bollen, 1989) and multiple regression or causal path analysis (a method developed in the 1930s by Wright e.g. (for a review: Hollander, 1999). Structural models examine multiple sources of influence on the dependent variable in an experiment.

Structural equation modeling is a hypothesis-driven multivariate statistical technique of data analysis that can be used with neuroimaging data. An increasing number of PET, fMRI and transcranial magnetic stimulation (TMS) studies have used SEM to investigate large-scale functional brain networks (Marrelec et al., 2008) and show specific networks involved either in working memory (Kondo et al., 2004; Schlosser et al., 2006; Charlton et al., 2007), within attentional processes(Büchel and Friston, 1997; Mottaghy et al., 2006; Querne et al., 2008), face perception (Iidaka et al., 2001; Nomura et al., 2003; de Marco et al., 2006; Stein et al., 2007), motor movement processing (Zhuang et al., 2005; Taniwaki et al., 2007), language (Fletcher et al., 1999; Fu et al., 2006; Karunanayaka et al., 2007; Quaglino et al., 2008) or with the processing of painful stimuli (Craggs et al., 2007).

SEM methods, in comparison with classical approaches such as linear regression, allows one to simultaneously analyze several types of interrelationships between variables in an experiment. The nature of the relation between variables is given by the path coefficient; it describes how much the dependent variable changes when an independent variable changes by one unit. SEM directly integrates the errors of measurement into a statistical model, by doing so the estimates of regression coefficients are more precise than they are with classical methods such as multiple regression, factorial analysis, or analysis of variance.

The older methods examine only one linear relation at the same time between independent and dependant variables and do so only within a range of values set by the researcher (McIntosh and Gonzalez-Lima, 1994). Contrary to classical methods, SEM is interested in a structure of variances and covariances in a dataset of observed variables and it will try to predict dependences among the variables. In other words, SEM seeks to explain as much of the variance in dependant variables as it can from the simultaneous measurement of the variances of independent variables that are included in the model. Similarly, SEM incorporates errors of measurement of the independent variables into the calculation of estimate, which reinforces the statistical power of the method and provides more precise estimates of path coefficients. Thus, we can validate a model of measurement from a theoretical model or empirical data (Krause et al., 2000). The objective of an effective connectivity analysis is to estimate parameters that represent influences among regions that may change over time and with respect to experimental tasks.

Therefore, to describe a functional network, network nodes and anatomical connections must be proposed in conjunction with a SEM model in order to explain interregional covariances and determine the intensity of the connections. When applied to PET or fMRI data, SEM allows modeling of paths of connection between cortical or sub-cortical areas and reveals relations, interdependencies and covariance among the various areas. Given an anatomical model, SEM shows the effects of an experimental task on specific network of connections (McIntosh and Gonzalez-Lima, 1994; Gonzalez-Lima and McIntosh, 1995a; Buchel and Friston, 1997; Horwitz, 2003). In this type of statistical analysis, normalized variables are considered in terms of the structure of their covariances. Thus, SEM allows one to infer interregional dependencies between various cerebral cortical areas.

SEM is a simple and pragmatic approach to effective connectivity when dynamical aspects can be discounted. A linear model is sufficient and the observed variables can be measured precisely, the input is unknown but stochastic and stationary. SEM comprises a set of regions and a set of directed connections (paths). Importantly, a causal relation is ascribed to these connections. So, causal relationships are not inferred from the data but are assumed a priori. We can therefore set the connection strengths so as to minimize the discrepancy between the observed and implied correlations and thereby fit a model to data. Changes in connectivity can be attributed to experimental manipulation by partitioning the data set. If, for example, we partition a given fMRI data set into those scans obtained under different levels of an experimental factor, then we can attribute differences in connectivity to that factor and so conclude that a pathway has been activated. An SEM with particular connection strengths implies a particular set of instantaneous correlations between regions. Structural equation models posit a set of causal relationships between variables and models instantaneous correlations, i.e., correlations between regions at the same time point. Instantaneous activity is assumed to be the result of local dynamics and connections between regions.

4.3. Structural equations modeling versus dynamic causal modeling

The suitability of applying SEM to fMRI neuroimaging data has been discussed in detail elsewhere (Mechelli et al., 2002;

Goncalves and Hall, 2003; Penny et al., 2004). SEM assumes that the interactions are linear and also instantaneous in that structural models are not really considered to be times-series models. The time-series with SEM are not treated as dynamic, as the temporal information is discounted. SEM models are considered to be 'static' as they model instantaneous interactions between regions and ignore the influence of previous states on current responses. The inputs (residuals) in the network drive each region stochastically from one measurement to another. These residuals are treated as unknowns and are assumed to be expressed instantaneously. The observed responses are then driven by endogenous or intrinsic noise. An SEM with a particular connection strength therefore implies a particular set of instantaneous correlations between regions. In a block design, we can assume that the interactions are instantaneous and continue between the regions. The various experimental conditions are treated separately; as each condition can be considered to incorporate different inputs. Block designs will be therefore well adapted for SEM analysis with fMRI data.

Nevertheless, SEM must be used very cautiously to analyze an event-related design. In an event-related design, contrary to the block design, each event is usually alternating and interactions between regions can no longer be considered to be instantaneous, and problems of non-linearity may also be observed. Moreover, with event-related designs, the BOLD signal intensity obtained is weaker (compared with block designs) and could be physiologically noisy if we do not fit the repetition times. Kruger and Glover (2001) and Triantafyllou et al. (2005) have shown that physiological noise is proportional to signal strength, so the faster repetition times (2 s and less) likely to be used in event-related designs would actually reduce the effects of physiological noise.

To circumvent all these methodological issues, DCM has recently been developed as a generalization of both convolution models and SEM (Penny et al., 2004; Friston et al., 2003). As described in Penny et al. (2004), SEM can be considered to be a simplified version of DCM which is also based on the definition of a structural model. The DCM model assumes a dynamic neuronal model of interacting brain regions, in which neuronal activity in a given brain region causes changes in the neuronal activity in other regions according to the structural model. This neuronal model is then supplemented with a forward model of how neuronal activity generates a measured BOLD response using the balloon model initially formulated by Buxton et al. (1998) and subsequently extended by Friston et al. (2000). A Bayesian inference scheme is devised to infer the model parameters from the data. The mathematical framework of DCM takes into account non-linearities and temporal correlations. It also quantifies the strength of interaction exerted by one brain region on another at the neuronal level, whereas SEM only quantifies the observed BOLD signal. Under this condition, SEM results must be interpreted carefully. For example, a positive path coefficient cannot always be interpreted as excitatory and a negative path coefficient cannot always be interpreted as inhibitory (McIntosh and Gonzalez-Lima, 1994). Positive and negative path coefficients reflect signs of covariance relationships between structures of a network. A positive (negative) coefficient is interpreted as the degree to which an increase in BOLD activity in the source region is predictive of an increase (decrease) in the target region. Since the signal is derived from the BOLD response, positive or negative coefficients cannot be naively assumed to represent excitation or inhibition, respectively. BOLD response is generally thought to be a combination of both excitatory and inhibitory input to a neuronal region that cannot be independently estimated using fMRI (Logothetis et al., 2001; Arthurs and Boniface, 2002), although some studies have shown neural excitatory input to be more representative of the BOLD signal (Waldvogel et al., 2000). The neural significance of a decrease in BOLD signal therefore remains controversial (Raichle, 1998; Harel et al., 2002), but a recent study has shown that a decrease in BOLD signal is correlated with suppression of neural activity (Shmuel et al., 2006).

Unlike SEM, DCM models neurobiologically plausible neural activities and takes into account dynamics and modulations; DCM also models the effect of experimental, external, and modulatory inputs on network dynamics; this mathematical framework would appear to be more advantageous than SEM. Nevertheless, DCM can be suspected to be less sensitive than SEM to the number of degrees of freedom. SEM allows the use of simpler models followed by more complex models by repeatedly testing the model fits to the actual data. SEM is useful when some information is available, such as a small set of potential structural models or partial information relative to connectivity. SEM is a well developed, computationally less intensive connectivity analysis technique suitable for neuroimaging data especially for block designs. The use of SEM may also be justified by the fact that, unlike DCM, the statistical model underlying SEM is quite simple and not computationally demanding.

4.4. Combined data-driven and hypothesis-driven methods

We propose to describe independent component analysis, a data-driven method, used to spatially identify circuits within brain networks, which can be used in conjunction with SEM or DCM (hypothesis-driven methods). ICA is a data-based multivariate statistical technique that uses higher order statistics to perform decomposition of linearly combined statistically independent sources (Hyvärinen, 1999). Each statistically independent component represents in fMRI a hemodynamic map of the whole-brain. Each independent component is supposed to describe a particular functional activity of the brain with its deployment over time (McKeown and Sejnowski, 1998; Esposito et al., 2002; Beckmann and Smith, 2004). Each independent component extracted by applying a spatial ICA is spatially independent of all other independent components (Jafri et al., 2008). Therefore, the contribution of a spatial independent component to each voxel is given by the independent component magnitude at that point modulated over time by the associated time-course. The main advantage of ICA is that it requires little knowledge about the nature of the data. The only necessary hypothesis concerns the presence of a sufficient amount of independent sources (temporal or spatial), which are linearly mixed. Conversely, one of the main drawbacks of ICA is the large amount of brain activations resulting from this kind of decomposition (McKeown et al., 1998). At some point, hypotheses are necessary to select relevant from spurious activations. For this reason, ICA can be used in conjunction with other well-established techniques (Hu et al., 2005) or further information may be associated with the reference time-course, such as the spatial localization of activities (Hong et al., 2005) and the covariate relation of independent component time-course (McKeown, 2000).

ICA has already been combined with DCM (Stevens et al., 2007); ICA could be also combined with SEM to extend the statistically and explanatory power of fMRI data. SEM coupled with ICA is capable to handle data from a large number of subjects (Karunanayaka et al., 2007). The biological relevance and cortical connections of the SEM models have also been evaluated with reference to available knowledge based on animal and human circuitries. The main advantage of spatial ICA is its ability to identify the distinct functional elements involved in the circuitry (Correa et al., 2007). Functionally connected brain regions encompassed in each independent component are active at the same time, suggesting that one or more anatomical connections are in use during performance of the task (Calhoun et al., 2001, 2006). Although this reasoning is more in line with the

"connectionist" approach to brain functions based on parallel processing mechanisms performed by a group of connected functional elements, the ICA approach lacks a statistical method to model the functional connections assumed to exist between regions. The addition of ICA to SEM can address this issue. Each ICA map or part of the map corresponds to one component in an SEM.

5. Conclusion

The concept of effective connectivity permits the study of specific circuits in networks which define in a more realistic way the dynamics of the central nervous system, which underlie various cerebral functions. Structural equation modeling or dynamic causal modeling, applied to the field of functional magnetic resonance imaging (fMRI), allows the study of directed brain interactivities. Based on theoretical and/or empirical hypotheses, the hypothesis-driven methods comprise a restricted set of regions and directed connections and permit to assess the effects of an experimental or cognitive task within a putative large-scale brain network. We have described in this article the SEM method and we have compared it with the DCM method. Despite the differences in the approaches, DCM and SEM lead to the same conclusions about the data when a block design is used. We have detailed the ICA data-driven approach and we have shown that it was possible to combine confirmatory (hypothesis-driven) and exploratory (data-driven) methods to reinforce the statistically and explanatory power of fMRI data.

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