The elusive concept of brain connectivity

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Abstract

Neurons and neural populations do not function as islands onto themselves. Rather, they interact with other such elements through their afferent and efferent connections in an orchestrated manner so as to enable different sensorimotor and cognitive tasks to be performed. The concept of functional connectivity and the allied notion of effective connectivity were introduced to designate the functional strengths of such interactions. Functional neuroimaging methods, especially PET and fMRI, have been used extensively to evaluate the functional connectivity between different brain regions. After providing a brief historical review of these notions of brain connectivity, I argue that the conceptual formulations of functional and effective connectivity are far from clear. Specifically, the terms functional and effective connectivity are applied to quantities computed on types of functional imaging data (e.g., PET, fMRI, EEG) that vary in spatial, temporal, and other features, using different definitions (even for data of the same modality) and employing different computational algorithms. Until it is understood what each definition means in terms of an underlying neural substrate, comparisons of functional and/or effective connectivity across studies may appear inconsistent and should be performed with great caution.
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Lee et al. (2003), in their accompanying paper, report on the main topics discussed at the recent Workshop on Functional Connectivity, which was organized by Rolf Kotter and Karl Friston and held in Düsseldorf, Germany. The commentary by Lee et al. does an admirable job of describing the main presentations and gives some flavor to the rather extensive discussions that took place. Because clear differences in opinion concerning the nature of anatomic, functional, and effective connectivity were presented by various participants, it seems appropriate that a second view of these terms, particularly functional and effective connectivity, be voiced. My position was that all three types of connectivity that were discussed at the workshop are extremely elusive concepts,[1] and that this should be made clear to the functional brain imaging/neuroscience community.

Functional and effective connectivity—a very brief history

To frame the issues that make defining brain connectivity so difficult, a brief historical review is necessary. Investigations of the brain during the last century have been marked by a peculiar dichotomy: whereas many neuroanatomists worked diligently to ascertain how different neuronal populations were connected to one another so as to form networks,[2] neurophysiologists, compelled generally to record from one neuron or neuronal ensemble at a time, focused their attention on at-

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[1] Although anatomic connectivity itself is a concept that is inherently difficult to define, given that structure and function converge at the microscopic domain of synapses and receptors, my discussion will focus primarily on functional and effective connectivity as used by the functional neuroimaging community. See Lee et al. (2003) for a discussion of some the issues associated with defining anatomical connectivity.

[2] Of course, work on determining the anatomical links between neuronal populations, continues. As discussed by Lee et al. (Lee, L., Harrison, L.M., Mechelli, A., unpublished data), a number of newer methods were discussed at the Workshop, including the use of diffusion-weighted tensor imaging (DTI). As was made clear in the Lee et al. commentary, some of these newer methods for examining anatomical connectivity were, themselves, the subjects of contentious discussion.

tempting to determine the recorded unit's functional specialization. This neurophysiological focus on functional specialization was abetted by neuropsychology, which examined the behavioral consequences of localized brain lesions (Heilman and Valenstein, 1985). Thus, modular specialization of function became the prevailing paradigm for (what we now call) cognitive neuroscience (e.g., Gazzaniga, 2000; see Fuster, 2000 for an insightful critique).

Nevertheless, for each technique for obtaining neurophysiological data, there were always a few investigators who attempted to acquire their data from two or more neural elements (or from two or more brain sites) simultaneously and to interpret these data in terms of neural interactivity.[3] Invariably, the way in which this was done involved the evaluation of some kind of covariance or correlation between the multiply obtained signals [note that a number of more complicated measures that go beyond simple correlation have been used (e.g., regression analysis, principal components analysis, and multidimensional scaling), but conceptually, these methods all embody the notion of covariation in activity].

At the neuron level, Gerstein, Perkel, Aertsen and their collaborators pioneered the analysis of electrophysiological data from multiple units (Aertsen et al., 1989, 1994; Aertsen and Preissl, 1991; Gerstein, 1970; Gerstein and Aertsen, 1985; Gerstein and Perkel, 1969). Much of this effort was directed at discovering Hebbian cell assemblies (Hebb, 1949), groups of neurons that act together in a coherent fashion. In this body of work the concepts of functional and effective connectivity appeared (Aertsen and Preissl, 1991). Functional connectivity was defined as the temporal coherence among the activity of different neurons, and was measured by cross-correlating their spike trains. Effective connectivity, a more abstract notion, was defined as the simplest neuron-like circuit that would produce the same temporal relationship as observed experimentally between two neurons in a cell assembly. As emphasized by Rolf Kotter (personal communication), effective connectivity is not a unique statement about the anatomic connectivity, because more than one arrangement of neurons could lead to the same overall behavior. A key experimental issue that shaped these definitions originated in the near-impossibility of knowing the exact anatomical relationship between a neuronal pair whose functional interactivity was being accessed (at least in mammalian experimental preparations).

At the macroscopic level, electroencephalography (EEG) was the first method to examine human in vivo brain activity noninvasively. The use of these data to attempt to examine the functional interactivity between different cortical regions has a long history (e.g., Adey et al., 1961; Barlow and Brazier, 1954; Gevins et al., 1985; Livanov, 1977), and a variety of techniques have been used, all of which amounted to evaluating the cross-correlation of the signals between pairs of scalp electrodes. Different methods focus on correlating different features of the spatiotemporal waveforms associated with the measured electrical activity. One approach evaluates the coherence, which is defined as the correlation in the frequency domain between EEG signals at different scalp sites (e.g., Pfurtscheller and Andrew, 1999). The amplitude of an EEG signal is thought to provide a measure of the amount of synchrony of a localized neural population within range of the scalp electrode. Coherence, on the other hand, reflects the dynamic functional interrelation between spatially separated electrode sites, and is assumed to correspond to synchronized activity between electrical activities in distinct brain regions in specific frequency bands. Other techniques investigate directly the dynamically changing cross-correlation of the time series between a pair of electrodes (e.g., Gevins et al., 1985), often using evoked potentials rather than the ongoing EEG (Gevins et al., 1989). A major interpretative problem for these approaches arises from the fact that due to the volume conduction of brain tissue, the electrical activity recorded at a scalp site does not represent just the local neural activity directly below the electrode.

Functional interactivity has also been examined using brain data acquired with methods that measure hemodynamic/metabolic activity. Prior to positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), the nontomographic xenon-133 inhalation technique was used to image functional brain activity in humans, and correlations between pairs of surface detectors (usually just the homologous left-right detectors) were evaluated (Prohovnik et al., 1980). Once PET studies of glucose metabolism began to be performed, several groups used region of interest methods to examine interregional correlations (across subjects) (Bartlett et al., 1987; Clark et al., 1984; Horwitz et al., 1984; Metter et al., 1984). Similar analyses were performed on autoradiographic data (usually ^{14}C-deoxyglucose) in nonhuman mammals (usually rats; e.g., Soncrant et al., 1992). Mostly, these studies, both human and nonhuman, examined subjects at rest, which meant that the subjects were awake, but not performing any set of specific sensorimotor or cognitive tasks.

In the mid-late 1980s, studies of cognitive function began to be performed with PET, in which regional cerebral blood flow (rCBF) was measured by using a tracer with a short half-life (e.g., $H_2^{15}O$), and analyses soon were undertaken to assess functional connectivity either using regions of interest (Horwitz et al., 1992), or a voxel-based approach (Friston et al., 1993; Horwitz et al., 1995; Zeki et al., 1991). At the same time, effective connectivity analyses of rat autoradiographic data obtained during specific tasks were appearing (McIntosh and Gonzalez-Lima, 1991, 1992), and were soon followed by human effective connectivity studies

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[3] I will use the term interactivity in a very loose way to denote either functional or effective connectivity, or some combination of the two, without having to be specific which is being referred to. Note that conceptually, effective connectivities among a group of neural units can be evaluated by combining their respective functional connectivities with a model specifying the causal links between the units.

using rCBF PET data from human subjects (Friston, 1994; Grafton et al., 1994; McIntosh et al., 1994). Subsequently, as fMRI became an established functional brain imaging tool, a number of studies of interregional functional inter-activity using fMRI data acquired from humans at rest (Biswal et al., 1995; Lowe et al., 1998), or while performing particular tasks (e.g., Bokde et al., 2001; Buechel and Friston, 1997; Bullmore et al., 2000; Hampson et al., 2002), were published. Although different investigators used different terminology to indicate the distinction between the correlated activities of PET/fMRI data and the strengths of the linkages in a causal model, the community eventually converged on Friston's use of the terms functional and effective connectivity (Friston, 1994) to designate these two notions.[4]

Definitional difficulties

As can be seen from this brief historical overview, numerous investigators over the years have claimed that they were examining something akin to functional or effective connectivity. However, the multiple types of data that are used to evaluate functional interactivity differ from one another in many features, including spatial and temporal resolution, and whether the data represent neuron activities, neural ensemble activities, or activities (electrical or hemodynamic) of macroscopic brain regions. Moreover, the actual computational algorithms that are used to determine these values differ between investigators, often even for the same data type. For example, for rCBF PET data, some investigators calculate interregional functional connectivity by correlating rCBF data within a task condition and across subjects (e.g., McIntosh et al., 1994), whereas others perform the correlations across tasks (e.g., Friston, 1994). The situation is even more diverse for EEG and magnetoencephalographic (MEG) data and for fMRI, where there are multiple features of the signals that can be correlated. For example, for fMRI data one can correlate the time series either across conditions (e.g., Bullmore et al., 2000) or within condition (e.g., Hampson et al., 2002); one can do either of these either within-subject (e.g., Goncalves et al., 2001), or for data obtained by averaging across subjects (e.g., Bokde et al.,

2001); in principle, one could also evaluate the interregional functional connectivity by correlating across the average fMRI responses for each block corresponding to a single experimental condition, or else by correlating across subjects the fMRI value averaged over the blocks (or trials) corresponding to a single condition.

This discussion thus leads to several points and, importantly, cautions I want to make about the elusive nature of the concepts of functional and effective connectivity. First, it is far from obvious that the multiple ways by which functional connectivity can be determined will necessarily lead to the same conclusion about whether two or more neural units/populations are strongly interacting with one another or not; this can even be the case for data from the same task and even for data obtained using the same modality. Using different definitions as to what constitutes functional connectivity may result in different conclusions about whether the associated functional connectivities for a particular neural system are strong or weak. For example, for fMRI the functional connectivity that is calculated may differ if one is assessing the trial-to-trial covariability, the block-to-block covariability, or the subject-to-subject covariability. Even if one just cross-correlates the time series between two brain regions (or voxels), the evaluated functional connectivity may differ depending on whether one uses (1) the complete time series of fMRI signal intensities (task of interest plus baseline), or (2) just the parts of the time series that included the task of interest.

This lack of uniqueness gets compounded as one goes from functional to effective connectivity, since the latter depends on both the functional connectivities and on the use of an hypothesized model. Depending on what aspect of the data an investigator thinks is important, it is quite possible that there could be a number of models that could be assumed to account for a particular data set. An additional source of definitional difficulty is related to how the effective connectivity is actually computed. For example, if a study has a complex experimental design consisting of multiple conditions, the computed effective connectivities can depend on which tasks are included in the modeling and which are excluded, and on how the experimental design is taken into account (an interesting example is found in Mechelli et al., 2002).

One key source of the lack of uniqueness follows from the fact that the relationship between each notion of functional connectivity and its underlying neural substrate is unknown. Thus, it is not clear which aspects of covarying neural activity are being assessed by any particular computation of functional connectivity, especially for functional brain imaging data. The neural generators of the sources of activity that enter into the computation of functional connectivity may or may not be related to one another in any kind of simple way. For example, how is EEG coherence related to fMRI functional connectivity (evaluated by cross-correlating two fMRI time series)? Given that we do not have a good handle on the neural substrates of either the

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[4] Even though the neuroimaging community agreed on a common set of terms (i.e., functional and effective connectivity), there was a divergence of opinion concerning exactly how these terms should be defined. For example, although functional connectivity was defined by Friston and colleagues as the temporal correlation between spatially remote neurophysiological events (and effective connectivity was defined as the influence that one neural system exerts on another), Friston (Friston et al., 1993) applied this notion first to PET data, where there is no explicit time-varying signal within a scan, but where long-term time-varying effects (such as changes in attentional set) may occur across scans and can be exploited to compute the interregional functional connectivity. On the other hand, other investigators computed the functional connectivity within an experimental condition (i.e., within a scan) by using the subject-to-subject variability to evaluate PET interregional correlations (e.g., Horwitz et al., 1998; Kohler et al., 1998).

EEG signal or the fMRI signal, or how to relate EEG and fMRI data to each other (Horwitz and Poeppel, 2002), it is not at all clear that strong coherence in the gamma band, let us say, will correspond to strong functional connectivity in fMRI. As mentioned in the Lee et al. (2003) paper, one approach to address this issue is by using biologically realistic large-scale neural modeling to investigate the relationship between functional connectivity and its underlying neural instantiation (Horwitz et al., 1999), but this effort is just starting and it will take time for the research community to generate a set of results that can sustain the support of neuroimaging investigators.

What conclusions should be drawn from the above discussion? First, we should think of functional (and effective) connectivity not as a single concept or quantity, but rather as forming a class of concepts with multiple members. Second, functional and effective connectivity must be operationally defined by each investigator who evaluates these quantities. Just because an author claims to have evaluated functional or effective connectivity in a specific study does not mean he/she is looking at the same quantity as another researcher. Each different measure may be accessing a different aspect of interregional interactions. Thus, comparisons of functional (or effective) connectivity from different studies should be done with caution; the devil will indeed be in the details as to how each researcher actually defined the concept. Finally, it is crucial to relate each of the macroscopic level definitions to an underlying neural substrate. Once we have a good idea as to which aspects of covarying neural activity are being embodied by each definition of functional connectivity, it will be easier for an investigator to choose the most appropriate kind of functional connectivity to evaluate from his/her data that enables the clearest understanding of how neuronal populations are interacting with one another.

Acknowledgments

References

Adey, W.R., Walter, D.O., Hendrix, C.E., 1961. Computer techniques in correlation and spectral analysis of cerebral slow wave during discriminative behavior. Exp. Neurol. 3, 501–524.

Aertsen, A., Erb, M., Palm, G., 1994. Dynamics of functional coupling in the cerebral cortex: an attempt at a model-based interpretation. Physica D 75, 103–128.

Aertsen, A., Preissl, H., 1991. Dynamics of activity and connectivity in physiological neuronal networks, in: Schuster, H.G. (Ed.), Non Linear Dynamics and Neuronal Networks, VCH, New York, pp. 281–302.

Aertsen, A.M.H.J., Gerstein, G.L., Habib, M.K., Palm, G., 1989. Dynamics of neuronal firing correlation: modulation of "effective connectivity." J. Neurophysiol. 61, 900–917.

Barlow, J.S., Brazier, M.A.B., 1954. A note on a correlator for electroencephalograhic work. Electroencephalogr. Clin. Neuophysiol. 6, 321–325.

Bartlett, E.J., Brown, J.W., Wolf, A.P., Brodie, J.D., 1987. Correlations between glucose metabolic rates in brain regions of healthy male adults at rest and during language stimulation. Brain Lang. 32, 1–18.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541.

Bokde, A.L., Tagamets, M.A., Friedman, R.B., Horwitz, B., 2001. Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. Neuron 30, 609–617.

Buechel, C., Friston, K.J., 1997. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modeling and fMRI. Cereb. Cortex 7, 768–778.

Bullmore, E., Horwitz, B., Honey, G., Brammer, M., Williams, S., Sharma, T., 2000. How good is good enough in path analysis of fMRI data? Neuroimage 11, 289–301.

Clark, C.M., Kessler, R., Buchsbaum, M.S., Margolin, R.A., Holcomb, H.H., 1984. Correlational methods for determining regional coupling of cerebral glucose metabolism. A pilot study. Biol. Psychiatry 19, 663–678.

Friston, K.J., 1994. Functional and effective connectivity in neuroimaging: a synthesis. Hum. Brain Mapp. 2, 56–78.

Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S.J., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab. 13, 5–14.

Fuster, J.M., 2000. The module: crisis of a paradigm (Review of The New Cognitive Neurosciences, 2nd ed., edited by M.S. Gazzaniga). Neuron 26, 51–53.

Gazzaniga, M.S., 2000. The New Cognitive Neurosciences. MIT Press, Cambridge.

Gerstein, G.L., 1970. Functional association of neurons: detection and interpretations, in: Schmitt, F.O., Quarton, G.C., Melnechuk, T., Adelman, G. (Eds.), The Neurosciences: Second Study Program, Rockefeller University Press, New York, pp. 648–661.

Gerstein, G.L., Aertsen, A.M., 1985. Representation of cooperative firing activity among simultaneously recorded neurons. J. Neurophysiol. 54, 1513–1528.

Gerstein, G.L., Perkel, D.H., 1969. Simultaneously recorded trains of action potentials: analysis and functional interpretation. Science 164, 828–830.

Gevins, A.S., Cutillo, B.A., Bressler, S.L., Morgan, N.H., White, R.M., Illes, J., Greer, D.S., 1989. Event-related covariances during a bimanual visuomotor task. II. Preparation and feedback. Electroencephalogr. Clin. Neurophysiol. 74, 147–160.

Gevins, A.S., Doyle, J.C., Cutillo, B.A., Schaffer, R.E., Tannehill, R.S., Bressler, S.L., 1985. Neurocognitive pattern analysis of a visuospatial task: rapidly-shifting foci of evoked correlations between electrodes. Psychophysiology 22, 32–43.

Goncalves, M.S., Hall, D.A., Johnsrude, I.S., Haggard, M.P., 2001. Can meaningful effective connectivities be obtained between auditory cortical regions? Neuroimage 14, 1353–1360.

Grafton, S.T., Sutton, J., Couldwell, W., Lew, M., Waterm, C., 1994. Network analysis of motor system connectivity in Parkinsons's disease: modulation of thalamocortical interactions after pallidoctomy. Hum. Brain Mapp. 2, 45–55.

Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., Gore, J.C., 2002. Detection of functional connectivity using temporal correlations in MR images. Hum. Brain Mapp. 15, 247–262.

Hebb, D.O., 1949. The Organization of Behavior. Wiley, New York.

Heilman, K.M., Valenstein, E., 1985. Clinical Neuropsychology. Oxford University Press, New York.

Horwitz, B., Duara, R., Rapoport, S.I., 1984. Intercorrelations of glucose metabolic rates between brain regions: application to healthy males in a state of reduced sensory input. J. Cereb. Blood Flow Metab 4, 484–499.

Horwitz, B., Grady, C.L., Haxby, J.V., Ungerleider, L.G., Schapiro, M.B., Mishkin, M., Rapoport, S.I., 1992. Functional associations among human posterior extrastriate brain regions during object and spatial vision. J. Cogn. Neurosci. 4, 311–322.

Horwitz, B., Long, T.W., Tagamets, M.A., 1999. The neurobiological substrate of PET-fMRI functional connectivity. Neuroimage 9, S392.

Horwitz, B., McIntosh, A.R., Haxby, J.V., Furey, M., Salerno, J.A., Schapiro, M.B., Rapoport, S.I., Grady, C.L., 1995. Network analysis of PET-mapped visual pathways in Alzheimer type dementia. Neuroreport 6, 2287–2292.

Horwitz, B., Poeppel, D., 2002. How can EEG/MEG and fMRI/PET data be combined? Hum. Brain Mapp. 17, 1–3.

Horwitz, B., Rumsey, J.M., Donohue, B.C., 1998. Functional connectivity of the angular gyrus in normal reading and dyslexia. Proc. Natl. Acad. Sci. USA 95, 8939–8944.

Kohler, S., McIntosh, A.R., Moscovitch, M., Winocur, G., 1998. Functional interactions between the medial temporal lobes and posterior neocortex related to episodic memory retrieval. Cereb. Cortex 8, 451–461.

Lee, L., Harrison, L.M., Mechelli, A., 2003. The functional brain connectivity workshop: report and commentary. Neuroimage.

Livanov, M.N., 1977. Spatial Organization of Cerebral Processes. Wiley, New York.

Lowe, M.J., Mock, B.J., Sorenson, J.A., 1998. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 7, 119–132.

McIntosh, A.R., Gonzalez-Lima, F., 1991. Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effect of acoustic startle habituation on the auditory system. Brain Res. 547, 295–302.

McIntosh, A.R., Gonzalez-Lima, F., 1992. Structural modeling of functional visual pathways mapped with 2-deoxyglucose: effects of patterned light and footshock. Brain Res. 578, 75–86.

McIntosh, A.R., Grady, C.L., Ungerleider, L.G., Haxby, J.V., Rapoport, S.I., Horwitz, B., 1994. Network analysis of cortical visual pathways mapped with PET. J. Neurosci. 14, 655–666.

Mechelli, A., Penny, W.D., Price, C.J., Gitelman, D.R., Friston, K.J., 2002. Effective connectivity and intersubject variability: using a multisubject network to test differences and commonalities. Neuroimage 17, 1459–1469.

Metter, E.J., Riege, W.H., Kuhl, D.E., Phelps, M.E., 1984. Cerebral metabolic relationships for selected brain regions in healthy adults. J. Cereb. Blood Flow Metab. 4, 1–7.

Pfurtscheller, G., Andrew, C., 1999. Event-related changes of band power and coherence: methodology and interpretation. J. Clin. Neurophsiol. 16, 512–519.

Prohovnik, I., Hakansson, K., Risberg, J., 1980. Observations on the functional significance of regional cerebral blood flow in "resting" normal subjects. Neuropsychologia 18, 203–217.

Soncrant, T.T., Holloway, H.W., Horwitz, B., Rapoport, S.I., Lamour, Y.A., 1992. Effect of nucleus basalis magnocellularis ablation on local brain glucose utilization in the rat: functional brain reorganization. Eur. J. Neurosci. 4, 653–662.

Zeki, S., Watson, J.D.G., Lueck, C.J., Friston, K.J., Kennard, C., Frackowiak, R.S.J., 1991. A direct demonstration of functional specialization in human visual cortex. J. Neurosci. 11, 641–649.