Theoretical neurobiology and schizophrenia

Karl J Friston

The Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK

This chapter addresses the idea that schizophrenia is a 'disconnection syndrome' from a theoretical and computational perspective. The distinction between anatomical and functional connectivity is reviewed and used as a framework to introduce empirical and computational evidence that schizophrenia involves, at some level, a disintegration of neuronal interactions. The chapter concludes with an example of computational neuroscience that relates observations on the dimensional complexity of neuronal dynamics in schizophrenia to the disconnection hypothesis.

The aim of this chapter is to bring together some current ideas about schizophrenia that have been developed in theoretical and computational neurobiology. Abnormal connectivity is central to most of these ideas and this chapter looks at schizophrenia as a subtle and pernicious 'disconnection syndrome'. The notion that schizophrenia represents a disintegration or fractionation of the psyche is as old as its name, introduced by Bleuler[1] to convey a 'splitting' of mental faculties. Many of Bleuler's primary processes, such as 'loosening of associations' emphasise a fragmentation and loss of coherent integration. The nature of this integration at a neurobiological level (**functional integration**) is now an important area in theoretical neurobiology. Functional integration is mediated by connections among neuronal systems and abnormal connectivity is a recurrent theme in theoretical accounts of schizophrenic phenomenology.

The chapter is divided into three sections. The first section considers different aspects of connectivity from the point of view of theoretical neurobiology. The second section presents evidence for abnormal connectivity in schizophrenia, with an emphasis on contributions from computational neuroscience. The final section represents an illustrative example of how computational and nonlinear methods can be used in schizophrenia research. The example chosen relates empirical observations on the dimensional complexity of electroencephalographic (EEG) activity in schizophrenia and the 'disconnection hypothesis'. There are many aspects of the disconnection hypothesis that are not discussed here (e.g. aetiology, neuro-developmental issues, plasticity, relation to cognitive models, regional specificity of disconnections, etc.) but their importance is acknowledged.

Postal address: Karl J Friston, The Wellcome Department of Cognitive Neurology, Institute of Neurology, 12 Queen Square, London WC1N 3BG, UK

Aspects of connectivity

Anatomical connectivity

One taxonomy of connectivity distinguishes anatomical, functional and effective connectivity. **Anatomical connectivity** refers to the infrastructure of neuronal processes and projections in the brain. This connectivity is either **intrinsic** to the grey matter (e.g. GABAergic inhibitory interneurons) or **extrinsic**, linking grey matter regions (e.g. glutaminergic cortico-cortical or cortico-fugal projections). Anatomical connectivity has played a key role in elucidating many principles of functional organisation in the brain, particularly in visual cortex[2–4].

Functional and effective connectivity

Functional connectivity pertains not to the infrastructure mediating neuronal interactions but, like effective connectivity, to the dynamical aspects. Functional connectivity is an operational measure and has been defined as the 'temporal correlations between spatially remote neurophysiological events'[5]. These concepts originated in the analysis of separable spike trains obtained from multiunit electrode recordings[6–8]. Functional connectivity is simply a statement about the observed correlations; it does not provide any direct insight into how these correlations are mediated. For example, at the level of multiunit microelectrode recordings, correlations can result from **stimulus-locked transients**, evoked by a common afferent input, or reflect **stimulus-induced oscillations** – phasic coupling of neuronal assemblies, mediated by synaptic connections[7]. To further characterise the integration within a system one turns to **effective connectivity**. Effective connectivity is closer to the intuitive notion of a connection (i.e. the influence one neuronal system exerts over another). In electrophysiology there is a close relationship between effective connectivity and (at a synaptic level) synaptic efficacy. In this chapter the two terms are used interchangeably.

There is an intimate relationship between these different sorts of connectivities. However, it should be noted that an observation on one does necessarily imply anything about another. Disconnection in schizophrenia may be neuroanatomical or inferred on the basis of abnormal dynamics. The latter may be abnormalities of functional connectivity (e.g. abnormal coherence in EEG) or effective connectivity (e.g. abnormal neuromodulation of synaptic efficacy).

Modulation of synaptic efficacy

Mesulam[9] has emphasised the distinction between 'anatomically addressed channels for transferring information content and chemically addressed pathways for modulating behavioural tone'. Modulatory neurotransmitters modify neuronal excitability, not necessarily by a direct effect on postsynaptic membrane potential but by altering responsiveness to other transmitters. An interaction between two or more neurotransmitter systems is implicit: For example, dopamine terminals in prefrontal cortex contribute to synaptic complexes that include excitatory (e.g. glutaminergic) inputs onto pyramidal cells[10]. This synaptic arrangement implicates dopamine in modulating the effective connectivity between the prefrontal and distant cortical units. Dopamine has been implicated in a wide range of cognitive processes and its importance in schizophrenia has been repeatedly emphasised There is evidence to suggest that dopamine neurotransmission in the dorsolateral prefrontal cortex (DLPFC) is important in the execution of mnemonic tasks. Brozoski *et al.*[11] have shown that the chemical depletion of dopamine produces an impairment in delayed spatial alternation performance comparable to that caused by ablation (see also[12]). Extracellular recordings in rat prefrontal cortex show that excitatory responses to stimulation of thalamic afferents are blocked by stimulation of ascending dopamine projections arising in the ventral tegmental area (VTA)[13]. More recently, Williams and Goldman-Rakic[14] have shown that dopamine antagonists can selectively potentiate the 'memory fields' of prefrontal units in monkeys, indicating a direct gating of excitatory synaptic inputs during cognition. In short dopamine modulates the efficacy of afferent prefrontal excitatory connections.

Disconnectionism vs dysplasia?

A fundamental aspect of connectivity that is not addressed above is **plasticity**. Connectivity is in a constant state of flux where neuronal dynamics affect the morphology of neuronal processes and synaptic specialisations, and the latter account for the ensuing dynamics. Connectivity is, therefore, constantly changing (particularly during development) both in the short and long-term. In relation to schizophrenia, plasticity [e.g. associative plasticity, self organisation, activity-dependent changes in synaptic efficacy or experimentally induced long-term potentiation (LTP)] render connectivity and neuronal dynamics inseparable (i.e. the consolidation of synaptic specialisations and neuronal processes are a direct function of neuronal activity and

neuronal dynamics are a function of the connectivity among units). This is important because 'dysplastic' theories of schizophrenia and 'disconnection' theories are essentially the same thing and, implicitly, both speak to a neuro-developmental perspective.

Schizophrenia: 'disconnection syndrome'?

Anatomical connectivity in schizophrenia

The evidence suggesting abnormal connectivity in schizophrenia is anecdotal but compelling. For a more complete review of this evidence see Hoffman and McGlashan[15]. Hyde *et al.*[16] argue that the neurological condition that most resembles acute schizophrenia is metachromatic leukodystrophy. Adult cases, with an early onset, present with delusions, hallucinations and cognitive disorganisation. Lesions (involving an accumulation of sulfatide) in these particular patients occurred primarily in the frontal white matter. The idea is that metachromatic leukodystrophy provides a good lesion-deficit model of schizophrenia, where the lesion is an anatomical disconnection preferentially affecting connections with the prefrontal cortex.

Evidence for an association between white matter pathology and positive schizophrenic symptoms can be found in a neuropathological study of epileptic patients with and without psychosis by Bruton *et al*[17]. Epileptic patients with schizophrenia-like psychosis were distinguished from all other groups by a significant excess of pinpoint peri-vascular white-matter softenings. The corpus callosum contains the majority of interhemispheric projections. Although the literature is far from consistent meta-analysis of magnetic resonance imaging (MRI) studies of callosal anatomy suggest a significant reduction in callosal area in schizophrenia[18]. Further studies could be cited in support of a disconnection syndrome[19]. Most rely on putative neuro-developmental and cytoarchitectonic sequelae of abnormal connectivity, but they are not discussed here.

Functional connectivity in schizophrenia

Evidence for abnormal functional connectivity in schizophrenia is now beginning to emerge since the advent of neuroimaging time-series [e.g. ^{15}O positron emission tomography (PET) and functional MRI (fMRI) activation studies]. The resulting correlation (or functional connectivity) matrices are usually characterised in terms of their eigenvectors (eigenimages) or principal components[5]. In our work we have focused on prefrontal and temporal responses to word generation tasks and the

abnormal integration of physiological responses in these two regions. Our analyses suggest that there is a profound disruption of large scale prefronto-temporal interactions in schizophrenia. These systems are particularly relevant if one considers that many positive symptoms of schizophrenia reflect a failure to integrate intrinsically generated representations and concurrent perception (see Friston and Frith[20] for more details). Figure 1 shows an eigenimage (**d**) that reflects the functional connectivity in a group of normal subjects that is, relatively speaking, the least expressed in a schizophrenic group. This eigenimage was obtained using a generalised eigenvector solution:

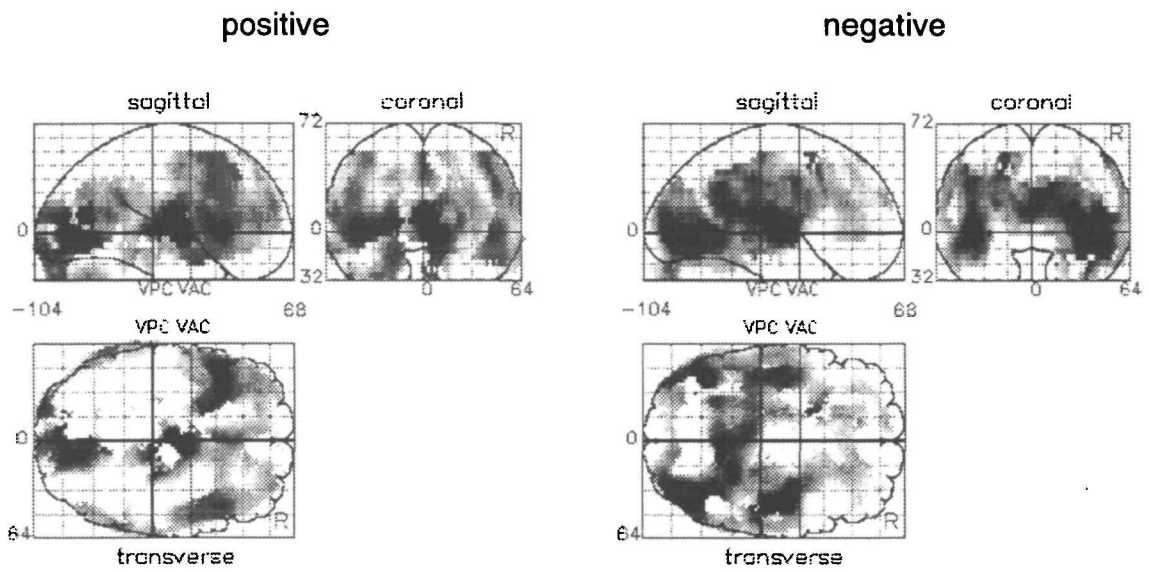
$$C_c.d = C_s d.\lambda \qquad 1$$

where C_s and C_c are the functional connectivity matrices from the schizophrenic and control groups respectively. λ is the largest eigenvalue. This example was based on a PET verbal fluency study of 6 control subjects and 6 schizophrenics. The top panels depict the positive and negative parts of **d**. This eigenimage is interpreted as showing profound negative correlations between left DLPFC/anterior cingulate/mediodorsal thalamus (positive) and bilateral superior temporal/posterior cingulate/extrastriate regions (negative). The amount to which this eigenimage was expressed in each subject is shown in the lower panel of Figure 1 using the appropriate 2-norm $\| \mathbf{d}^T.C.\mathbf{d} \|$. This measure simply reflects the amount to which an eigenimage **d** contributes to the functional connectivity or correlation structure C_s or C_c.

Effective connectivity in schizophrenia

Neurochemical disconnections Phencyclidine (PCP) is a psychomimetic drug that induces schizophrenia-like symptoms. PCP psychosis is characterised by delusions, hallucinations and disorganised speech[21]. Unlike many other psychomimetics, PCP also affects cognition, attention and motor function in a way that closely mimics the deficits seen in schizophrenia. PCP is a potent inhibitor of *N*-methyl-D-aspartate (NMDA) glutamate receptors. The majority of projections

Fig. 1 Eigenimage analysis of the schizophrenic and control subjects. Top left and right: positive and negative loadings of the first eigenimage that is maximally expressed in the normal group and minimally expressed in the schizophrenic group. This analysis used ^{15}O PET activation studies of word generations with 6 scans per subject and 6 subjects per group. The activation study involved three word generation conditions (word shadowing, semantic categorisation and verbal fluency) each of which was presented twice. The grey scale is arbitrary and each image has been normalised to the image maximum. The display format is standard and represents a maximum intensity projection from three orthogonal views of the brain (from the right, from behind and from above). This eigenimage is virtually absent in the schizophrenic data. This point is made by expressing the amount of functional connectivity attributable to the eigenimage in both groups, using the appropriate 2-norm (lower panel).



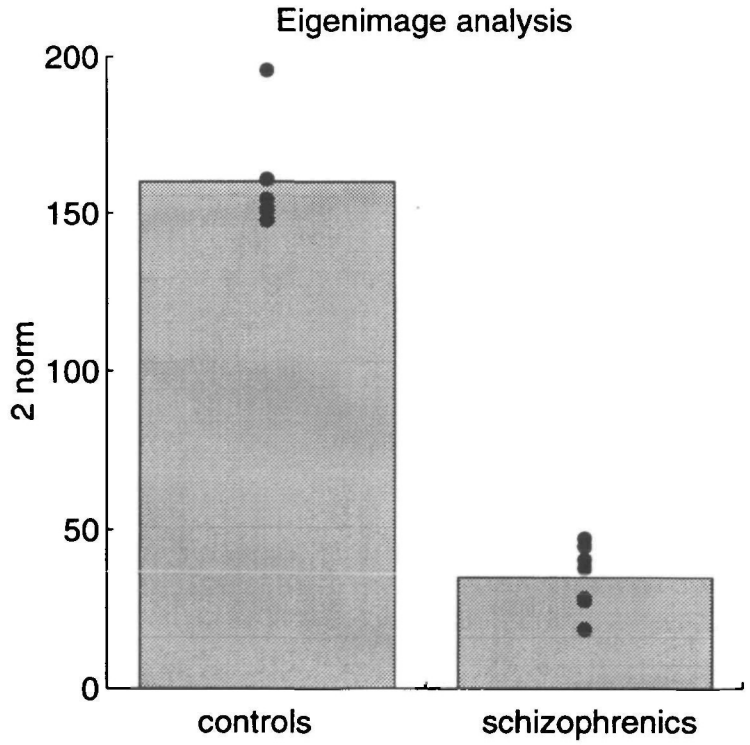


Fig. 1 (see opposite page)

in the brain are extrinsic (e.g. cortico-cortical) and use glutamate as an excitatory neurotransmitter. Two lines of evidence suggest reduced synaptic glutamate in schizophrenia. The first relies on abnormal markers of glutamate function in postmortem material: for example reduced glutamate release from isolated synaptosomes sampled from the prefrontal and temporal regions of schizophrenics[22] (see also Deakin *et al.*[23]). The second line of evidence suggests reductions in glutamate in the left prefrontal cortex of schizophrenics (relative to controls) using ^{1}H-magnetic resonance spectroscopy *in vivo*[24]. In short, PCP psychosis could be construed as a transient chemical effective disconnection syndrome, preferentially affecting excitatory cortico-cortical connections.

Parallel distributed processing (PDP) models Cohen and Servan-Schreiber[25] have used connectionist models in a compelling way to explore the relationship between cognitive deficits and biological abnormalities in schizophrenia. They have focused on attention and language processing in relation to dopaminergic modulation of prefrontal cortical interactions. The models simulate normal and schizophrenic-like performance on the Stroop task, continuous performance tasks and a lexical disambiguation task. The cognitive deficits can be modelled in terms of a 'gain' parameter corresponding to the neuromodulatory effect of dopamine on synaptic efficacy in the prefrontal cortex.

$$s_i = (1 + e^{-\text{gain}.\Sigma C_{ij}.s_j + \text{bias}})^{-1} \qquad 2$$

where s_i is the activity of unit i and C_{ij} is the connection strength between units i and j. What is remarkable about this work is that a diversity of deficits (observed in schizophrenics during the performance of selective attention and language tasks) could be emulated quantitatively by manipulating just one control parameter – the gain. From the current perspective this control parameter changes effective connectivity. (See Cohen and Servan-Schreiber[25] for a full review.)

Attractor networks Hoffman has used PDP models (fully interconnected Hopfield-type networks) as a model of associative memory to emulate many phenomena that share some features with the experiential symptoms of schizophrenia. Recent work (fully reviewed in Hoffman and McGlashan[15]) has explicitly addressed the breakdown of communication (connectivity) between cortical areas. Simulations of this pathology suggest two consequences: (i) some cortical circuits will become functionally autonomous; and (ii) a subset of these circuits will yield 'parasitic foci' that slavishly reproduce the same output. These parasitic foci are one symptom of interactional pathology in PDP networks that ensue when increasing numbers of connections are removed or pruned.

Parasitic foci can be thought of as attractor states (representing the output or 'memory') that are unaffected by activity in other parts of the system. Moreover, these foci arose *de novo*, in the sense they do not resemble any previously stored memory, striving relentlessly to reproduce themselves. Hoffman argues that delusions of control, paranoid delusions, thought broadcasting and auditory hallucinations can all be framed in terms of parasitic foci, located at different levels of language processing. This theme of disintegration, with the emergence of autonomous and chaotic local dynamics is central to the next section; where empirical measurements of chaos, in brain dynamics, and theoretical predictions are brought together.

Nonlinear dynamics and dimensional complexity

Background

In this section we relate empirical nonlinear characterisations of neuronal dynamics in schizophrenia, to the disconnection hypothesis discussed above. Nonlinear dynamics have become increasingly important in computational neurobiology and synthetic neuronal modelling[26]. The most common nonlinear characterisation of (putative) chaotic electrophysiological time-series is the correlation dimension (D_2). The correlation dimension (sometimes known as dimensional complexity) measures the degree of chaos of a strange attractor. Although there are problems associated with its measurement and validation, in application to real neuronal systems, the correlation dimension is a useful index if one accepts a 'strange attractor' metaphor for brain dynamics. Koukkou *et al.*[27] assessed the correlation dimension over the left temporo-parietal region of first-episode unmedicated schizophrenics. Compared to a controls and medication free neurotics the first-episode schizophrenics had a significantly ($p<0.001$) higher D_2 (schizophrenics 4.44, neurotics 4.11 and controls 3.96). Is this consistent with a disconnection syndrome? In fact it is: the simulations below suggest that as extrinsic excitatory connectivity is reduced, the correlation dimension increases. The intuitive reason for this relates to the progressive isolation of local neuronal systems, allowing each to express its own distinct dynamics. Each of these functionally isolated components contributes its own dimensions to the global attractor. As extrinsic or between group connectivity increases the functional interactions cause the dynamics to be integrated into a single low-dimensional attractor with a much smaller D_2. The expression of locally-specific dynamics in the absence of extrinsic connectivity is very reminiscent of Hoffman's 'parasitic' attractors that reproduce the same dynamics unfettered by activity in other areas.

The nonlinear simulation

The simulation comprised 3 groups of 8 units. Within each group every unit was vicariously connected to every other unit with one excitatory connection and 7 inhibitory connections (c.f. GABA inhibitory interneurons). These intrinsic or within-group connectivities were chosen to ensure chaotic dynamics. The connections between groups were sparse and excitatory (c.f. glutaminergic cortico-cortical projections). The within-group excitatory and inhibitory connectivity matrices (E_w and I) and the between-group excitatory connectivity matrices E_b were scaled to a Frobenius norm of one. Dynamics were obtained by integration of:

$$\partial s_i/\partial t = \sum Eij.sj - s_i . \sum Iij.sj$$

or in matrix notation

$$\partial s/\partial t = E.s - diag(s).I.s$$

where

$$E = E_w + \alpha.E_b \qquad 3$$

The relative amount of extrinsic or between-group connectivity was varied using a control parameter α.$\partial s/\partial t$ is the change in activity of unit i per iteration. The form of this equation means that excitatory inputs from unit j increase activity in unit i according to the excitatory connection strength E_{ij}. The inhibitory inputs, mediated by the inhibitory connections I_{ij} are modulated by activity intrinsic to the unit in question. This nonlinear interaction can be thought of as emulating shunting inhibition, where the effect is only realised in the presence of postsynaptic depolarisation. Although Equation 3 may seem very simple it can lead to markedly nonlinear dynamics reminiscent of neuronal systems with spontaneous periodic bursting.

The dimensional complexity (D_2) was measured (as described in Friston *et al.*[28]) as a function of extrinsic connectivity α. As predicted, the dimensional complexity fell monotonically with increases in α. Figure 2 (middle panel) shows this relationship and provides examples of the simulated EEG at low (left) and high (right) levels of between-group connectivity. In summary, progressive disconnection at the level of

Fig. 2 Top: examples of the excitatory and inhibitory connectivity matrices corresponding the E and I in the main text. Middle panel: Dimensional complexity (D_2) as a function of extrinsic connectivity (α) between the three simulated neuronal groups. Lower panels: examples of the dynamics at two values of α (dotted lines in the middle panel) over 1024 iterations of Equation 1. These simulated EEGs correspond to the summed activity over all 24 units.

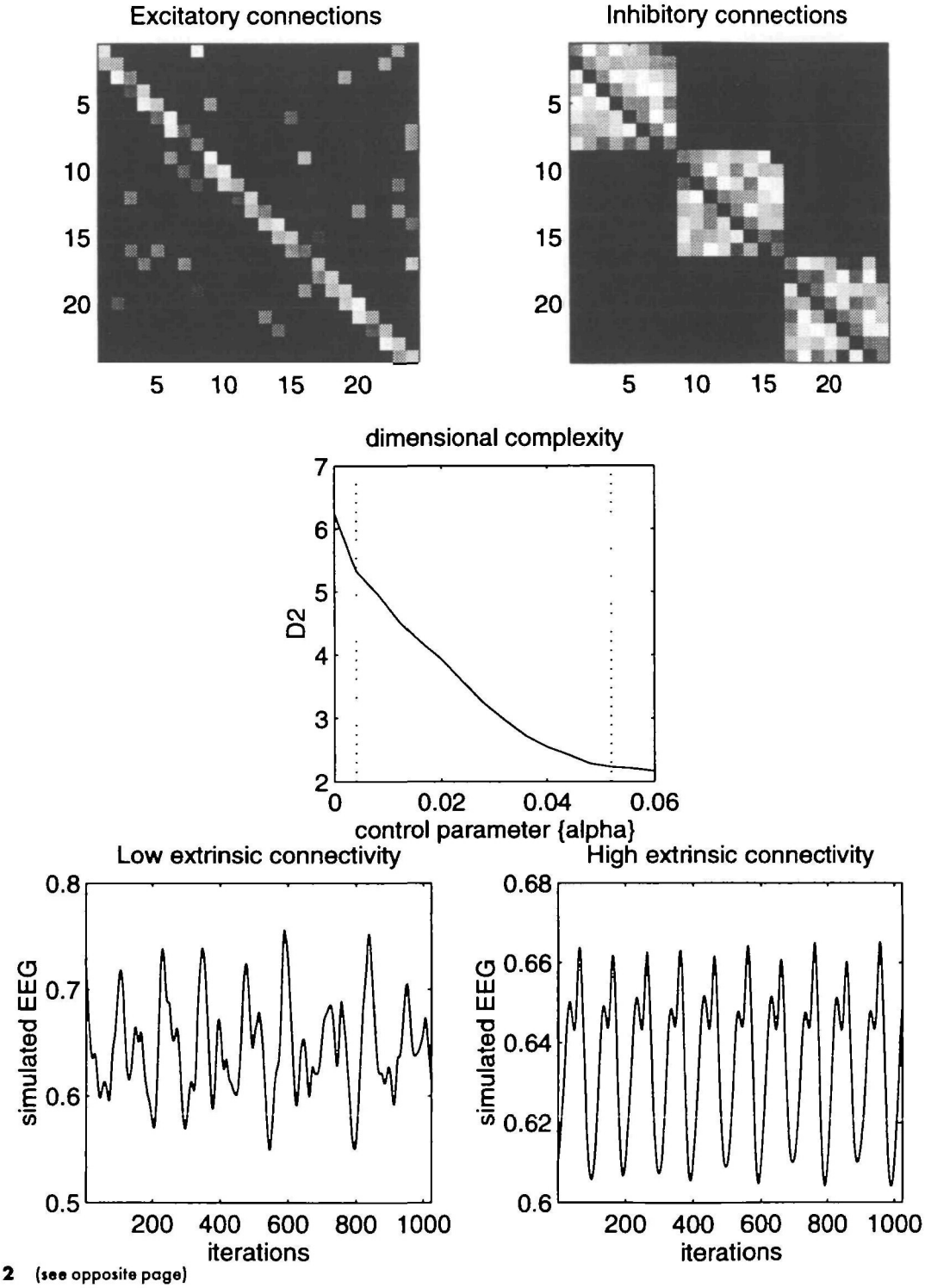


Fig. 2 (see opposite page)

simulated extrinsic excitatory connectivity increases the correlation dimension. The correlation dimension based on the EEG of unmedicated schizophrenics has been shown to be higher than normal.

Conclusion

There is large and diverse body of evidence to support the notion that schizophrenia can be thought of as a disconnection syndrome. Theoretical considerations and computational neurobiology may inform the interpretation of some empirical observations that may, at first glance, seem difficult to understand intuitively.

Acknowledgements

KJF is supported by the Wellcome Trust. I would like to thank my colleagues for help with this work, particularly Chris Frith.

References

1 Bleuler E. Dementia Praecox or the group of schizophrenias: Translated into English 1987. In: Cutting J, Shepherd M. (Eds). *The Clinical Routes of the Schizophrenia Concept.* Cambridge: Cambridge University Press, 1913
2 Maunsell JHR, Van-Essen DC. Connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J Neurosci* 1983 3: 2563–86
3 Zeki S. The motion pathways of the visual cortex. In: Blakemore C (Ed). *Vision: Coding and Efficiency.* Cambridge: Cambridge University Press, 1990; 321–45
4 Baizer JS, Ungerleider LG, Desimone R. Organization of visual inputs to the inferior temporal and posterior parietal cortex in Macaques. *J Neurosci* 1991; 11: 168–90
5 Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal component analysis of large (PET) data sets. *J Cereb Blood Flow Metab* 1993; 13: 5–14
6 Gerstein GL, Perkel DH. Simultaneously recorded trains of action potentials: analysis and functional interpretation. *Science* 1969; 164: 828–30
7 Gerstein GL, Bedenbaugh P, Aertsen AMHJ. Neuronal assemblies. *IEEE Trans Biomed Eng* 1989; 36: 4–14
8 Aertsen AMHJ, Preissl H. Dynamics of activity and connectivity in physiological neuronal networks. In: Schuster HG. (Ed). *Non Linear Dynamics and Neuronal Networks.* New York: VCH, 1991; 281–302
9 Mesulam MM. Large scale neurocognitive networks and distributed processing for attention language and memory. *Ann Neurol* 1990; 28: 597–613
10 Goldman-Rakic PS, Leranth C, Williams SM, Mons N, Geffard M. Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. *Proc Natl Acad Sci USA* 1989; 86: 9015–9
11 Brozoski TJ, Brown RM, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in the prefrontal cortex of Rhesus monkey. *Science* 1979; 205: 929–32
12 Sawaguchi T, Goldman-Rakic PS. D_1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science* 1991; 251: 947–50

13 Mantz J, Milla C, Glowinski J, Thierry AM. Differential effects of ascending neurons containing dopamine and noradrenaline in the control of spontaneous activity and of evoked responses in the rat prefrontal cortex. *Neuroscience* 1988; 27: 517–26
14 Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D_1 receptors in prefrontal cortex. *Nature* 1995; 376: 572–5
15 Hoffman RE, McGlashan TH. Parallel distributed processing and the emergence of schizophrenia symptoms. *Schizophr Bull* 1993; 19: 119–40
16 Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy – insights into the neurobiology of psychosis. *Arch Neurol* 1992; 49: 401–6
17 Bruton CJ, Stevens JR, Frith CD. Epilepsy, psychosis and schizophrenia: clinical and neuropathologic correlations. *Neurology* 1994; 44: 34–42
18 Woodruff PW, McManus IC, David AS. Meta-analysis of corpus callosum size in schizophrenia. *J Neurol Neurosurg Psychiatry* 1995; 58: 457–61
19 Benes FM, Davidson J, Bird ED. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch Gen Psychiatry* 1986; 43: 31–5
20 Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome?. *Clin Neurosci* 1995; 3: 88–97
21 Allen RW, Young SJ. Phencyclidine-induced psychosis. *Am J Psychiatry* 1978; 135: 1081–4
22 Sherman AD, Davidson AT, Baruah S, Hegwood TS, Waziri R. Evidence of glutaminergic deficiency in schizophrenia. *Neurosci Lett* 1991; 122: 77–90
23 Deakin JFW, Slater P, Simpson MDC *et al.* Frontal cortical and left temporal glutaminergic dysfunction in schizophrenia. *J Neurochem* 1989; 52: 1781–6
24 Pettegrew JW, Keshavan MS, Panchalingam K *et al.* Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first episode, drug-naive schizophrenics: a pilot study of the dorsal prefrontal cortex by phosphorus 31 nuclear magnetic resonance spectroscopy. *Arch Gen Psychiatry* 1991; 48: 563–8
25 Cohen JD, Servan-Schreiber D. Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychol Rev* 1992; 99: 45–77
26 Sporns O, Gally JA, Reeke GN, Edelman GM. Re-entrant signalling among simulated neuronal groups leads to coherence in their oscillatory activity. *Proc Natl Acad Sci USA* 1989; 86: 7265–9
27 Koukkou M, Lehmann D, Wackermann J, Dvorak I, Henggeler B. Dimensional complexity of EEG brain mechanisms in untreated schizophrenia. *Biol Psychiatry* 1993; 33: 397–407
28 Friston KJ, Tononi Sporns O, Edelman GM. Characterising the complexity of neuronal interactions. *Hum Brain Mapping* 1996; In press