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Functional integration in schizophrenia: Too little or too much? Preliminary results on fMRI data

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The disconnectivity hypothesis proposes that schizophrenia results from poor or miswired anatomical connections. Theoretically, its functional counterpart should be disintegration. Integration is thought to allow segregated neurons to interact as a coherent whole, referred to as the "core", while the non-interacting part of the brain is referred to as the "rest". In this study, it is suggested that schizophrenia is the result of rest noise interfering with core activity. Two possible causes are assessed: (i) defective core integration, making the core more vulnerable to noise from the rest, or (ii) the rest being too highly integrated, meaning that it can interfere with the core.

These hypotheses were tested using fMRI data acquired from 13 stabilized medicated schizophrenic subjects compared to 11 matched controls. Subjects were required to perform a series of lexical decision and retrieval tasks in separate sessions. The brain was divided into 90 components. Integration was defined as the amount of information shared between the components of a sub-system. An iterative aggregation procedure made it possible to identify a core on the basis of the functional clustering index, which assesses the integration of the core relative to its integration with the rest. Correlation of component-pairs within the core was also compared between the two groups. This procedure was repeated for each subject and for each task.

Cores did not differ between the two groups, either in terms of integration or in terms of functional clustering index. However, the core was still highly integrated with the rest and the rest was overly integrated in schizophrenic subjects. Both anomalies were correlated with the negative symptoms. These findings were consistent regardless of the task considered. Furthermore, within the core, anterior–posterior correlations were lower in patients (between the frontal and the parietal and posterior cingulate cortices), whereas frontal left–right correlations were excessive. No significant correlation was found with the medication. Thus, it appears that schizophrenia entails a deleterious combination of too much "noisy" integration (from the rest) and too little "significant" integration (anterior–posterior functional connectivity).

Keywords: Schizophrenia; Functional integration; Functional connectivity; fMRI; Consciousness; Episodic memory

It is generally accepted that schizophrenia is related to an information processing disorder linked with cryptic brain anomalies (Gold and Harvey, 1993). Classical neurological models have failed to account for the whole range of symptoms: schizophrenia cannot be fully explained in terms of a defect, such as a frontal or temporal–hippocampal impairment, or a mere dopamine dysregulation. An exciting hypothesis has been gaining popularity over the past few years, which proposes that schizophrenia results from poor or miswired anatomical connections (Akbarian et al., 1993; Bullmore et al., 1997; Goodman, 1989; Hoffman and Dobscha, 1989; Weinberger et al., 1994). Empirical evidence has been gathered, not only from the observation of synaptic deficit, for example, lower density of synaptic staining (Harrison, 1999), lesser mRNA for synaptic proteins (Mirnics et al., 2000) and replication of psychotic symptoms by glutamate antagonist (Wachtel and Turski, 1990), but also from the observation of white matter abnormalities, for example, defective myelination gene expression (Hakak et al., 2001), white matter disorganization (Foong et al., 2001; Lim et al., 1998, 1999) and replication of schizophrenia symptomatology by white matter diseases (Betts et al., 1968; Filley and Gross, 1992; Hyde et al., 1992).

Looked at from the viewpoint of the whole system, the functional counterpart of this anatomical disorder should be a dysfunctional integration (Tononi and Edelman, 2000). Integration is supposed to allow segregated neurons to interact as a coherent whole (Tononi and Edelman, 1998b; Varela, 1995). From a neurophysiological standpoint, the reason why it is important for a

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neuronal population to fire coherently is that it must have a sufficient "mass effect" to influence other neurons (Singer, 1999). Neurons are more likely to follow inputs from an integrated assembly because they will be coincident, resulting in a larger summation and thus a higher probability of spiking (Abeles, 1982; Konig et al., 1996; Usrey, 2002). Looking at the issue from a broader perspective, it has also been proposed that neuronal integration accounts for the phenomenological feeling of the unity and non-reducible whole of conscious awareness (Singer, 1998; Tononi and Edelman, 1998a; Varela, 1995). Clinically, this is precisely what schizophrenic patients run short of (Tononi and Edelman, 2000), an observation which first prompted Bleuler to call this disorder schizophrenia or "split thoughts" (Bleuler, 1911, 1950). In Bleuler's opinion, this fragmentation or, in his own words, this *spaltung* of mental unity lay at the very heart of the disease (but see (Klosterkotter et al., 2001; Parnas, 2003) for evidence of other disturbances of consciousness in schizophrenia—"basic symptoms").

A physiological marker for an integrated neuronal assembly is its coherent activity (Singer, 1993; Varela, 1995). At the mesoscopic scale, this group activity is proportional to the amplitude of EEG (Varela et al., 2001) and perhaps to the fMRI-BOLD signal (Foucher et al., 2003; Logothetis et al., 2001). Differences in mesoscopic integration account for differences in activation intensity between patients and controls in classical voxel-based comparison of functional imaging data. At the macroscopic scale, integration is proportional to the interdependence of the signal arising from several mesoscopic elements (Varela et al., 2001). Physiologically, the integration of many neurons spread across the cortex is likely to become more challenging as the integration scale grows larger (Munk et al., 1996). Accordingly, information processing relying on large-scale integration should be more likely to be affected by disconnectivity, for example, top-down attention, executive functions or episodic memory, all of which have been demonstrated to be affected in schizophrenia (Green, 1998). Consequently, large-scale integration will be the focus of this study.

So far, most attempts at translating a large-scale anatomical connectivity disorder into functional terms have focussed on the correlation between 2 selected areas, referred to hereinafter as "functional" connectivity (Buchel and Friston, 1997; Friston, 1997). Where schizophrenia is concerned, PET and fMRI studies have mainly provided evidence of lower correlation (Clark et al., 1984; Friston et al., 1995a; Mallet et al., 1998). However, EEG-coherence or synchrony measurements provide a more contrasted pattern with both higher (Giannitrapani, 1979; Shaw et al., 1983; Wada et al., 1998a) and lower coherence measures (Ford et al., 2002; Hoffman et al., 1991; Spencer et al., 2003).

But the question of integration could also be raised with regard to the whole brain. This is precisely what this paper investigates using the theoretical framework provided by Tononi et al. (1998). They have proposed that effective brain functioning is based on an integrated neuronal assembly which is separated from the remaining part of the brain. The former is referred to as "the core" (Edelman and Tononi, 2000) and the latter as "the rest". It was proposed that the distinction between the two relied on the optimum (highest value) of the functional clustering index which evaluates the high integration within the core and its low integration relative to the rest (Tononi et al., 1998). A corollary of the low integration between the core and the rest should be that at a given moment, the core is unique, at least at a macroscopic scale (Edelman and Tononi, 2000); otherwise, the mass effect of the other cores could have a deleterious influence on the main one (Singer, 1999). Although the rest is thought to remain in a low-integrated state, that does not mean that it is in a resting state. The preservation of a low-integrated state may result from an active process, for example, EEGs show more coherent activity (i.e., higher functional connectivity) in slow wave sleep than in normal alert state (Edelman and Tononi, 2000; Niedermeyer, 1999).

In view of these basic premises, schizophrenia might result from a failure of the core, as it accounts for conscious awareness, cognition and behavior (Tononi and Edelman, 2000). There are two main possible causes of defective functioning of the core: (i) weak core integration, making the core more vulnerable to noise from the rest, or (ii) the rest being too highly integrated, meaning that it can interfere with the core. In both cases, core dysfunction is brought about by breakthrough of uncontrolled rest activity within the core, which results in excessive core-rest integration. However, in the first hypothesis, the excess would be relative to core integration, whereas in the second hypothesis, the excess could also be absolute (i.e., not dependent on core integration). The prevailing interpretation of the anatomical disconnectivity hypothesis argues that poor integration of the core lies at the heart of schizophrenia (Tononi and Edelman, 2000). Alternatively, inhibition may not be sufficient to ensure active maintenance of the rest in a low integration state. As a result, the whole system may be too highly integrated (Kurachi, 2003; Wada et al., 1998b).

The purpose of this study was to address these two interlinked questions: (i) could schizophrenic patients' problems be the result of a dissolution of the core within the rest? (ii) and if so, is this due to insufficient integration of the core, or too much integration of the rest?

Thirteen stabilized, medicated schizophrenic subjects were compared to 11 matched controls. The computation was performed on fMRI measurements because of their good spatial resolution. However, a core is presumed to change from one second to the next, that is, to be "dynamic" (Edelman and Tononi, 2000). Since fMRI does not have the proper time resolution, participants had to be in a reasonably constant cognitive state to allow the estimate of one stable core during scanning. Accordingly, they were instructed to perform only one lexical decision or verbal-information retrieval task during each fMRI run. We measured integration at the whole brain level, but also between pairs of components within the core, that is, functional connectivity, in order to study finer core differences and to ascertain that our population was not different from other populations covered in the literature.

Methods

Participants

Thirteen right-handed schizophrenic subjects with no prior history of neurological injury (4 females, 35 $\pm$ 8 years ranging from 25 to 50 years, 12 $\pm$ 3 years of education) took part in the study. They all satisfied the DSM IV criteria for the diagnosis of schizophrenia, had been stable for at least 3 months and, in all but one case, were being treated with antipsychotics (of the 12 patients, 7 were under an atypical—Chlorpromazine equivalent