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Small-world networks and disturbed functional connectivity in schizophrenia

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Abstract

Disturbances in "functional connectivity" have been proposed as a major pathophysiological mechanism for schizophrenia, and in particular, for cognitive disorganization. Detection and estimation of these disturbances would be of clinical interest. Here we characterize the spatial pattern of functional connectivity by computing the "synchronization likelihood" (SL) of EEG at rest and during performance of a 2Back working memory task using letters of the alphabet presented on a PC screen in subjects with schizophrenia and healthy controls. The spatial patterns of functional connectivity were then characterized with graph theoretical measures to test whether a disruption of an optimal spatial pattern ("small-world") of the functional connectivity network underlies schizophrenia. Twenty stabilized patients with schizophrenia, who were able to work, and 20 healthy controls participated in the study. During the working memory (WM) task healthy subjects exhibited small-world properties (a combination of local clustering and high overall integration of the functional networks) in the alpha, beta and gamma bands. These properties were not present in the schizophrenia group. These findings are in accordance with a partially inadequate organization of neuronal networks in subjects with schizophrenia. This method could be helpful for diagnosis and evaluation of the severity of the disease, as well as understanding the pathophysiologic mechanisms underlying cognitive dysfunction in schizophrenia.

Keywords: Schizophrenia; EEG; Synchronization; Functional connectivity; "Small-world" networks; Working memory; Mental illness

1. Introduction

During recent years, the symptoms of schizophrenia have been explained in terms of disturbed functional connectivity between different brain regions (Andreasen et al., 1998, 1999; Breakspear et al., 2003; Peled, 1999; Friston, 1998, 1999, 2005). Histological, biochemical, PET, and fMRI studies as well as studies of bioelectrical signals have been used to interpret functional connectivity in schizophrenia (Brambilla et al., 2005; Burns et al., 2003; Foucher et al., 2005; Kim et al., 2005; Mitelman et al., 2005a,b; Scherk et al., 2003; Schloesser et al., 2005). These

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studies suggest the existence of inadequate functional integration although the exact nature of this inadequacy has not yet been fully clarified (Breakspear et al., 2003; Foucher et al., 2005). The "disconnection hypothesis" (Andreasen et al., 1996, 1999; Breakspear et al., 2003; Conklin et al., 2005; Friston, 1998, 1999; Peled, 1999) and WM deficits (Başar et al., 1999; Harmony et al., 2004; Silver et al., 2003) are well established in the literature on schizophrenia.

Coherence has been widely applied to EEG signals to investigate the functional connectivity in schizophrenics between brain regions. Early studies reported a variety of findings – most typically increased coherence – in contrast to more recent reports that show decreased coherence during different tasks in schizophrenics, in relation to health individuals. (Giannitrapani, 1979; Knott et al., 2002; Michelogiannis et al., 1991; Peled et al., 2001; Spencer et al., 2003; Strelets et al., 2002; Slewa-Younan et al., 2004; Winterer et al., 2001). Coherence is not sensitive to nonlinear dynamical interdependences (Breakspear et al., 2003). However, in recent years, evidence has been reported for weak but significant nonlinear properties of EEG signals and their interdependencies (Fingelkurts et al., 2004; Sporns et al., 2004; Stam et al., 2003; Stam, 2005; Varela et al., 2001). For this reason, we used the Synchronization Likelihood (SL), a method which is sensitive to both linear and nonlinear synchronization between signals, hence giving more accurate information about functional interactions (Stam and Dijk, 2002).

A further approach to study the topographical characteristics of both local and long distance functional connectivity in complex networks is the application of measures derived from "Graph" theory. Interest in using graph theory to study neural networks has risen rapidly in recent years (Atay and Biyikoglou, 2005; Buzsaki et al., 2004; Micheloyannis et al., 2006; Sporns and Zwi, 2004; Stam, 2004; Stam et al., 2006). This approach offers a unique window into the balance of local and distributed interactions occurring in the brain (Fingelkurts et al., 2004; Varela et al., 2001). It has been used in different neuroscience studies, in animals and humans, such as in studies of anatomical connectivity, fMRI BOLD, EEG and MEG signals (Eguiluz et al., 2005; Kaiser and Hilgetag, 2004; Micheloyannis et al., 2006; Sporns and Zwi, 2004; Stam et al., 2006; Watts and Strogatz, 1998).

The method enables the detection of so-called "small-world" network architecture which should be distinguished from either ordered or random networks. Networks with "small-world" architecture are characterised by a combination of strong local clustering and a short characteristic path length (an index of global integration). This has been proposed as a sign of "optimal organization" during specific functions (Sporns and Zwi, 2004; Stam, 2004, 2005; Watts and Strogatz, 1998). In contrast, ordered networks have high clustering but low global integration, and random networks have low clustering and high global integration.

In the present study, patterns of functional connectivity were determined with SL in different frequency bands of the EEG since these are known to have differing functional significance and interplay (Sauseng et al., 2005; Stein and van Sarnthein, 2000). These patterns were then used to construct and evaluate the graph parameters. We sought to test the disconnection hypothesis by applying these measures to EEG data acquired at rest, and during the performance of a working memory (WM) task. The combined application of the SL and graph measures to different EEG bands may provide additional information into the properties and consequences of any putative "disconnection".

2. Materials and methods

2.1. Subjects

We examined 20 young subjects (15 male, 5 female) with schizophrenia who were sufficiently stable to work and were on typical or atypical pharmacological treatment (with no change in treatment for at least six months). The diagnosis was made according to DSM-IV criteria with consensus agreement between the treating psychiatrist and an independent psychiatrist. The mean age of the 20 patient group was 32.4 years, 18 right handed. The mean duration of illness was 10 years, mean number of hospitalizations 2.5, and the mean treatment was 692 mg chlorpromazine-equivalent antipsychotics (11 received atypical antipsychotics, 6 were on conventional neuroleptics, 2 were on an atypical plus a conventional medication and 1 had no treatment at the time of examination).

For controls we choose a group of 20 educated individuals (mean education years of patients were 11.4 and of controls 18.3 years) mean age 27.4 years, 19 right-handed, 15 male, 5 female. The important issue of appropriate education comparison is raised in the Discussion. They had unremarkable developmental histories and no relatives with schizophrenia or other psychotic illness. After approval of the hospital ethics committee and complete description of the study to the subjects, written informed consent was obtained.

2.2. Neuropsychological tests

The neuropsychological investigation of both groups consisted of the two back WM test (reaction time and error rates), Digit span F and B, Digit symbol, Stroop test and

Table 1
Mean scores (and SD) for the neuropsychological tests

	Schizophrenia	Control
Back2 reaction time (ms)	1434.9 (697.7)	1043.2 (245.0)*
Back2 error rates	7.2 (6.7)	0.0*
Digit span F	5.3 (0.6)	6.7 (1.2)*
Digit span B	3.9 (1.3)	5.9 (1.4)*
Digit symbol	40.8 (10.5)	63.0 (9.1)*
Stroop interference	−2.1 (7.9)	7.0 (8.6)*
Verbal IQ	99.6 (10.8)	129.9 (8.1)*

Asterisks indicate significant differences by Mann–Whitney test.

Verbal IQ. The group of normals were examined with the Mini International Neuropsychiatric Interview to exclude major psychiatric disturbance.

2.3. EEG recording and analyses

The EEG signals were recorded from 28 cap electrodes, placed according to the 10/20 international system, referred to linked A1+A2 electrodes. We analysed epochs at rest i.e. while the individual were requested to fix their eyes on a small point on a screen 80 cm in front of them and then during a two-back working memory test using capital Greek letters (which differed from the letters used in the clinical stage). The SL between all pairs of electrodes was calculated for the traditional EEG frequency bands (theta: 4–8 Hz, alpha1: 8–10 Hz, alpha2: 10–13 Hz, beta: 13–30 Hz, gamma1: 30–45 Hz, gamma2: 45–90 Hz). Graph theoretical analysis was based on the full matrix of all possible pair wise combinations of electrodes. The SL matrix was converted into a graph by choosing a threshold T and the graph theoretical measures (cluster coefficient: Cp and characteristic path length: Lp) were derived from this binary graph. Calculations were done off-line with the DIGEEGXP software written by one of the authors (C.J. Stam). A formal description of the SL, Cp and Lp are given in (Posthuma et al., 2005; Stam and Dijk, 2002). We calculated the Cp, Lp as well as the ratios Cp/Cp-s and Lp/Lp-s where Cp-s and Lp-s denote the values of Cp and Lp for appropriate ordered and random reference graphs, for $K=4$, 5 or 6 (Sporns and Zwi, 2004) where K is the average number of edges per vertex.

2.4. Statistical analyses

Statistical comparison of SL, Cp and Lp between the two groups was achieved using t-tests. The neuropsychological results were further compared for the two

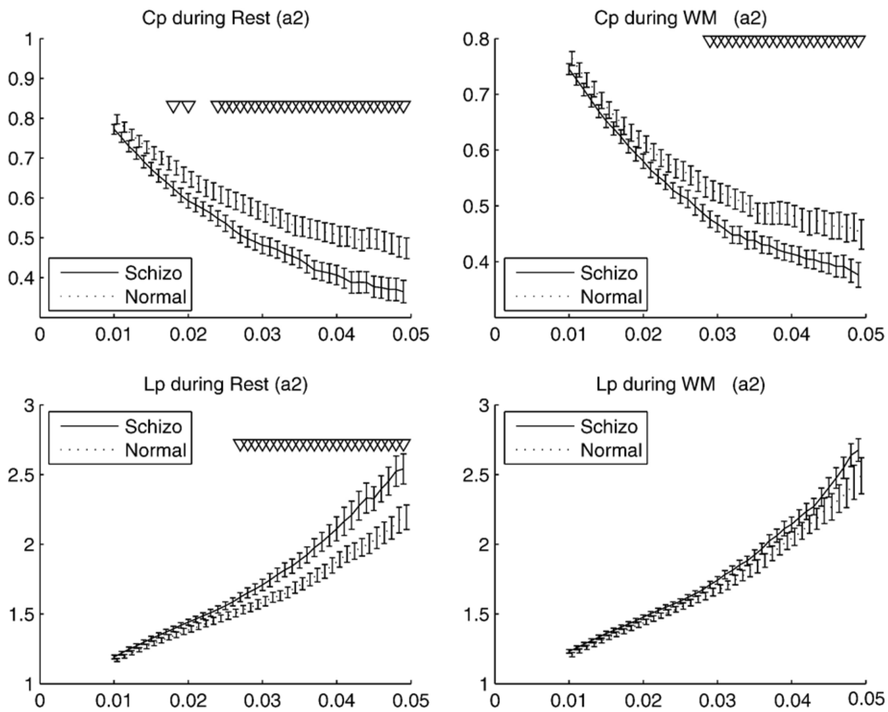

Fig. 1. Mean cluster coefficient Cp and characteristic path length Lp of alpha2 EEG frequency band at rest and during WM for different values of threshold (0.01–0.05). The bars indicate the standard error of mean and the triangles where there are statistically significant differences (t-test, $p<0.05$) between the groups. Increasing the values of threshold, decrease the values of Cp, due to the fact that more and more edges are lost (providing that SL<T). In contrast, increasing the values of threshold, the average Lp increases due to the fact that more and more edges drop out.

Table 2
Mean values of Cp/Cp-s and Lp/Lp-s during WM with $K=5$

Bands	WM: Controls	WM: Controls	WM: Schizophrenia	WM: Schizophrenia
	Cp/Cp-s	Lp/Lp-s	Cp/Cp-s	Lp/Lp-s
Theta	**1.948**	**1.188**	**1.824**	**1.134**
Alpha1	**1.916**	**1.186**	1.749	1.192
Alpha2	**1.877**	**1.139**	1.732	1.160
Beta	**1.882**	**1.145**	1.599	1.164
Gamma1	**1.881**	**1.164**	1.521	1.132
Gamma2	1.281	1.100	1.417	1.118

Bold numbers indicate the presence of a large Cp/Cp-s and Lp/Lp-s difference. We see a large difference between Cp/Cp-s and Lp/Lp-s during WM in the healthy but not the clinical group for the alpha1, alpha2, beta and gamma1 bands. The differences between Cp/Cp-s and Lp/Lp-s for alpha1, alpha2, beta, and gamma1 between the two groups were statistically significant.

populations, using the Man–Whitney test. The relationship between drug doses and SL, Cp and Lp were explored using Pearson's correlation coefficient. Finally, Fisher's test was employed to compare the differences between Cp/Cp-s and Lp/Lp-s of the two groups.

3. Results

As shown in Table 1, the clinical neuropsychological tests differed between patients and controls.

The results of the mean Cp and the Lp both as a function of threshold for alpha2 band at rest and during WM are shown in Fig. 1. There were significant between-group differences in alpha2 in addition to alpha1, beta and gamma1 bands (not shown) at rest and during the WM test. Specifically, the schizophrenia group showed a significantly lower Cp at rest and during WM across the range of thresholds from 0.025 to 0.05 at rest and 0.03 to 0.05 during WM for the alpha2 band. Lp for alpha2 activity was significantly higher in the schizophrenia group for thresholds ranging from 0.025 to 0.05 at rest. This finding was not present during WM.

Using the *t*-test, the mean values of SL, Cp, and Lp of patients and normals did not show significant differences. Importantly, using Pearson's correlation coefficient no significant correlation was found between chlorpromazine-equivalent drug doses and SL values, as well as the graph parameter values Cp and Lp of alpha2 band either at rest or during the WM task. To control for the potential influence of subtle (non-statistical) differences in mean SL between the groups, additional results were obtained using constant K values of 4, 5 or 6. Recall, that undertaking the analysis for fixed node degree K instead of fixed threshold T, and constructing appropriate reference graphs, preserving the "degree distribution", we normalize the networks and correct for the influence of any differences in the mean level of SL between the groups. Hence we focus on the ratio of Cp and Lp derived from the observed EEG data to matching values derived from the reference random networks (Cp-s and Lp-s): Cp/Cp-s and Lp/Lp-s.

Small-world network organization is evident when values of Cp/Cp-s are significantly greater than 1 whilst values of Lp/Lp-s are near the value of "1". Simultaneous values of Cp/Cp-s and Lp-/Lp-s significantly greater than 1 are indicative of ordered networks. The most striking findings in this study are at $K=5$, as presented in Table 2 and Fig. 2 where SWN organization is lower for the schizophrenia group. To render the differences between groups more clear, we subtracted the Lp/Lp-s from Cp/Cp-s separately for each group and the bands alpha1, alpha2, beta, gamma1. The resulting values differed significantly.

4. Discussion

In this study, scalp EEG data of subjects with schizophrenia without intellectual impairment and able to

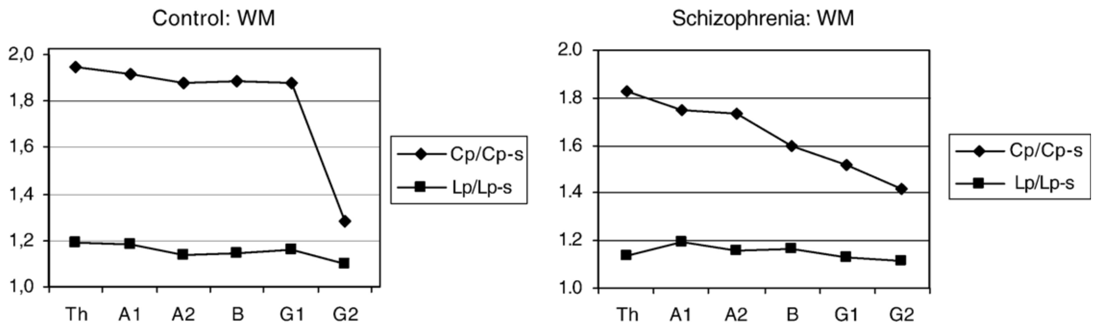

Fig. 2. The Cp/Cp-s and Lp/Lp-s during WM, as shown in Table 2, are represented. For theta, alpha1, alpha2, beta and gamma1 frequency bands, the control group show low values of Lp/Lp-s, near the value of one and the Cp/Cp-s high values, near the value of two. It is a sign of "small-world" organization. The group of the schizophrenic patients shows a similar organization only for the theta band.

work and healthy controls were evaluated at rest and during a WM task using measures derived from graph theory. Disturbed patterns of functional integration were found for alpha1, alpha2, beta and gamma1 EEG frequency bands in the schizophrenia group during WM. The "small-world" pattern was disrupted in the schizophrenic patients.

In a previous study, using the same method, we compared the SWN indices of the present control group (with high levels of education) to another healthy group but with less years of education, similar to the level of the present schizophrenia group (Micheloyannis et al., 2006). The less educated group had higher SWN indices than the educated group, whom in turn had higher SWN indices – according to the present study – than the schizophrenia group. As a corollary then, the schizophrenia group must clearly have lower SWN indices than the group matched to them in years of education. These findings are indicative of a partial disorganization of neural networks in schizophrenic patients because of the disease i.e. the present findings are supporting the hypothesis of a "partial functional disconnection".

Decreased thalamic input to the cerebral cortex, disturbed functional connectivity of cortical neurons – particularly in the prefrontal and temporal regions – and callosal connectivity have been observed in schizophrenics. The "hypofrontality" and evidences of thalamic dysfunction as well as cerebellum involvement using PET studies support this hypothesis. MRI studies showed fronto-temporal dissociation and anterior corpus callosum size in schizophrenics (Andreasen et al., 1998; Woodruff et al., 1997a,b). Recent such studies have investigated functional connections at rest and during cognitive tasks (e.g. Burns et al., 2003; Grecius et al., 2003; Langheim et al., 2006; Liang et al., 2005; Lowe et al., 1998; Mitelman et al., 2005b). The disconnection hypothesis requires further investigation in the light of such studies (Breakspear et al., 2003; Conklin et al., 2005; Friston, 2005).

The neurophysiological concept of functional connectivity expresses that the coordination of activity between different neural assemblies is required in order to achieve a complex cognitive task to complete a perceptual process (Lee et al., 2003; Strelets et al., 2002; Symond et al., 2005). Our findings are indicative of a partial disturbance of such assemblies in middle and higher frequencies and/or across regional and local regions. The group differences in graph parameters Cp and Lp and the diminishment of small-world organization in schizophrenia, especially during WM when compared to reference graphs, are indicative of this disorganization.

Using scalp EEG signals has some disadvantages such as the known volume conduction problem, the coarse spatial resolution of scalp EEG, and the influence of the reference electrodes. Comparisons between tasks and groups using the same procedures, diminishes these disadvantages. The WM evaluation has some limitations since some of the brain regions involved in WM (e.g. hippocampus) are too deep to influence directly the EEG and thus, the information is collected from the interplay of the regions involved. An additional point is the lack of a longitudinal aspect — i.e. whether changes in symptom severity over time may be associated with corresponding changes in SWN measures. Nevertheless, comparison of groups using the same procedure is assumed to give valuable information.

In regards to antipsychotic medication, the medication of our patients was in 2/3 of the cases atypical antipsychotics which may in fact act to correct functional connectivity (Cerdán et al., 2005). Both atypical and conventional neuroleptics have a "restorative effect", for the symptoms of the disease and it is likely that this occurs by targeting those areas involved in the disease process in the first place. There are also additional findings for improvements in neurophysiological functioning with medication (Breakspear et al., 2003; Cerdán et al., 2005; Schloesser et al., 2005). Importantly, the lack of a significant correlation between the (chlorpromazine-equivalent) medication doses and the SL, Cp and Lp strengths in our study argues against a direct treatment effect accounting for the between-group differences.

Small world networks have been shown to efficiently transfer information whilst simultaneously maintaining a local "working group" of neurons. That is, they satisfy the apparently competing needs for functional integration and functional segregation (Sporns et al., 2000; Strogatz, 2001). Small world functional connectivity has been previously described in different frequency bands of healthy, resting state MEG (Stam, 2004). Of particular interest are findings indicative of disconnection in Alzheimer disease similar to those in the present study (Stam et al., 2006). Our previous study comparing the neuronal organization related to the neural efficiency is indicative of the usefulness of the method to study brain function situations (Micheloyannis et al., 2006). The present findings of small-world network disturbances in schizophrenia are indicative of a partial disorganization of neural networks in this illness. To our knowledge, this is the first such study in schizophrenia research.

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