



Title	Working memory abnormalities in chronic interictal epileptic psychosis and schizophrenia revealed by magnetoencephalography
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学 位 論 文 名	Working memory abnormalities in chronic interictal epileptic psychosis and schizophrenia revealed by magnetoencephalography (慢性発作間歇期てんかん精神病と統合失調症における脳磁図を用いた作業記憶異常に関する検討)
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論 文 内 容 の 要 旨

[目 的]

Clinically, chronic interictal psychosis (CIP) closely resembles schizophrenia with a typical presentation as a paranoid hallucinatory syndrome, which is why it is also referred to as *schizophrenia-like psychosis of epilepsy* (SLPE). In addition, these disorders also converge on impairments in cognitive functions. Particularly in schizophrenia, deficits in working memory (WM) are considered a core cognitive abnormality of the disease. Despite the similarities, there is an ongoing debate as to whether CIP and schizophrenia share common pathophysiology. In this study we used magnetoencephalography (MEG) during a WM task performed by patients with CIP, non-psychotic epilepsy (nPE) and schizophrenia, and by healthy subjects, and focused on source-power changes in brain oscillatory activity. We aimed at determining functional cognitive abnormalities in CIP, and to assess whether these abnormalities are distinguishable from those seen in schizophrenia in terms of WM deficits. The working hypothesis was that patients with CIP and those with schizophrenia have similar patterns of abnormal oscillatory activity related to WM dysfunction based on converging clinical and neuropsychological features.

[方法ならびに成績]

Twelve patients with CIP, 14 patients with non-psychotic epilepsy (nPE), 14 patients with schizophrenia, and 14 healthy subjects participated in this study. The epileptic groups consisted of patients with secondary or cryptogenic focal epilepsy matched for age, gender, side of seizure foci, and type of epilepsy (i.e., temporal or frontal lobe epilepsy). Epilepsy diagnosis and seizure focus localization were determined on the basis of (1) seizure semiology, (2) findings from ictal or interictal scalp EEG, and (3) MEG dipole fitting or coregistration of spatially filtered MEG data with MRI results. Patients with postictal or brief interictal psychotic episodes, and psychoses in the context of status epilepticus or drug toxicity/withdrawal were excluded, as were patients with organic lesions other than intrinsically epileptogenic cortical dysplasia ($N = 2$) or hippocampal sclerosis ($N = 2$). Other exclusion criteria were: age older than 55 years, history of drug or alcohol abuse, and an IQ score below 70. Neuromagnetic data were recorded at 625 Hz with a bandwidth of DC-100 Hz using a 64-channel MEG system equipped with a whole-head array of first-order radial SQUID gradiometers (NeuroSQUID Model 100, CTF Systems Inc., Canada). Source imaging of MEG data in the time-frequency domain was performed using

multiple source beamformer (MSBF). We analyzed frequencies between 1 and 60 Hz (delta, theta, alpha, beta, and gamma). The beamformer three-dimensional images superimposed onto a standard anatomical magnetic resonance image revealed locations of the generators of the induced oscillatory activity in the specified frequency. These functional images were exported for further statistical analysis to the Brain Voyager QX software. A Talairach-transformed Montreal Neurological Institute (MNI) T1-weighted brain template was used, and the anatomical T1 coordinates in the statistical maps were transformed into Talairach coordinates to identify brain regions with significant between-group differences in source-power changes in changes across three groups: (1) patients with CIP versus patients with nPE, (2) patients with schizophrenia versus healthy controls, and (3) patients with CIP versus those with schizophrenia. Analysis of groups 1 and 2 focused on patterns of WM dysfunction, whereas analysis of group 3 tested whether CIP and schizophrenia differed in functional cognitive abnormalities. Correlation analyses were carried out to examine the association of medication dose with peak ERD/ERS values at sources with significant power changes in a given frequency band in patients with CIP and schizophrenia. Our main findings are: (1) patients with CIP have WM deficits involving a frontotemporal network, (2) the neurophysiological basis for these deficits is primarily changes in the alpha frequency band (8–13 Hz), and (3) patients with CIP and schizophrenia compare to each other with respect to the WM-compromising brain regions, namely, the right dorsolateral prefrontal cortex (DLPFC) and the left temporal cortex, although patients with schizophrenia manifested wider activation in prefrontal areas. In addition, our results showed that the two groups perform at equal levels on a visual-object WM task as far as answer correctness and reaction time are concerned. No correlation was found between ERD/ERS sources and chlorpromazine equivalents or antiepileptic drug plasma levels in either psychotic group. This indicates that medication did not influence our findings.

[総 括]

In this study we found a similar MEG pattern of right DLPFC and left temporal functional abnormalities in patients with CIP and those with schizophrenia during performance of Sternberg's visual WM task, which argues against the concept of CIP as a nosological entity different from schizophrenia. Consistent with this idea, recent studies have demonstrated that in addition to clinical features, the profile of neuropsychological impairment in CIP closely resembles that of schizophrenia, especially regarding temporal and prefrontal function. Structural MRI of patients with CIP and schizophrenia has further revealed that they share a similar topographic pattern of deficits in temporal and extratemporal cortical gray matter. Together, these data suggest that similar pathophysiological mechanisms may operate in these two disorders, and that frontotemporal dysfunction may be a key factor in the association between epilepsy and schizophrenia-like symptoms.

論文審査の結果の要旨

The pathophysiological mechanisms underlying a chronic schizophrenia-like psychosis in patients with epilepsy are unknown. Despite converging clinical and neuropsychological features, there is an ongoing debate as to whether chronic interictal psychosis (CIP) and schizophrenia share common pathophysiology. Since working memory (WM) deficits are considered a core cognitive dysfunction in schizophrenia, we attempted to determine cognitive abnormalities in CIP, and to assess whether these abnormalities are distinguishable from those seen in schizophrenia in terms of WM deficits. For that purpose, we used magnetoencephalography during a WM task performed by patients with CIP, non-psychotic epilepsy, and schizophrenia and by healthy subjects. Multiple-Source Beamformer and Brain-Voyager were used to detect between-group difference in brain oscillatory activity. In both patients with CIP and those with schizophrenia, we found dorsolateral prefrontal hyperactivation and left inferior temporal hypoactivation, as indicated by alpha event-related desynchronization (ERD) and synchronization (ERS), respectively. Direct comparison of CIP and schizophrenia patients rendered no difference in oscillatory activity source-power changes. Correlation analysis revealed that these results were not influenced by medication. Our findings indicate that like patients with schizophrenia, patients with CIP have functional cognitive abnormalities in the prefrontal and left temporal cortex, which supports the possibility that these disorders share common pathophysiology, and that frontotemporal dysfunction may be a key factor in the association between epilepsy and schizophrenia-like psychosis.

We consider that this is an interesting study that meets the requirements for the doctoral degree at Osaka University.

関連同期・脱同期を12人の慢性てんかん性精神病患者、14人の精神症状のないてんかん患者、14人の統合失調症患者、14人の健常者で比較検討したものである。空間フィルター法による解析を行った結果、慢性てんかん性精神病患者と統合失調症患者には共通して、前頭前野背外側において α 地域の事象関連同期が認められ、この部位における過活動が、また左下側頭葉には同帯域における事象関連同期が認められ、この部位における低活動が認められた。また相関解析では、これらの結果に薬物の影響は認められなかった。この結果より認知機能の異常について、慢性てんかん性精神病患者は統合失調症患者と同様に、前頭前野や左側頭葉にその関連が認められ、両疾患に共通している病態生理であり、てんかんと精神病症状の関連について前頭側頭機能不全を示唆することができた。

本研究は、慢性てんかん性精神病患者と統合失調症患者に対し脳磁図を用いて認知課題時の脳内の事象関連同期・脱同期を検討した初めての研究であり、その病態生理の解明に傍証を与えたものである。よって、本研究は大阪大学博士（医学）の学位授与に値すると考えられる。