



Decreased cortical complexity in methamphetamine abusers

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ARTICLE INFO

Article history:

Received 24 November 2010

Received in revised form 18 May 2011

Accepted 11 July 2011

Keywords:

Methamphetamine

EEG

Cortical dynamics

Approximate Entropy

ABSTRACT

This study aimed to investigate if methamphetamine (MA) abusers exhibit alterations in complexity of the electroencephalogram (EEG) and to determine if these possible alterations are associated with their abuse patterns. EEGs were recorded from 48 former MA-dependent males and 20 age- and sex-matched healthy subjects. Approximate Entropy (ApEn), an information-theoretical measure of irregularity, of the EEGs was estimated to quantify the degree of cortical complexity. The ApEn values in MA abusers were significantly lower than those of healthy subjects in most of the cortical regions, indicating decreased cortical complexity of MA abusers, which may be associated with impairment in specialization and integration of cortical activities owing to MA abuse. Moreover, ApEn values exhibited significant correlations with the clinical factors including abuse patterns, symptoms of psychoses, and their concurrent drinking and smoking habits. These findings provide insights into abnormal information processing in MA abusers and suggest that ApEn of EEG recordings may be used as a potential supplementary tool for quantitative diagnosis of MA abuse. This is the first investigation to assess the “severity-dependent dynamical complexity” of EEG patterns in former MA abusers and their associations with the subjects’ abuse patterns and other clinical measures.

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1. Introduction

The abuse of methamphetamine (“speed”) and its pure crystalline form (“crystal meth”, “ice”, or “glass”) has reached epidemic proportions. The estimated lifetime prevalence of methamphetamine abuse is 5.3% in the United States, and 33 states exhibited a 100% increase in the numbers of people admitted to treatment centers for methamphetamine abuse between the years of 1992 and 2001 (Office of Applied Studies, 2005). On the other side of the world, the United Nations reported that approximately 33.4 million people use methamphetamine in Asia, particularly in eastern and southeast Asian countries such as Japan and South Korea, where its abuse is one of the most pressing social concerns (Farrell et al., 2002; Chung et al., 2004; Kulsudjarit, 2004). These behaviors frequently lead to profoundly harmful social and public health consequences (Seivewright, 2000; London et al., 2004; Sekine et al., 2006). Despite the high prevalence and destructive effects of methamphetamine abuse, the long-term effects of methamphetamine on the neurodynamics of the cortical network are poorly understood.

Methamphetamine (MA) is a potent neurotoxin causing long-term damage to the central nervous system. Animal studies suggest that continuous administration of MA produces long-lasting reductions in striatal dopamine (DA) concentrations, DA transporter levels, and rate-limiting synthetic enzymes, as well as autophagocytosis of the neuritis and apoptosis of the DA neurons in the striatum (Ricaurte et al., 1980; Wagner et al., 1980; Villemagne et al., 1998). *In vivo* studies on acute neurobiological effects of MA in humans have documented marked alterations to the DA neurotransmitter systems and rates of neural metabolism in the cerebrum and the basal ganglia. Recent neuroimaging studies have shown that long-term use of MA decreases the density of DA transporters in reward circuits (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001a,b; Sekine et al., 2003) and the density of serotonin transporters in cortical regions (Sekine et al., 2006). In particular, long-term MA abuse is associated with glucose hypometabolism in the frontal regions (Kim et al., 2005b), low activity in the dorsolateral and ventromedial prefrontal cortices (Paulus, 2002), and cortical structural abnormalities of the medial temporal lobe and the cingulate-limbic cortex (Thompson et al., 2004; Kim et al., 2005a). These studies suggest that MA intoxication is not limited to the subcortical structures, but also extends to cortical regions.

Only a few studies have investigated patterns of the electroencephalogram (EEG) that characterize MA abusers to detect electrophysiological abnormalities of their cortical networks and their associations

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with behavioral factors, including reduced working memory performance (Newton et al., 2004). Power spectrum analysis revealed an apparent EEG slowing in MA abusers (Newton et al., 2003, 2004), but correlations with abuse patterns and social factors were not examined.

While pre-clinical and clinical investigations have shown that methamphetamine (MA) causes long-term damage to the DA reward circuits resulting in motor and cognitive deficits (Volkow et al., 2001b; Johanson et al., 2006; McCann et al., 2008), but little is known about dynamical disturbance of cortical network in MA abusers. The aim of the present study was to determine whether abstinent MA abusers exhibit alterations in complexity of the EEG. Tononi et al. (1998) suggested that optimal brain functioning requires the dynamic interplay between local specialization and global integration of brain activity. They proposed that this optimal state produces complex activity and that a neural complexity measure is capable of estimating the optimal balance between localization and integration of neural networks (Tononi et al., 1998; Tononi and Edelman, 1998; Sporns et al., 2000). Indeed, reduced complexity of EEG patterns has been reported in patients with Alzheimer's disease (Jeong et al., 1998; Abasolo et al., 2005), schizophrenia (Roschke et al., 1994; Breakspear et al., 2003; Paulus and Braff, 2003; Keshavan et al., 2004; Micheloyannis et al., 2006), and depression (Roschke et al., 1994; Thomasson et al., 2002; Bob et al., 2006; Fingelkurts et al., 2007), many of whom are hypothesized to suffer from reduced functional connectivity between cortical regions. A previous study also found that EEG complexity is reduced as sleep goes deeper and increased during REM sleep (Burioka et al., 2005b). Thus, in this study, we examined the interplay between the functional integration and segregation of cortical networks and consequently the efficiency of information processing the cortex through quantification of the complexity in EEG patterns in MA abusers.

To estimate complexity of EEG patterns in MA abusers, we used Approximate Entropy (ApEn), an information-theoretic measure of irregularity. ApEn can stably quantify the complexity of a noisy and short time series as in physiological recordings (Pincus, 1991; Pincus, 1995). Several studies have reported that ApEn can be used to discern various neuropsychiatric conditions such as Alzheimer's disease, coma (Abasolo et al., 2005; Lin et al., 2005), and epilepsy (Radhakrishnan and Gangadhar, 1998; Hornero et al., 1999; Burioka et al., 2005a). A previous study also reported that ApEn analysis of heart rate in cocaine abusers showed reduced complexity, suggesting that impaired function, isolation and network diminution are manifest across multiple axes (Newlin et al., 2000).

MA is known to induce a variety of symptomatic behaviors during intoxication or withdrawal that include irritability, anxiety, excitement, hallucinations, paranoia (both delusional and psychotic), and aggressive behavior. Social abnormalities such as criminal misconduct or sexual intercourse are also observed in MA abusers during MA intoxication. Psychotic behaviors of MA users are correlated with their ages, possibly associated with disturbance of neurotransmitters in cortical–subcortical circuits during the aging process (Chen et al., 2003). Another commonality found among MA abusers is the consumption of other substances such as alcohol and nicotine during MA intoxication. These multifaceted factors result in the difficulties in treating MA dependencies in abusers. Despite the prominent and detrimental effects of MA on the nervous systems and social behavior, few neuroimaging or electrophysiological studies have been performed to investigate the relationship between cortical alterations and critical factors including abuse patterns and social behaviors. Therefore, we aimed to determine the association between the complexity of EEG patterns in MA abusers and their drug abuse patterns.

2. Methods

2.1. Subjects

Currently abstinent MA abusers ($N = 48$, average age = 36.7 ± 5.8 years; range = 26–49 years, all males) and 20 control subjects ($N = 20$, average age = 34.5 ± 7.7 years,

range = 23–48 years, all males) were recruited from Bugok National Hospital in South Korea. The MA abusers were hospitalized patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Spitzer et al., 1994) criteria for lifetime MA abuse ($N = 31$) or dependence ($N = 17$). There were no significant correlations between abused and dependent patients in the period of MA use ($p = 0.970$), the age of first abuse ($p = 0.437$), and the cumulative amount of MA ($p = 0.820$). All subjects were men only because of extensive prior evidence that MA-induced neurotoxicity is sex-specific, particularly greater in men than in women (Wagner et al., 1980; Dluzen et al., 2002; D'Astous et al., 2005; Kim et al., 2005b). They showed no signs of neurological abnormalities such as seizure, dyskinesia, or coma. MA abusers were excluded if they had a past or present history of a comorbid psychiatric illness except substance abuse (DSM-IV axis I or II diagnosis). After complete description of the study, written informed consent was obtained from all subjects prior to participation, in compliance with the procedures of the Ethics Committee of the Bugok National Hospital.

For the accuracy of patient profiles, detailed clinical information on MA use patterns was obtained through interviews with the abuser and his family members as well as by referral to patient medical records using the Structured Clinical Interview for DSM-IV (SCID). The clinical information includes the period of MA use, the age of first abuse, and other substance abuse such as nalbuphine, nicotine, alcohol, and inhalant solvents. A heavy drinker was defined as consuming on average more than four drinks daily, and a heavy smoker was defined as smoking two or more packs per day. We also obtained the clinical information about sexual exploitation and criminal records. In the MA binge abuse cycle, during the initial response of the rush, the MA abuser's heartbeat races and metabolism, blood pressure, and pulse increase. During this "high," they partake in a wide range of risky behaviors that include having an increased level of sexual behavior (sexual exploitation) and that incorporate unsafe behaviors, driving, or committing crimes.

These evaluations were performed within 3 days of the EEG examination by a trained research psychiatrist blind to the EEG data. All MA abusers had taken MA intravenously for at least 2 years, and each subject had been abstinent for more than 6 days at the time of the EEG examination. The drug was only to be taken intravenously since this is the most common method of use in South Korea (Chung et al., 2004). Urine tests were performed just prior to EEG recording for the proof of negative current intoxication.

The controls were recruited from the local community in Bugok and Busan, South Korea. They were group-matched with the MA abusers by age, sex, and socioeconomic status (income: <\$25,000; education: college or high school graduates). They had no history of MA use or abuse of other substances. None had a personal or familial history of psychiatric illness based on an unstructured interview conducted by a trained psychiatrist. No subjects could be taking medication at the time of the study, and all had negative urine toxin screens to ensure the absence of psychoactive drug use. Controls were excluded if they reported drinking alcohol more than once per day or >40 g per week or reported smoking more than 10 cigarettes per day.

After evaluation of the EEG, IQ was measured for all subjects as the psychometric index of intellectual functioning (Sattler, 2001) using the Korean–Wechsler Adult Intelligence Scale (K-WAIS)-Short form (Yeom et al., 1992). The four sections of this shortened test required the subjects to answer questions about the information that was provided, picture completion, arithmetic, and block designs. It was revised and given in Korean. The estimated IQ score was normalized according to the respondent's age.

2.2. EEG recording

EEGs were recorded from 16 channels using EEG amplifier (Model 9 EEG Grass Instrument Co.) in the morning (10:30–11:30 AM) to minimize the circadian and homeostatic modulation of wakefulness (Taillard et al., 2003). Subjects were instructed to lie with their eyes closed, think of nothing in particular, and not fall asleep in a sound-attenuated room. Ag-AgCl electrodes were placed according to the international 10–20 System. Data were collected using a Cz referential montage and were digitized at 200 EEG samplings per second which were obtained by the QINGY, MASS system (bandpass filtered 0.3–70 Hz). At least 20 min of EEG activity was recorded and a minimum of 30 s of artifact-free EEG was selected by visual inspection and then was analyzed. To obtain maximally long stationary EEG data, the first 2 min of data were discarded. Three epochs of 10-s of EEG recordings were randomly selected to estimate the ApEn values and their means were used. An additional three epochs of 10 s of EEG recordings were randomly selected. We found that the ApEn values were robust to epoch selection and the results were consistent in that MA abusers exhibited decreased ApEn values compared with those of the healthy subjects in all 15 channels ($p < 0.001$) except F4 ($p > 0.05$). There was no effect of epoch selection ($p > 0.3$). Using stationary EEG data and random epoch selection might help to control the possibly variable cognitive processes involved in the resting state. Moreover, robustness of the ApEn results to epoch selection might indicate that a rather consistent cognitive state was maintained in our resting supine condition.

2.3. Approximate Entropy analysis

The recorded EEG data were reformatted offline to compute the power spectrum (see supplementary material for power spectrum analysis and results) and ApEn values. First introduced by Pincus, the ApEn is an index that quantifies the irregularity or complexity of a dynamical system (Pincus, 1991). It is particularly efficient to use with short and noisy time-series data such as physiological data. The ApEn measures the logarithm frequency with which neighborhoods of temporal patterns of length m that are within a certain distance (r) in phase space remain close together ($<r$) for patterns that are augmented by

one point of time (i.e., for patterns of length $m + 1$) (see supplementary material for detailed algorithm). Thus, smaller values of the ApEn imply stronger regularity or persistence in a time series. Conversely, larger values of the ApEn signify the presence of greater fluctuations, or irregularity, in a time series. ApEn values of EEG are possibly determined by the balance between the functional segregations and integrations of cortical regions.

2.4. Statistical analysis

Group comparisons of the demographic variables were conducted using *t*-tests. The average values of the ApEn of the EEG in the MA-dependent group and the control group are presented as “mean \pm standard error” across all subjects. The one-way analysis of variance (ANOVA) procedure was used to compare the severe and moderate MA abusers and the control group. If the results from the ANOVA achieved statistical significance ($p < 0.05$), multiple comparisons were performed afterwards (LSD test). The effects of abuse patterns, clinical/social measures, and comorbidity on the cortical complexities of MA abusers were evaluated separately using *t*-tests. Pearson's correlation coefficient was used for the linear correlation analysis, while a statistical software package (SPSS 11.0.1, SPSS Inc., Chicago, IL, USA) was used. Statistical significance was defined to have an alpha level of 0.05. Adjacent electrodes were grouped for pair-wise correction for multiple comparisons (Fp1–F3, Fp2–F4, F7–T3, F8–T4, C3–P3, C4–P4, T5–O1, T6–O2).

For normality test of the data, we used the ‘Kolmogorov–Smirnov test’ before ApEn analysis and did not use outliers to maintain the normality of the data. Outliers were detected through visual examination of the scattergrams and normal probability distribution plots. Fewer than three channels out of the total electrodes for each subject were removed from the study through the normality test. In comparisons of two samples (*t*-test), the variances of some EEG data are not equal between the groups. Thus, we employed ‘Levene's Test for Equality of Variances’ to select a proper statistic. Levene's Test with $p < 0.05$ indicated that variance was not homogeneous. If Levene's Test indicated that variances were homogeneous between groups, then Student's *t*-test was used. Otherwise, Welch's *t*-test was used. Welch's *t*-test is a variation of Student's *t*-test intended for use with two samples having unequal variances.

3. Results

3.1. Decreased cortical complexity of MA abusers

Table 1 summarizes the demographic characteristics displaying the similarities between the former MA abuser and control groups. The two groups did not differ significantly in age, but there was a difference in their IQ levels ($p < 0.05$). To assess the possible presence of abnormal complexity of cortical activity in MA abusers, we estimated the ApEn values of EEG patterns in 48 MA abusers and compared them with those of 20 control subjects. We found that MA abusers exhibited decreased ApEn values compared with those of the healthy subjects in all 16 channels (Student's *t*-test; $p < 0.00001$) (Fig. 1). We also calculated a multivariate general linear model (dependent variables: ApEn values of 16 channels, fixed factor: MA abusers/controls, covariate: IQ, smoking amount). Including IQ and smoking amount as a covariate decreased the statistical difference between MA and control groups. However, most channels were still significantly different between groups (Fp1, T6, O1, O2, $p < 0.0001$; T5, $p < 0.001$; Fp2, P3, P4, F7, F8, T3, $p < 0.01$; F3, C3, C4, T4, $p < 0.05$).

To investigate the effects of severity of MA abuse on the ApEn values of EEGs, we classified the MA group into two separate subgroups based on the period of MA abuse and recent intake amount: a moderate and a severe MA abuse group. The “severe MA abusers” (average age was 37.7 ± 5.52 years; age range: 29–49 years; the average cumulative amount of MA was 14.3 ± 15.2 g) consisted of subjects who used MA for at least 6 years or more than 0.75 g of MA injection in the most recent year, compared with ‘moderate MA abusers’ (average age 30.6 ± 3.31 years; age range 26–35 years; average MA cumulative amount 0.92 ± 0.52 g). ANOVA analysis revealed that severe and moderate MA abuser groups and the control group exhibited significant differences in ApEn values in all channels ($p < 0.0001$), indicating the significant influence of the duration of MA abuse and the dosage received during the previous year. To control the possible age difference between groups, we applied an analysis of covariance (ANCOVA). We selected age, IQ, and smoking amount as covariates. All channels except F4 were still significantly different between severe and moderate MA abuser and control groups (Fp1, T6, O1, O2, $p < 0.0001$; P4, T3, T5, $p < 0.001$; F3, C3,

Table 1
Demographic profile of the study samples.

	MA group ($n = 48$)	Control group ($n = 20$)
Age (years)	37.0 (5.8)	34.5 (7.7)
IQ (points)	97.8 (6.1)	116.5 (5.3)*
Duration of MA use (years)	11.8 (6.5)	N/A
Abstinence period (days)	30.5 (27.2)	N/A
Total amount in a previous year (g)	1.125 (1.095)	N/A

Means are presented with standard deviations in parentheses.

* $p < 0.05$.

P3, F7, F8, $p < 0.01$; Fp2, C4, T4, $p < 0.05$). In post-hoc analyses, the significant differences were found between the moderate and the severe MA groups in the left cortical areas (LSD test; F3, $t(43.999) = 51.638$, $p = 0.042$; C3, $t(44.421) = 65.289$, $p = 0.031$; P3, $t(44.793) = 40.909$, $p = 0.049$; F7, $t(42.743) = 30.308$, $p = 0.043$; T5, $t(41.146) = 25.373$, $p = 0.037$; O1, $t(44.979) = 23.934$, $p = 0.030$). The severe MA abuse group had significantly lower ApEn values than the control group in most channels (Fp1, Fp2, C3, P3, F7, F8, T3, T5, T6, O1, O2, $p < 0.005$; F3, C4, P4, T4, $p < 0.05$). The moderate MA group exhibited significantly decreased ApEn values of the EEG in Fp1 channel compared with the values of the control subjects (LSD test; $t(43.592) = 24.366$, $p < 0.0001$) (Table 2). These results indicate the period-dependent, MA-induced reduction in cortical complexity in the MA group (Fig. 2).

3.2. Correlations of ApEn values with clinical/social measures

To investigate the associations between ApEn values and clinical factors, we divided MA abusers into several groups according to their sexual histories, their drug-related criminal records, and if they experienced common symptoms of psychosis (such as hallucinations or delusions). We found no significant correlation between the ApEn value of the EEG and the age at which a subject first used MA. The MA patients exhibiting delusions or hallucinations ($N = 37$) had higher ApEn values in most channels than the abusers without these symptoms (Fp1, Fp2, F3, F4, C4, P4, F7, F8, T3, T4, T5, T6, O1, O2; $p < 0.05$) (Fig. 3(a)). MA patients who participated in sexual intercourse during their MA binges ($N = 25$) had higher ApEn values in the centro-parietal areas than the other abusers who did other activities (such as driving cars or playing video games) (C3, P3; $p < 0.05$) (Fig. 3(b)). The MA patients with drug-related criminal records ($N = 21$) had lower ApEn values than the other subjects (all channels, except Fp1 and F3; $p < 0.05$) (Fig. S2). However, the MA patients with other types of criminal records had lower ApEn values that were limited to the centro-parietal areas (C4, P4; $p < 0.05$). These results demonstrate that reductions in cortical complexity (measured

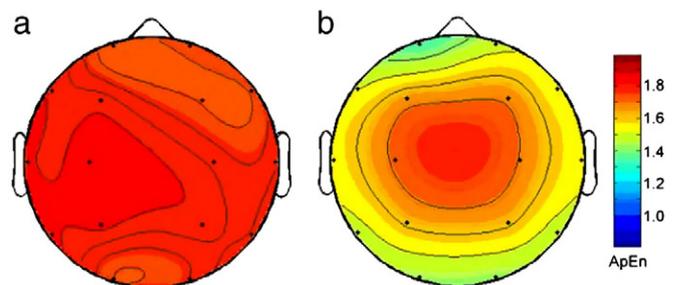


Fig. 1. Topographic map of average ApEn values in (a) healthy subjects and (b) MA abusers. MA abusers exhibited reduced ApEn values compared with healthy subjects in all channels (Student's *t*-test; $p < 0.00001$).

Table 2

Significant differences of ApEn values of EEGs in MA abusers and controls. Group 1 corresponds to a group having lower ApEn values than those of group 2.

Group 1	Group 2	
MA*	Control	Fp1, Fp2, F3, C3, P3, P4, F7, F8, T3, T4, T5, T6, O1
Severe-MA*	Moderate-MA	F3, C3, P3, F7, T5, O1
No psychosis*	Psychosis	Fp1, Fp2, F3, F4, C4, P4, F7, F8, T3, T4, T5, T6, O1, O2
No sex acts*	Sex acts	C3, P3
Drug-related	No criminal record	Fp2, F4, C3, C4, P3, P4, F7, F8, T3, T4, T5, T6, O1, O2
Criminal records*		
Heavy smoking*	Light smoking	C4, P4, F8, T4, T5, T6, O1, O2
No nalbuphine*	Nalbuphine	Fp2, F4, C3, C4, P3, P4, F7, F8, T3, T4, T6, O2

Severe-MA: 6 or more years of MA abuse or taking at least 0.75 g of MA in the previous year.

Moderate-MA: under 6 years of MA abuse and taking less than 0.75 g of MA in the previous year.

Heavy smoking: More than or equal to two packs/day.

Light smoking: Less than two packs/day.

* $p < 0.05$.

by the ApEn values of the EEGs) of MA abusers are associated with the pathological behaviors that occur during MA abuse.

3.3. Correlation of the ApEn values with comorbidity

We determined the relationship between the ApEn values of the EEGs in MA abusers and the presence of comorbidity of other substance abuse. Although other co-morbid abuse of inhalant solvents ($N = 7$) did not have an effect on the ApEn values, we found heavy smoking ($N = 5$) (more than or equal to two packs/day) decreased the ApEn values in the right frontal and central areas and both sides of the temporal and occipital areas (C4, P4, F8, T4, T5, T6, O1, O2, $p < 0.05$) (Fig. S3). The ApEn values revealed that MA abusers who were heavy smokers exhibited greater cortical dysfunctions than those who smoked fewer cigarettes or did not smoke at all. The abuse of nalbuphine hydrochloride or other similar opioid medications ($N = 7$) increased the ApEn values in the global cortical areas (Fp2, F4, C3, C4, P3, P4, F7, F8, T3, T4, T6, O2; $p < 0.05$) (Fig. 4).

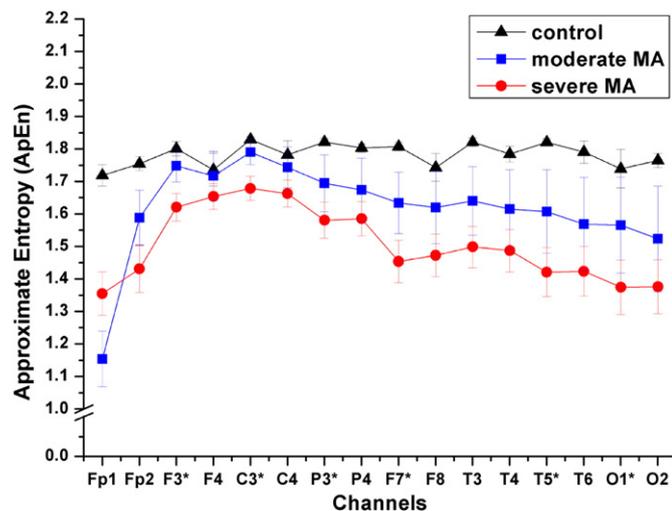


Fig. 2. ApEn values of the EEG in control, moderate MA abuse, and severe MA abuse groups. Significant differences were found in cortical regions marked with an asterisk (*) between the moderate and the severe MA user groups (F3, C3, P3, F7, T5, O1; $p < 0.05$).

4. Discussion

In the present study, we detected significantly reduced ApEn values of EEG patterns (i.e. cortical complexity) in former MA abusers in the global cortical regions compared with those of healthy subjects. Within the MA abuser group, severe MA abusers had more disproportionate reductions in cortical complexity compared with moderate MA abusers. Although the EEG has a poor spatial resolution and possibly topographical implications of these findings must be interpreted with extreme caution, this reduction was more prominent in fronto-temporal and occipital regions. MA patients that suffered from delusions and hallucinations or those that participated in sexual intercourse during MA intoxication exhibited increased levels of cortical complexity compared with those MA abusers that had not experienced similar psychotic symptoms or sexual intercourse during MA intoxication. MA patients having histories of drug-related criminal activities had the most decreased cortical complexity among the MA abusers. The MA abusers who smoked heavily had decreases in cortical complexity in the right frontal, central, temporal, and occipital areas. The subjects concurrently using nalbuphine hydrochloride had increases in cortical complexity in most areas among the other MA users. These findings indicate overall reductions in dynamical complexity in the cortical networks of MA

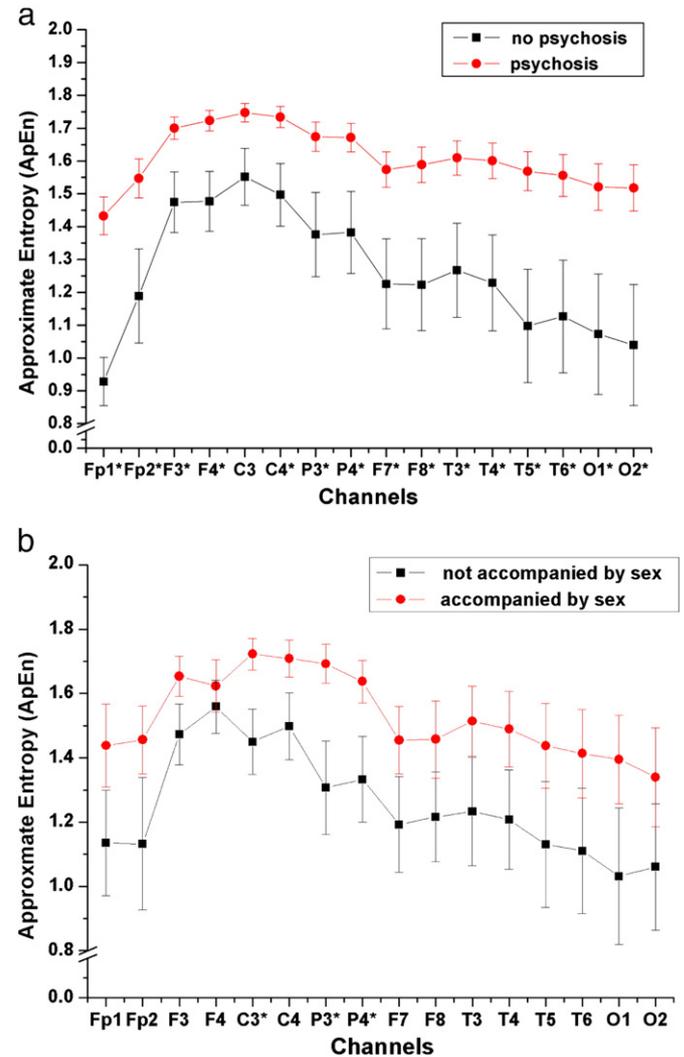


Fig. 3. ApEn values of the EEG correlated with (a) the presence of psychoses and (b) sexual intercourse during MA intoxication. The asterisk (*) indicates significant differences in ApEn values ($p < 0.05$).

abusers, possibly due to the severe and long-lasting presence of toxins in the monoaminergic neurotransmitter systems of the brain in MA abusers. To the best of our knowledge, this is the first investigation to assess the “severity-dependent dynamical complexity” of EEG patterns in former MA abusers and their associations with the subjects’ abuse patterns and other clinical measures.

ApEn reflects the dynamic balance between the functional integration and segregation of neural networks (Pincus and Goldberger, 1994; Tononi et al., 1994). ApEn appears to decrease when the functional cortical network is isolated or decoupled, and this reduced integration leads to hypoactivity, or slow signal transmission in the cortical networks (Pincus, 1994). This reduction in cortical complexity, particularly in the temporal and frontal regions, probably stems from the anatomical and functional disconnections among the regions that are most affected by the long-term toxicity of MA. This speculation may be consistent with the decreases in the metabolism rates of frontal white matter in MA abusers, and it suggests that persisting deficiencies can be found in the frontal lobes (Kim et al., 2005b). The frontostriatal circuit might be affected in MA abusers so the decreased striatal metabolism rates cause the lower levels of metabolism in the frontal cortical regions. This hypo-metabolism found in cortical regions possibly decreases the integrations of the neural networks. This in turn leads to the isolation or decoupling of the network.

Alternatively, the reductions in dynamical complexity of EEG patterns may reflect the toxicity of MA to several cortical monoaminergic neurotransmitter systems such as dopamine and noradrenalin, and thus reduced local activities of cortical regions. The most prominent and toxic effects are on the neurites of dopaminergic neurons in the deep brain including the striatum, caudate, and putamen (Kraemer and Maurer, 2002; Kita et al., 2003). Brain damage by MA is not limited to deep brain structures, but also extends to global cortical areas (Ciraulo et al., 2003; Kim et al., 2005a). The involvement of dopamine in the process of drug addiction is likely to be accompanied by functional and structural changes to the circuits, including the cortical areas. The vast damage of cortical and subcortical regions to which these monoaminergic systems project as found in previous studies may account for the reductions in global dynamical complexity observed in the former MA abusers of our study. Regardless of the resulting reductions in dynamical complexity that might be consequences of MA abuse on a functionally coupled neural system or the drug’s comparable effects on multiple monoamine systems, the estimated duration and amount of MA abuse

correlated strongly with global and dynamical EEG complexity across all portions of these monoaminergic and functional networks. These findings suggest that the duration and amount of exposure to MA accounts for a substantial amount of variance found in the severity of its long-term and system-wide neurotoxic effects in people.

In previous reports, delusions and hallucinations found in MA abusers were associated with abnormalities in the dopamine receptors or transporters of the caudate, putamen, and nucleus accumbens (Wada and Fukui, 1990; Sekine et al., 2001). The ApEn revealed that MA abusers exhibiting delusions or hallucinations had more complex cortical activity than the abusers without these psychotic symptoms. It seems that psychotic symptoms might not only explain certain dopaminergic system deficits, but the presence of these symptoms might also be the reason for the reorganization or partial recoveries of the deficits (Lautenschlager and Forstl, 2001; Kato et al., 2006) resulting from the toxicity of the drug and the damage to the cortical and sub-cortical systems, such as the serotonergic system, stemming from the psychoses initiated by using MA (Sekine et al., 2006).

Elevated complexity in EEG patterns mainly in the left centroparietal areas was found in those MA abusers that participated in sexual intercourse during their MA binges. Previous reports have suggested that the parietal regions are associated with erotic, especially visual, stimuli (Montorsi et al., 2003; Mouras et al., 2003). Our results suggest that the sexual intercourse that occurs concurrently with MA abuse is, to some extent, associated with relatively intact brain function, rather than a simple recreational behavior. Further investigation is required to examine not only former abusers but also current and potential abusers to confirm the measure’s diagnostic power.

Our findings must be interpreted in light of the limitations of this study. First, the precise mental processes during resting remain essentially uncontrolled. Different mental states might have influenced the measured entropy. This is probably the main limitation for utilizing resting state dynamics. However, random mind wandering could be canceled out in between-subjects level statistics. Second, the duration and amounts of MA use were determined by retrospective self-reports, which have limited validity and precision. Third, the decision to study only males, who likely are more susceptible than are women to the neurotoxic effects of methamphetamine, limited the generalizability of our findings to men only. Fourth, detailed neuropsychological testing was not conducted, and therefore the functional correlates of the altered EEG complexity patterns detected in this study could not be assessed. Finally, although we excluded subjects with extensive nicotine or alcohol use, the methamphetamine abusers likely consumed larger amounts of other drugs during their lifetimes than did the comparison group, thereby confounding our ability to attribute the causes of hypoactivity to MA alone. Nevertheless, the complexity analyses from our EEG screenings might provide insights into how information is abnormally processed in the cortical networks of MA abusers. This study suggests the possibility of dynamical complexity measures like ApEn as a potential, supplementary quantitative diagnostic tool for MA abuse.

Acknowledgments

The authors thank Mr. Seung Min Shin for his technical assistance of EEG recordings. This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST) (No. R01-2007-000-21094-0 and No. M1064400013-06N4400-01310).

Appendix A. Supplementary data

Supplementary data to this article can be found online at [doi:10.1016/j.psychres.2011.07.009](https://doi.org/10.1016/j.psychres.2011.07.009).

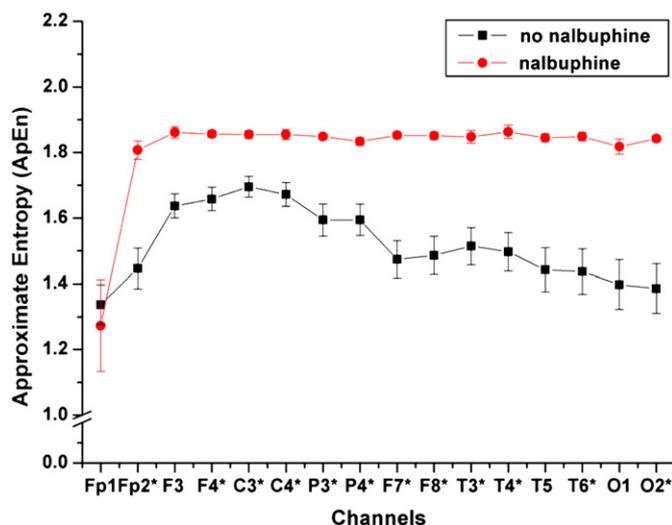


Fig. 4. ApEn values of MA abusers correlated with the presence of nalbuphine abuse. The asterisk (*) indicates significant differences in ApEn values ($p < 0.05$).

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