DRUG POLYCONSUMPTION IS ASSOCIATED WITH INCREASED SYNCHRONIZATION OF BRAIN ELECTRICAL-ACTIVITY AT REST AND IN A COUNTING TASK

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Drug abusers typically consume not just one but several types of drugs, starting from alcohol and marijuana consumption, and then dramatically lapsing into addiction to harder drugs, such as cocaine, heroin, or amphetamine. The brain of drug abusers presents various structural and neurophysiological abnormalities, some of which may predate drug consumption onset. However, how these changes translate into modifications in functional brain connectivity is still poorly understood. To characterize functional connectivity patterns, we recorded Electroencephalogram (EEG) activity from 21 detoxified drug abusers

and 20 age-matched control subjects performing a simple counting task and at rest activity. To evaluate the cortical brain connectivity network we applied the Synchronization Likelihood algorithm. The results showed that drug abusers had higher synchronization levels at low frequencies, mainly in the θ band (4–8 Hz) between frontal and posterior cortical regions. During the counting task, patients showed increased synchronization in the β (14–35 Hz), and γ (35–45 Hz) frequency bands, in fronto-posterior and inter-hemispheric temporal regions. Taken together 'slow-down' at rest and task-related 'over-exertion' could indicate that the brain of drug abusers is suffering from a premature form of ageing. Future studies will clarify whether this condition can be reversed following prolonged periods of abstinence.

Keywords: Addiction; polydrug use; EEG; resting state; synchronization; functional connectivity.

1. Introduction

Drug addiction is at the root of one of the most severe public health problems, with extensive social and individual consequences, including family disintegration, loss of employment, failure in school, domestic violence, child abuse, mental health disorders and other diseases (HIV, Hepatitis, etc.), and massive economic costs (Office of National Drug Control Policy, 2004). Drug addicts are often polydrug users,[1] the typical individual trajectory starting with alcohol and cannabis consumption during adolescence, and subsequently escalating to heavier substances, including amphetamines, heroin, cocaine.

Drug addiction has been associated with a broad range of cognitive deficits in domains, including emotional regulation and motivation, attention and flexibility, working memory, learning, and decision making.[2] Neurophysiological studies showed that drugs of abuse exert their reinforcing and addictive effects by acting on the mesolimbic and mesocortical dopamine-mediated reward system either directly,[3] or indirectly, through other neurotransmitters e.g. glutamate, γ-aminobutyric acid, opioids, acetylcholine, cannabinoids and serotonin in the reward circuit[4] (see for a review). Furthermore, chronic drug abuse affects function in dopaminergically innervated corticolimbic areas, including the orbitofrontal and anterior cingulate cortices, which mediate processing of reward salience, motivation, and inhibitory control.[2]

Structural imaging studies have shown up to 20% loss in gray matter density or thickness at various prefrontal areas, including dorsolateral prefrontal, anterior cingulate and orbitofrontal cortices, across addiction populations, sometimes lingering after several years of abstinence.[2] Consistent with neurophysiological studies, recent neuroimaging evidence showed that drugs of abuse are associated with significant alterations in extensive areas of the cortex, especially in the frontal and temporal areas.[5] Compelling evidence suggests that drugs may cause orbital cortex dysfunction and contribute to the transition to drug addiction, while even brief periods of drug exposure can lead to long-lasting functional and structural deficits associated with the orbito-frontal cortex.[6] In addition, abnormalities in drug abusers may predate drug abuse onset, pointing to a possible proneness of these subjects to slide towards drug addiction.[7] Electrophysiological studies of drug abuse have mainly been devoted to the analysis of band-power modifications in various forms of addiction. Enhanced power in the α frequency band (8–12 Hz) was shown in associations with cocaine abstinence relative to a control group.[8] Substance-dependent subjects have also consistently been associated with increased power in the β frequency range (13–25 Hz).[9–11] However, in most studies, β power was associated neither with substance abuse variables, e.g. length of exposure to drugs, time since last use of drugs, age or frequency of drug use, nor with clinical symptoms such as the severity of craving.[12] For instance, in cocaine withdrawal patients, resting absolute lower β power in the left temporal region and δ power (0.5–4 Hz) in the right hemisphere temporal region, was shown to increase with drug abstinence duration,[13] suggesting that chronic cocaine use may be characterized by electrophysiological abnormalities persisting during short-term abstinence. These results suggest that Electroencephalogram (EEG) power may be more related to pre-morbid individual differences rather than to the effects of drug abuse.[12]

1.1. *Functional brain connectivity and drug addiction*

Drug consumption initiates a broad reorganization of cortical activity, which goes beyond the activity in the reward-related neural circuit.[14] Thus, a sensible way to understand the pattern of reorganization of activity involves studying connectivity between distant brain regions.[15,16]

Functional connectivity, i.e. the temporal correlation between spatially remote neurophysiological events,[17] is believed to play a prominent role in such reorganization and is useful in quantifying disturbances in the coordination of activity between different neural systems associated with psychiatric or neurological pathology.[18–23]

Functional imaging studies of resting-state functional connectivity in drug addiction generally pointed at a decrease in functional connectivity. An inverse correlation between dorsal anterior cingulate cortex–striatal (ACC) connectivity and severity of nicotine addiction was found in cigarette smokers. The coherence strength of several ACC connectivity paths was significantly boosted by the use of a nicotine patch.[24] In abstinent smokers, withdrawal symptom improvement after nicotine replacement therapy was associated with altered functional connectivity within the default mode network, with increased inverse correlation between the executive control network and the default mode network, and with altered functional connectivity between the executive control network and regions mediating reward.[25] Decreased functional connectivity was also reported for other forms of addictions, including cocaine[26,27] and heroin addiction.[28,29] Furthermore, a recent functional magnetic resonance study showed reduced prefrontal interhemispheric connectivity in cocaine-dependent participants relative to control subjects, in a network comprising bilateral lateral frontal, medial premotor, and posterior parietal areas.[30]

The sort of connectivity measured by functional brain imaging only captures slow stationary correlations between blood flow amplitudes at different brain sites. Rapid and transient synchronization between distant brain regions can be measured using electrophysiological techniques.[31,32] Long range synchronization between distant neuronal populations has been proposed as an important brain mechanism for communication and information integration.[33–35] Binding phenomena in perception[36] or the formation of new memories[37] seem to be based on synchronization of electrical activity, between two brain regions, at specific frequency bands. Significant deviations from connectivity patterns seen in healthy subjects have been associated with various pathologies, e.g. epilepsy, Parkinson's disease, schizophrenia, dementias, traumatic brain injury, and compensatory strategies following brain damage.[38–47]

Only few electrophysiological studies analyzed functional connectivity in drug addiction. Early studies used coherence analysis, a technique that focuses on pairwise correlations of power spectra obtained from different electrodes. Coherence is a measure of the functional interactions between brain areas at different frequency bands. One study compared the spatial organization of electrophysiological activity of alcoholics, heroin addicts and healthy controls.[48] Changes in spectral-coherence characteristics were revealed at all frequency bands, with maximal changes at θ frequencies in drug addicts and in narrow-frequency α subranges in alcoholics. Ethanol and heroin consumers were characterized by different effects in the β band (19–21 Hz). Polysubstance abusers have been associated with reduced interhemispheric δ and θ bands, and frontal β band coherence.[9] Most recently, heroin-dependent subjects, with a two week abstinence period, were found to have increased left fronto-occipital intrahemispheric γ coherence, as well as higher relative $\beta 2$ power, compared to control subjects.[12]

Fingelkurts and colleagues used structural synchrony analysis,[49] to evaluate connectivity in a group of opioid-dependent patients during acute dependence[15] and short-term withdrawal.[50] Opioid-dependent patients had significantly decreased remote connectivity at rest, during acute opioid influence,[15] but abnormally enhanced during short-term withdrawal, i.e. after a two week detoxification period,[50] for both α and β frequencies. For withdrawal subjects, the number and strength of remote functional connections, was significantly higher in patients than in healthy controls, most prominently at β frequencies and to a lesser extent in the α range, particularly at frontal scalp locations, but also in central-temporal, left occipital and parietal cortical areas. In addition, functional connectivity measures

correlated with severity of opioid withdrawal patients with the strong withdrawal symptoms having denser and stronger synchronicity between cortical areas than patients with mild withdrawal symptoms. The authors interpreted the results for acute subjects as reflecting the disorganization and relative lack of integration of different cognitive functions reported in the acute phase of opiate abuse.[51] The enhanced synchronicity reported for withdrawal patients, particularly within frontal areas, was suggested as the possible underlying activation mechanism of emotional attention subserving drug-related cognitive processes including chronic opioid- related thought maintenance and craving urges.[50]

Whether the pattern of abnormal synchronization associated with drug administration persists over periods longer than the short-term withdrawal considered in Ref. 50, and whether hypersynchronization is observed for both resting brain connectivity and task-induced activations is still unclear.

In the present study, we addressed these two issues by investigating long-range synchronization in a population of polydrug users having undergone a three-month detoxification period. Synchronization likelihood (SL) is a method based on the concept of generalized synchronization which detects nonlinear and linear dependencies between two signals.[52] It is a robust algorithm which overcomes the limitations of linear approaches, which has widely been used as a functional connectivity measure in different pathologies.[47–49] SL could be complementary to other measures of functional connectivity such as mutual information and phase synchronization.

The SL main virtue is that it is able to give robust information about the general patterns of functional connectivity between two relatively long time series. However, it is not as useful as phase synchronization (for example) for short time series.[53]

Since we are mainly interested in differences between controls and patients for relatively long time series (50 s), SL was the chosen metric for the present study.

We expected differences between controls and patients in the ways in which brain regions are coordinated both at rest and while performing a very simple cognitive task (counting). Different topographical and/or frequency patterns of connectivity would imply a distinct functioning manner for controls and polydrug abusers, and would allow characterising the brain networks affected by drug abuse.

2. Methods

2.1. *Subjects*

A total of 54 male patients (age range 21–61 years) from the *Centro Terapéutico Barajas, Madrid* participated in the study. Patient diagnosis was established according to the International Statistical Classification of Diseases and Related Health Problems (10th Revision, viz. F19 "Mental and behavioral disorders due to psychoactive substance use"). This category should be used when two or more psychoactive substances are known to be involved, but it is impossible to assess which substance is contributing most to the disorders. It should also be used when the exact identity of some or all the psychoactive substances being used is uncertain or unknown, since many multiple drug users themselves often do not know the details of what they are taking. In addition, only patients with an abstinence period from psychoactive substances of at least three months were included in the study. During that period of abstinence none of the subjects consumed any substances. To have certainty of this fact, the participants were hospitalized in the Therapeutic Center where they passed periodic urinalysis.

A total of 29 age-matched control subjects were recruited for the study. An individual interview verified that they had no past history of psychoactive substance consumption.

Table 1 summarizes the demographic information for both groups.

2.2. *Task*

All participants underwent a 5-min resting state condition and a counting forward task. In the counting forward task, subjects were asked to mentally count forward, trying to follow a 1 Hz rate. After 30 s, in order to validate the test, participants were asked to stop counting, the result being correct if the number was 30 ± 5. Under both conditions, subjects were asked to keep their eyes closed.

Before the EEG recording, all participants gave informed consent to participate in the study. The study was approved by the Local Ethics Committee.

Table 1. Demographic information for both groups (Patients and Controls).

Patients		Controls	
Average age	39.5	*Average age*	32.4
Sex		*Sex*	
Male	100%	Male	100%
Education		*Education*	
No formal education/primary school	43 (79.63%)	No formal education/primary school	2 (6.9%)
Secondary education	9 (16.67%)	Secondary education	7 (24.2%)
University education	2 (3.7%)	University education	20 (68.9%)

2.3. *EEG recording*

All EEG records were performed between 10:00 and 12:00 a.m.

A 40-channel EEG system (Neuroscan, model NuAmps), with electrodes positioned according to the International 10–20 System was used. The signal was recorded at a sampling rate of 1 KHz. A notch filter (50 Hz) was applied online. The 50 Hz band was eliminated to avoid line noises. An average reference montage was calculated offline to avoid possible problems with a unique reference.

People in charge of analyzing the EEG recordings were blind to the drug history of the subject/control.

2.4. *Synchronization likelihood*

SL[52] is arguably the most popular index to estimate Global Synchronization in neurophysiological data. It gives a normalized estimate of the dynamical interdependencies between two or more simultaneously recorded time series. This index, which is closely related to the concept of generalized mutual information,[54] relies on the detection of simultaneously occurring patterns, which can be complex and widely different in the two signals.

Considering two simultaneous time series $x_{k,i}$, where $k = 1, 2$ and i denotes discrete time ($i = 1, 2, \ldots, N$).

We reconstructed with time-delay embedding[55] both time series:

$$X_{1,i} = (x_{1,i}, x_{1,i+1}, x_{1,i+2l}, \ldots, x_{1,i+(m-1)l}),$$

$$X_{2,i} = (x_{2,i}, x_{2,i+1}, x_{2,i+2l}, \ldots, x_{2,i+(m-1)l}),$$

where l is the lag and m is the embedding dimension. Each time series (1 and 2) was reshaped into a matrix with m columns and N rows (for example: lag = 1). Then, for each time series and each row ($r_{k,i} = i, i+1, i+2, \ldots, i+m-1$) of the matrix, by an iterative process (increasing an ε value, from $\varepsilon \sim 0$), we determined the value ε for which $P^{\varepsilon}_{k,i} = p_{\text{ref}}$, where $p_{\text{ref}} \leq 0.05$.

$$P^{\varepsilon}_{r_{k,i}} = \frac{1}{2(w_2 - w_1)} \sum_{j=1}^{N} \theta(\varepsilon - |r_{k,i} - r_{k,j}|) \quad \text{with } w_1 < |i - j| < w_2, \tag{1}$$

where $|\cdot|$ is the Euclidean distance and θ is the Heaviside step function ($\theta(x) = 0$ if $x \leq 0$ and $\theta(x) = 1$ if $x > 0$); w_1 and w_2 are two time windows; w_1 is the Theiler correction for autocorrelation time[56]; w_2 is a window that sharpens the time resolution of the synchronization measure, chosen so that $w_1 \ll w_2 \ll N$ (see Ref. 57 for the w_2 calculation procedure).

This yields the $\varepsilon_{r_{k,i}}$ value corresponding to each time series and each row of the mentioned matrix, from which the SL can finally be calculated.

For each discrete time i (row) and each of both time series, we quantify the number of coincidences within $w_1 < |i - j| < w_2$. Thus, if

$$H_{r_{1,i}\, r_{1,j}} = \theta(\varepsilon_{1,i} - |r_{1,i} - r_{1,j}|) = 1 \tag{2}$$

and

$$H_{r_{2,i}\, r_{2,j}} = \theta(\varepsilon_{2,i} - |r_{2,i} - r_{2,j}|) = 1, \tag{3}$$

then

$$S_{r_{1,i}\, r_{2,i}} = S_{r_{1,i}\, r_{2,i}} + 1. \tag{4}$$

Repeating for $w_1 < |i - j| < w_2$, we get the synchronization value ($S_{r_{1,i}\, r_{2,i}}$) between both time series at time i. Finally, by adding all rows of the matrix, we will obtain the SL between two time series. The range of the SL is: $0 \leq \text{SL} \leq 1$.

2.5. *EEG analysis*

Prior to functional connectivity analysis, all records were visually inspected by an experienced investigator, and all of them containing visible blinks, eye movements or muscular artifacts were excluded from further analysis. Only completely artefact-free subjects (21 patients and 20 control subjects) were retained for further analysis. For each subject, 50 s of eyes-closed activity and 50 s of eyes-closed while counting were selected. These 100 s were split into epochs of 1 s length, yielding a total of 50 epochs of resting state (eyes-closed) and 50 epochs of counting forward (eyes-closed).

An in-house Fortran code was used to implement the SL algorithm.[52] The SL algorithm was applied to the 100 extracted artifact-free one second epochs for each subject. For each frequency band optimal SL parameter values were chosen according to Montez,[57] for each frequency band and one second length: Lag : $L = \mathrm{fs}/(3 * \mathrm{HF})$, Embedding dimension: $M = 3 * \mathrm{HF}/\mathrm{LF}$, Theiler window: $W1 = 2 * L * (M - 1)$, Percentage of close vectors: $P_{\mathrm{ref}} < 0.01$, Window length: $W2 > 10/\mathrm{Pref} + W1 - 1$, where fs (1 KHz), HF and LF are respectively the sampling rate and the high and low frequency bound.

The following frequency bands were considered: θ (4–8 Hz), $\alpha 1$ (8–11 Hz), $\alpha 2$ (11–14 Hz), $\beta 1$ (14–25 Hz), $\beta 2$ (25–35 Hz), $\gamma 1$ (35–45 Hz) and $\gamma 2$ (55–80 Hz). The 50 Hz band was eliminated to avoid line noises. The SL was calculated for each of the 100 one-second epochs with $34 * 33/2$ channel pairs for each frequency band and each subject (20 controls and 21 patients). The SL index was not computed for bands below 4 (Hz) as the epoch length and sampling rate do not allow accurate enough estimations.[57]

2.6. *Statistical analysis*

A nonparametric permutation test was applied to find channel pairs with significant differences in SL between groups.[58] For the purpose of performing paired or unpaired comparisons, randomization methods consist of random permutations of data. Randomization methods are also often called permutation methods or tests (for details, see 'Statistical Methods', Delorme A.). Permutation tests provide exact, strong control of Type I error rates.

Permutation tests were performed according to the following procedure: First, for each condition (rest or task), and for each channel pair (i, j), a two-sample Kruskal–Wallis test was carried out using SL values as independent variable, so as to obtain the corresponding p-value between the two original samples, x_i (20 patients) and y_j (21 controls).

The randomization method involves pooling together the data of x_i and y_j into a new set z, so that subjects are permutated. Then, two groups x_i' and y_j' of the same size as x_i and y_j respectively are randomly drawn from z (without replacement).[59] The p-value is then computed (by a Kruskal–Wallis test) for each randomized pair of samples (x_i' and y_j'), yielding the corresponding p-value. This randomization procedure was repeated 10,000 times to get the distribution of the estimator (total of 10,001 p-values). Finally, the 1st percentile of the distribution was identified, and p-values corresponding to the original samples (x_i and y_j) below that threshold were considered as statistically significant.

This procedure was repeated for each channel pair and each condition (resting or task).

3. Results

Once the nonparametric permutation testing was applied to localize channel pairs with significant differences between both groups, in order to discriminate the group (Patients or Controls) showing higher synchronization values, we performed the average synchronization value for each channel and for each group. This indicated which group had increased synchronization.

Patients showed increased synchronization at rest when compared to the healthy control group in the θ band (4–8 Hz). Figures 1(a) and 1(b) show that the patient group had higher average synchronization values at each channel with respect to all other channel, with a similar topographical pattern for both groups. Figure 2 shows that differences are most pronounced at prefrontal scalp sites, particularly in the right hemisphere and in posterior regions.

During the counting condition, patients also displayed elevated synchronization, particularly at high frequencies (β and γ) (see Figs. 3 and 4). At $\beta 1$ frequencies (14–25 Hz), hypersynchronization was found in prefrontal and temporal regions bilaterally (see Fig. 3). In the $\beta 2$ range (25–35 Hz), the synchronization pattern was very similar to that for $\beta 1$ synchronization, with a possibly more pronounced

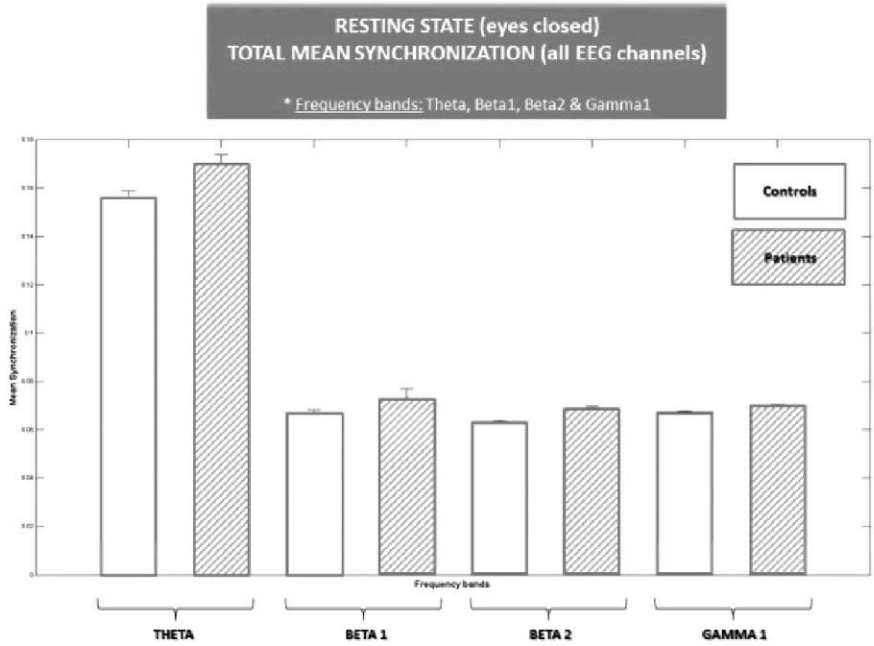

Fig. 1(a). Mean synchronization (SL) per frequency band (Theta, Beta 1, Beta 2 and Gamma 1), indicated per group (patients and controls). Error bars indicate standard deviation. Mean synchronization values for each group (patients and controls), was calculated among all EEG's channels.

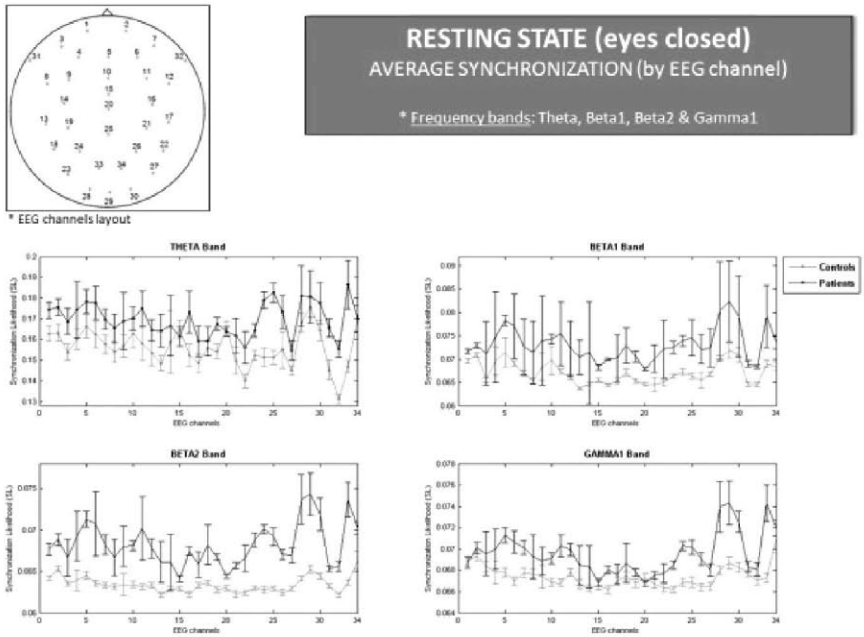

Fig. 1(b). Average synchronization values at each channel with respect to all other channel, in frequency bands: Theta, Beta 1, Beta 2 and Gamma 1. The total number of EEG channels is 34.

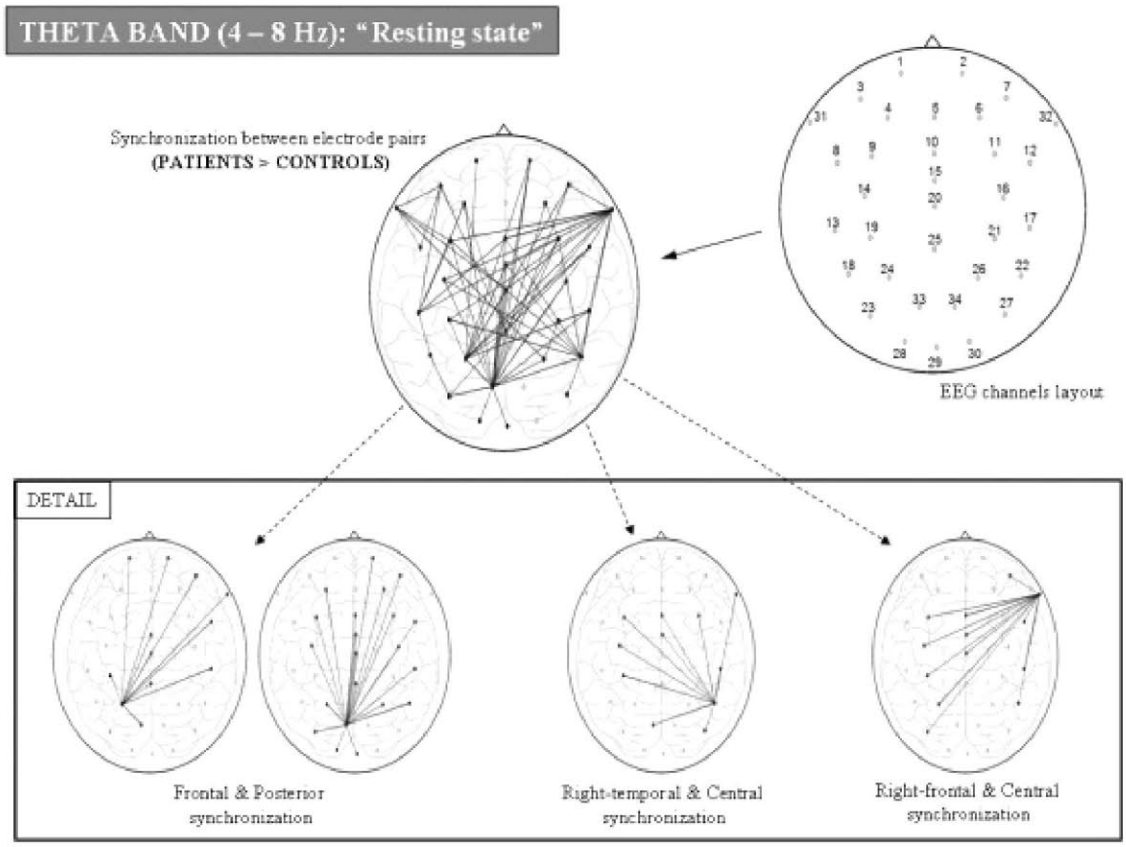

Fig. 2. Significant differences in SL between electrode pairs in "resting state" and for the θ frequency band (Patients > Controls). Around 10% of the pairs (51/561) were found to have statistically significant difference. Nonparametric permutation testing was applied to find channel pairs with significant differences between both groups.

prefrontal character (see Fig. 3). Finally, in the γ band (35–45 Hz), synchronization values had a markedly fronto-posterior pattern (see Fig. 4).

4. Discussion

We studied long-range synchronization of electrical brain activity in a population of polydrug users after a three-month long detoxification period.

Although potentially relevant to the study, we do not have any information related to the amount of sleep the subjects in both groups had the night before the recording (EEG).

As said in the EEG recording section, for the EEG analysis an average reference montage was used. In this sense, we want to point out that the average reference methods involve mixing the amplitude and phase from different scalp locations resulting in phase and coherence distortions as shown in Refs. 60–62. Moreover, this montage avoids artifacts when a high spatial electrode density is available and when a large area of the head is covered.[63] Additionally, the posterior alpha rhythm appears to be mirrored at the central coronal line (for empirical demonstrations, see Refs. 64 and 65. Thus, a possible increasing anterior alpha activity might be interpreted as an artifact of the reference. At any rate, since the outcomes in the present study are mainly found in the Theta, Beta and Gamma frequency bands, this type of artifact, due to the montage used, should not strongly affect our results.

Our results show that polydrug abusers presented a higher synchronization level than controls. Drug abusers presented hypersynchronization of low frequency brain activity at rest, mainly in fronto-posterior and fronto-temporal regions. Finally, drug abusers were characterized by high-frequency hypersynchronized activity during the execution of a

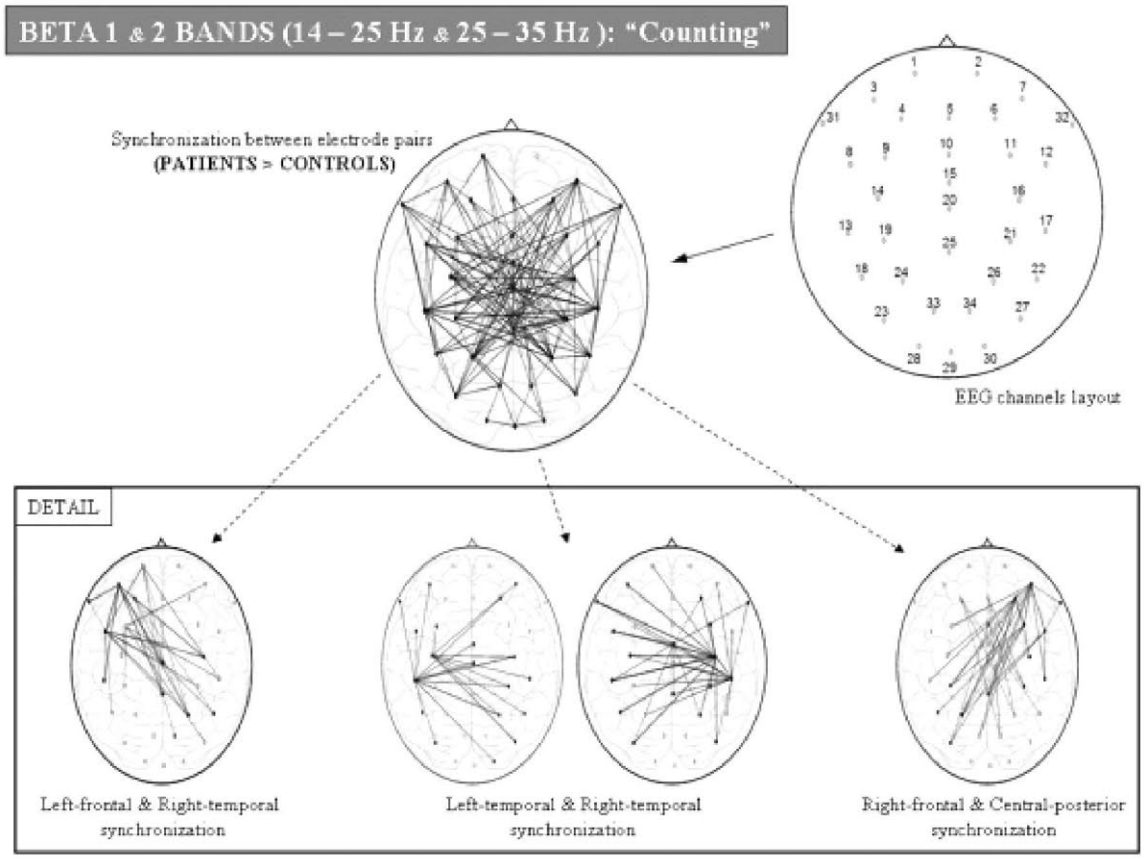

Fig. 3. Significant differences in SL between electrode pairs during "counting" task for $\beta 1$ and $\beta 2$ frequency bands (Patients > Controls). Around 15% of the pairs (87/561) were found to have statistically significant differences. Nonparametric permutation testing was applied to find channel pairs with significant differences between both groups.

counting task, which was prominent at inter-hemispheric temporal, fronto-posterior, and fronto-temporal regions.

Although *decreased* high frequency synchronization levels are commonly thought to reflect decreased functional cortico-cortical connectivity, the general interpretation of *increased* synchronization is less clear.

Sleepiness is indeed a plausible interpretation. In fact, it is known that sleepiness may directly influence EEG signal characteristics.[66,67] Alpha and Theta power density showed highly significant increase at the Karolinska Sleepiness Scale a scale that is frequently used for evaluating subjective sleepiness.[66]

Unfortunately, we do not have any information related to the amount of sleep for the night prior to the recording session (EEG).

However, while sleepiness may be an issue, there is no *a priori* reason to consider that this particular issue differentially affected the two groups, so that individual differences within groups may well exceed inter-group ones.

Excessive synchronization may indicate that two brain areas have an excessive level of functional connection reflecting, for instance, an attempt to compensate for local malfunctioning.[12] In this sense[44] found that during Mild Cognitive Impairment (considered an intermediate state between healthy aging and dementia) the brain is still able to compensate for potential initial anatomical defects resulting in an increase of functional connectivity. Posterior studies even associated the increased synchronization in posterior regions with dementia.[68]

Thus, although our study does not allow concluding whether hypersynchronization at rest is

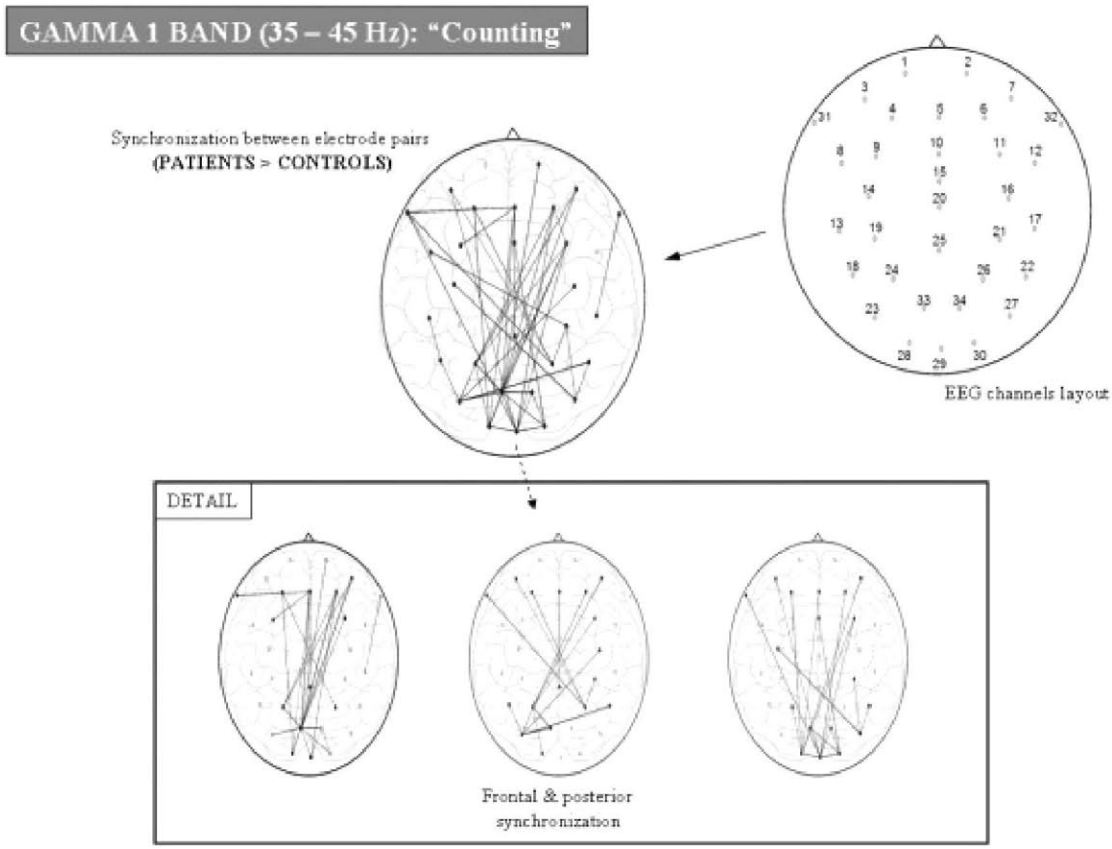

Fig. 4. Significant differences in SL between electrode pairs during "counting" task for the $\gamma 1$ frequency band (Patients > Controls). Around 10% of the pairs (49/561) were found to have statistically significant differences. Nonparametric permutation testing was applied to find channel pairs with significant differences between both groups.

reversible or not, our results may hint at a premature deterioration of polydrug consumers' brain, consistent with a recent study suggesting that chronic cocaine exposure may interfere with the processes of brain ageing.[69]

Recently, it was proposed that abnormal inferior prefrontal cortical connectivity at rest underlies an increased risk for developing stimulant drug dependence.[7] Thus, although employing a different technique from the one used here, these results may lend support to the notion of resting prefrontal hypersynchronization as a predisposing factor for drug abuse.

A plausible related explanation would be in terms of slowing of cognitive processes, and decreased ability of drug abusers to cope with the demands of a constantly changing environment.[15] This explanation would be consistent with studies on patients under acute opioid influence reporting (i) increases in the size, functional life span, and stability of quasi-stationary brain activity, in both α and β frequency bands,[15] which diminished but did not disappear during short-term withdrawal,[50] and (ii) with a correlation between life-span of neuronal assemblies and reaction times.[70]

Alternatively, enhanced synchronization may reflect enhanced arousal level, when at β, a plausible interpretation in the case of short-term drug abstinent subjects.[12–15] In addition, stronger synchronicity at these frequencies was found to correlate with the strength of withdrawal symptoms during short term withdrawal in opioid-dependent patients.[50] Interestingly, in our study, we found no signs of β synchronization at rest. This is probably due to the fact that in the cited work,[50] a short-term abstinence was studied, whereas in ours, the abstinence was a long-term one.

Frontal hemispheric α coherence was found to be associated with craving in heroin abstinent subjects.[12] Enhanced α synchronization may

reflect relative attentional rigidity, anxiety, and arousal in patients during withdrawal. In turn, these altered processes may trigger craving, drug-related expectancies and intrusive thoughts related to drugs.[71] Thus, our results may suggest that cognitive disorganization, hyperarousal and craving alleviate as the withdrawal period decreases.

The high-frequency hypersynchronization associated with the execution of a counting task may indicate an excessive task-induced effort.[7] These studies show that with increasing task difficulty, synchronization increases, indicating that patients need an extra amount of synchronization to perform the same task. The different frequency from the one associated to resting hypersynchronization (β and γ versus θ frequencies respectively) points to at least partially dissociable phenomena. On the other hand, both the frontal topography and the frequency in the β and γ range for task-related hypersynchronization mirror prior reports of enhanced connectivity at rest in short-term drug-abstinent heroin-dependent subjects.[12]

In conclusion, the present study represents one of the still rare attempts at quantifying the effects of drug addiction in terms of cerebral functional connectivity, both at rest and during the execution of a cognitive task. Our results show that drug administration affects not only resting but also task-induced brain connectivity, and that this effect can still be observed after a drug abstinence period of at least three months. This persistent elevated level of synchronous communication among cortical areas may constitute the neural basis of the bias in motivation and in cognitive processes including attention, emotions, and memory characterizing withdrawal from drugs. We propose to interpret resting and task hypersynchronicity as slow-down at rest and task-related over-exertion. Consistent with prior suggestions[69] we propose that the brain of drug abusers may undergo a premature form of ageing. Taken together with the result of existing studies,[15,50] our results contribute to the delineation of a time-varying pattern of abnormal long-range synchronization in various stages of drug addiction, from acute dependence to short and medium term withdrawal. Future studies will clarify the extent to which hypersynchronization is permanent, and whether it stems from drug abuse or represents a pre-morbid factor predisposing individuals to drug use and addiction.

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