



EEG coherence in post-LSD visual hallucinations

Henry David Abraham^{a,*}, Frank Hopkins Duffy^b

^aDepartment of Psychiatry, Mt. Auburn Hospital, 330 Mt. Auburn St., Cambridge, MA 02138, USA

^bDepartment of Neurology, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

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Abstract

LSD use in certain individuals may result in chronic visual hallucinations, a DSM-IV syndrome known as hallucinogen persisting perception disorder (HPPD). We studied 38 HPPD subjects with a mean of 9.7 years of persistent visual hallucinations and 33 control subjects. Measures of local and medium distance EEG spectral coherence were calculated from all subjects. Coherence, a measure of spectral similarity over time, may estimate cortical coupling. In the eyes-open state in HPPD subjects, widespread reduction of coherence was noted. However, upon eye closure, the occipital region demonstrated augmented regional coherence over many frequencies but with reduced coherence of the occipital region to more distant regions. This occipital coherence increase correlated with previously reported shortened occipital visual evoked potential latency for HPPD subjects. We speculate from coherence and known clinical and psychophysical data that, in HPPD, there is widespread cortical inhibition in the eyes-opened state, but localized and isolated occipital disinhibition upon eye closure, a state known to facilitate hallucinatory experiences. An analogy is drawn to findings in the interictal and ictal epileptic focus. In HPPD, we speculate that occipital EEG hypersynchrony resulting from increased regional coherence, when coupled with relative isolation of visual cortex, especially upon eye closure, facilitates hallucinations and illusions. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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* Corresponding author. 175 Bedford St., Lexington, MA 02420, USA. Tel.: +1-781-863-2229.
E-mail address: abraham861@aol.com (H.D. Abraham).

1. Introduction

While drug abuse appears to have been declining over the past half decade, the use of LSD has risen 77% over the last decade (Johnston et al., 2000) and is associated with prolonged visual disturbances in certain individuals (Cooper, 1955; Hollister, 1962; Rosenthal, 1964; Robbins et al., 1967; Horowitz, 1969; Holsten, 1976). This disorder, hallucinogen persisting perception disorder (HPPD), is characterized by a variety of pseudohallucinations, including geometric imagery, trails behind moving objects, false perceptions of movement in the peripheral fields, and flashes of color, haloes and afterimages (Abraham, 1983). The pathogenesis of HPPD is unknown, but the disorder has been shown to be associated with psychophysical abnormalities in color identification, dark adaptation, and flicker fusion, consistent with the hypothesis of chronic visual disinhibition following the use of LSD (Abraham, 1982; Abraham and Wolf, 1988). The mechanism for such visual disinhibition in this disorder is unknown. Findings from our previous quantitative EEG (qEEG) studies (Abraham and Duffy, 1996) included evidence of a surprising over-enhancement of occipital activity in HPPD subjects, also felt to be consistent with disinhibition. Pathological influences typically slow EEG alpha and lengthen evoked potential latencies. Paradoxically, in HPPD, alpha peak frequency was increased and the latency of the P2 component of the visual evoked potential (VEP) was shortened.

The current study was undertaken to search for additional evidence of electrophysiological abnormalities in HPPD. In particular, we hypothesized that we would be able to detect changes in EEG spectral coherence. Coherence between two scalp electrodes may best be understood as the correlation between the EEG spectral power from the two electrodes over time on a frequency by frequency basis (Saltzberg et al., 1986). Coherence values, which range from 0 to 1, are often taken as measures of coupling or connectivity between the brain regions beneath the measuring electrodes (Saltzberg et al., 1986) which may be influenced by factors such as the activity of cortical-cortical fiber tracts connecting the two in-

involved brain regions. For example, interhemispheric coherences are greatly reduced upon surgical transection of the corpus callosum (Montplaisir et al., 1990). Alternatively, coherence may be influenced by the activity of a third site connected to both regions beneath the chosen cortical electrodes. As an example of the latter possibility, thalamocortical activity has been implicated as an important synchronizing influence on occipital cortex which may serve to facilitate cortical visual information processing (Eckhorn et al., 1988; Gray et al., 1989; Sillito et al., 1994; Crick and Koch, 1995). In general, an ability to estimate cortical coupling between brain regions with spectral coherence measures has been shown to add information not available by simple visual inspection or spectral analysis of the electroencephalogram (EEG) (Colter and Shaw, 1982).

2. Methods

2.1. Subject recruitment, screening and selection

Our subjects and the methods used in this study have been previously described (Abraham and Duffy, 1996). The study protocol was reviewed and approved by the Institutional Review Board of the Children's Hospital of Boston. To perform this study, HPPD were recruited from patients recently discharged from local drug treatment programs. Control subjects were recruited from the staff of several local teaching hospitals. HPPD subjects were included if they reported continuous daily visual hallucinations for at least 1 month following the use of LSD. HPPD and control cases underwent structured diagnostic interviews by a board-certified psychiatrist (H.D. Abraham) to exclude those with psychosis and other brain disorders. Subjects who reported a history of spontaneous hallucinations prior to the use of LSD were eliminated. Control subjects were screened by a psychiatrist (H.D. Abraham) and a neurologist (Frank Duffy). None of the 33 selected control subjects had histories of significant mental, medical or neurological illness, had histories of drug abuse or hallucinations, or were taking medications on a regular basis.

The 38 selected HPPD cases reported first mean LSD use at 18.1 ± 6.0 years (range 12–46 years), and reported lifetime use of LSD with a median of 16 times (range 1–450 estimated times). Three subjects reported the acute and persistent onset of visual hallucinations after a single use of the drug. The median time of onset of continuous symptoms after the first use was 21 months, with 13.5% becoming symptomatic within the first month of drug use. At the time of the study, HPPD cases had continued to have daily visual hallucinations (9.67 ± 7.68 years). They reported 7.11 ± 2.2 different types of visual hallucinations on a visual disturbances scale previously described (Abraham, 1983). The majority of subjects reported an intensification of visual hallucinations on emerging into a dark environment, consistent with previous findings. All had used LSD prior to the onset of HPPD. Apart from hallucinogens, there were no statistically significant differences between groups for alcohol or marijuana dependence. Of the HPPD subjects, 8.1% had histories of alcohol dependence within the last year, and 2.7% reported marijuana dependence.

For all 71 subjects, a breath test for alcohol and an EMIT urine screen for abusable drugs was performed on three separate occasions over a 10-day span prior to neurophysiological testing. This included screens for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine and propoxyphene. Subjects were asked to refrain from taking any medication for at least 10 days prior to EEG testing. No subject failed the drug screen.

The two groups were matched for age (HPPD subjects, 29.2 ± 8.2 years, and control subjects, 32.3 ± 8.0 years, respectively, NS) and handedness (HPPD 86.5% right-handed vs. control subjects 87.9%, NS). HPPD subjects demonstrated a male/female ratio of 17:2 compared with the control subjects ratio of 4:7 ($P < 0.001$). This gender asymmetry resulted, in part, from the known male dominance in HPPD (Abraham, 1983) but also from an unanticipated reluctance of males to participate as control subjects in a study that involved drug testing. We did not encounter such reluctance in our female control population. Ac-

ordingly, statistical steps were added to assess the potential confounding effects of gender difference upon our results.

2.2. Acquisition of neurophysiologic data

Quantitative EEG (qEEG) studies were performed at the Developmental Neurophysiology Laboratory of the Boston Children's Hospital under a strict protocol controlling for light, sound, muscle tension, mouth and tongue movement, blink, sleepiness, and other possible sources of artifact; see Abraham and Duffy (1996) for details. Data were obtained from 20 scalp electrodes (standard 19, 10–20 clinical EEG placement plus OZ) (Sharborough et al., 1991) and four other bipolar electrodes strategically placed to monitor artifact. EEG were digitized, and analyzed to compare the EEG spectra — for this study — and the visual evoked potentials — from the prior study — between hallucinators with control subjects. The latency to the second large positive component of the visual evoked record, P2, as reported in our prior study (Abraham and Duffy, 1996), was defined between 80 and 280 ms, from occipital electrodes at electrodes O1, OZ and O2.

For the current study, neurophysiologic data were analyzed during the resting, awake state with eyes open (EO) and separately with eyes closed (EC). The EEG was continuously monitored to detect and avoid state change. If clinical or EEG signs of drowsiness were detected, data acquisition was suspended and the subjects alerted (Santamaria and Chiappa, 1987). When necessary, subjects were allowed up to 1 h of sleep to subsequently facilitate alertness.

Following amplification by a Grass polygraph set to bandpass from 1 to 300 Hz, the data were digitized by a Masscomp computer. A through-system sine wave calibration signal at 10 Hz was recorded for all channels. Spectral analysis was performed after tight low pass filtering 90 Hz (48 dB per octave) and digitization at 256 Hz per channel. In this manner, contamination of the EEG spectral frequencies due to undersampling

formed on the 38 LSD and 33 control subjects using a combination of coherence factors, representing approximately 50% of the initial variance

for both the adjacent and medium distance analyses. Accordingly, the first three adjacent (AD-JFAC1-3) and the first 10 medium distance fac-

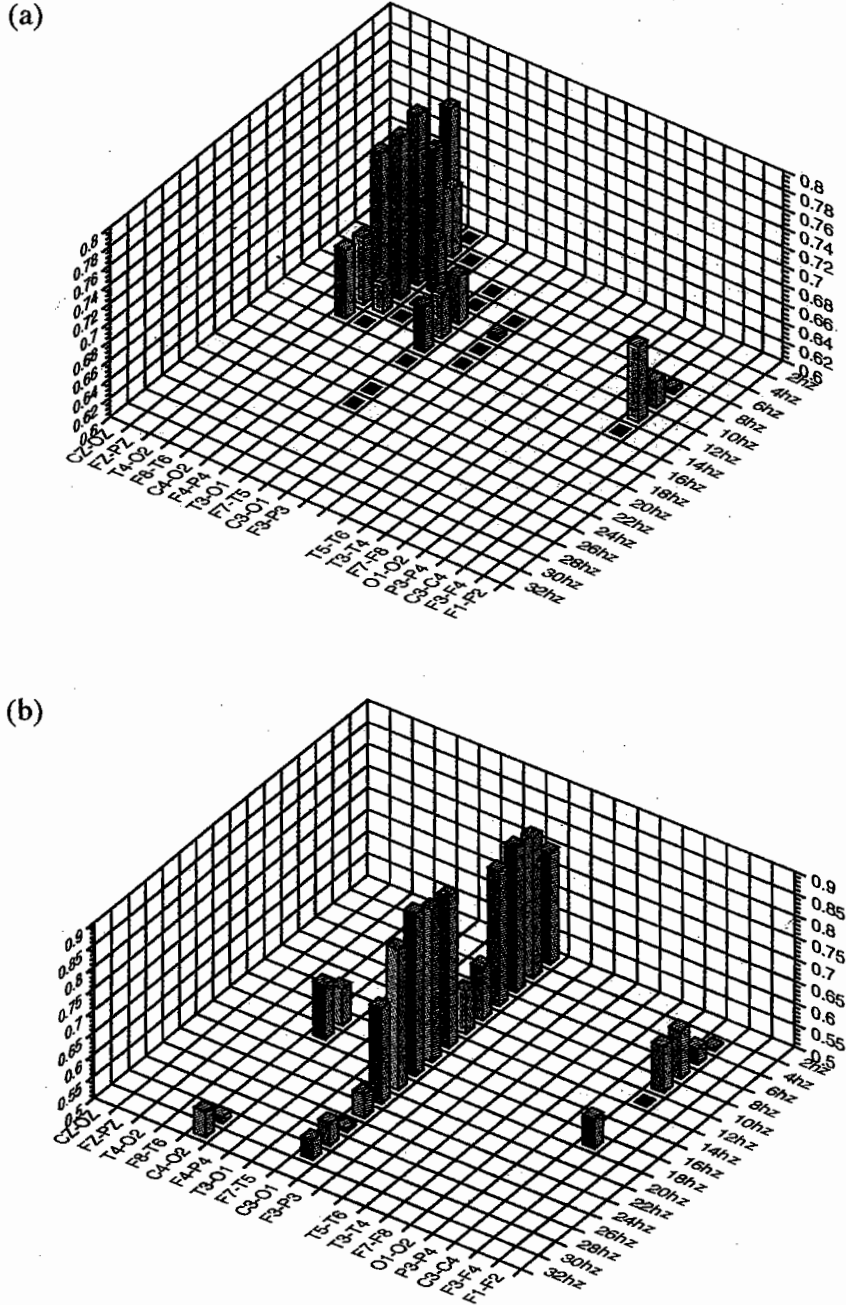


Fig. 1.

tors (MDFAC1-10) were entered into the analysis. The result of the DSC was significant: Wilks Lambda = 0.420; $F = 22.77$; d.f. = 4, 66; $P < 0.001$. Four variables were chosen in order: MDFAC1, ADJFAC2, MDFAC3 and ADJFAC1. Overall, there was 87.3% correct classification of subjects, dropping slightly to 85.9% correct with jackknifing (Lachenbruch and Mickey, 1968). Classification rates are shown in Table 1.

To determine the potentially confounding effect of the gender difference in group composition, the DSC was repeated, forcing gender as a variable to remain in the analysis. The result of the DSC was significant: Wilks Lambda = 0.348; $F = 24.34$; d.f. = 5, 65; $P < 0.001$. Four variables were chosen, after gender was forced, in the order: ADJFAC2, ADJFAC1, MDFAC3 and MDFAC1. Although the order of choice was slightly different, the same four variables were chosen when gender was forced. Overall, there was 94.4% correct classification of subjects, dropping to 88.7% correct with jackknifing. Classification rates are shown in Table 2.

Thus, forcing gender into the DSC does not alter the choice of coherence factors or significantly alter the jackknifed classification success.

3.3. Path analysis

We used path analysis to determine whether group status best explained each of the four DSC chosen variables directly or via an intermediate variable; in this case, gender. The Direct Effect (P13) represents the effect of group status on the index variable (each of the four factors). The Indirect Effect (P23*P12) represents the effect of group status on the index variable through gender. The results are shown in Table 3.

As can be seen, in every case, the direct effect and overall correlation were significant whereas the indirect effect through gender never reached statistical significance. Thus, age cannot explain the relationship between group status and the four DSC chosen factors.

3.4. Original coherence variable loadings upon DSC chosen coherence factors

Loadings of the original coherence variables on the four DSC selected coherence factors are graphically illustrated in Fig. 1 (MDFAC1, MDFAC3) and Fig. 2 (ADJFAC1, ADJFAC2). Three factors represent decreased coherence for the HPPD group (ADJFAC1, MDFAC1, MDFAC3). ADJFAC2 represents increased HPPD coherence. The findings in the EO dominated factors (MDFAC1, ADJFAC1) and EC dominated factors (ADJFAC2, MDFAC3). Fig. 3, which shows the between-group T -statistic SPM for electrode OZ and the 6-Hz spectral band, nicely summarizes the coherence findings of this study. In the EC state, coherence within the broad occipital region (O1, OZ, O2 — right more than left) is increased, as is coherence between the occipital and midline parietal (PZ) and right mid-temporal (T4) regions. In contrast, coherence between the occipital and more anterior regions (C3, C4, P3, FP1, FP2) is decreased.

3.5. Canonical correlation between coherence and visual EP variables

We questioned whether the increased coherence variables from the occipital region during

Fig. 1. Loading of medium distance (MD) coherence variables on MD factors 1 and 3: both graphs represent three-dimensional representations of coherence variable loadings upon factors resulting from a PCA (see text). Fig. 1A illustrates factor MDFAC1 and Fig. 1B shows MDFAC3. For both illustrations, the vertical axis shows the loading values, which vary from 0 to 1. One horizontal axis shows the 16 2-Hz wide spectral bands and the other the 18 electrode pairs used for the coherence calculation. Loadings of 0.6 or greater are shown as scaled vertical bars. Loadings between 0.5 and 0.6 are shown as black squares. White squares represent values below 0.5. For factor MDFAC1 (Fig. 1A), all electrode pair coherence values were derived from the EO state. The most involved electrode pairs are F8-T6 and C4-O2 in the right posterior quadrant. Taking into account loading on the PCA and DSC analyses and sign of the discriminant function, the MDFAC1 loadings represent decreased coherence for the HPPD population. For MDFAC3 (Fig. 1B), most electrode pairs were derived from the EC state and primarily involve the C3-O1 electrode pair in the left posterior quadrant. MDFAC2 loadings also represent decreased coherence for the HPPD population.

dence for both increased and decreased coherence depending upon state (EO, EC) and head region. There is a general tendency for reduced coherence in the EO state (see Fig. 1A). However, increased posterior coherence may be seen in the EC state (see Fig. 2B). The pattern of coherence differences is best summarized in Fig. 3 by the group difference *T*-statistic SPM. Here we see that when the eyes are closed (the state most likely to produce hallucinations in HPPD), regional within-occipital coherence is increased whereas coherence between the occipital and more anterior regions is reduced. Thus, the occipital visual system appears to be functioning more in isolation than normal, i.e. more internally synchronized and less under the influence of other regions. This may be just the pattern necessary to facilitate hallucinations. In addition, using data from a previous analysis of flash VEP data on the same subjects, we were able to demonstrate, by canonical correlation, that increased EC occipital coherence and reduced VEP latency are highly correlated (see Table 4) across members of our population.

This interpretation of our findings is consistent with previous reports that the commonest precipitant of the LSD-related visual symptoms of HPPD is emergence into a dark environment (Abraham, 1983). We speculate that post-LSD visual symptoms intensify on closing one's eyes by two processes: a reduction in the environmental signal to noise ratio, and the brain's conversion of residual noise to a signal through visual system overactivity, possibly related to some underlying disinhibition. Potential sources of visual noise include signals from the environment and entoptic sources, such as retinal vessels and cells. Environmental stimuli resulting in post-LSD hallucinations may depend on stimulus amplitude, contrast, and temporal or spatial frequencies.

Our finding of a predominance of increases in coherence in HPPD slightly more marked in the theta range of frequencies (EC state, see Fig. 2B) is consistent with findings of Llinas et al. (1999) who recently described increased theta coherence in other abnormal sensory experiences not necessarily driven by external stimuli, including neurogenic pain and tinnitus. It is possible that in-

creased coherence, especially in the theta spectral range, is a non-specific indicator of disturbed homeostasis in perception.

The relationship between coherence and cortical disinhibition is not known. Computer simulation of neural networks suggests that synchrony between units is dependent on inhibitory units for coordination (Lytton and Sejnowski, 1991). Our data support the hypothesis that an increase in measures of disinhibition in VEP data is associated with increases in EC occipital coherence in subjects with a long-term post-LSD hallucinatory state. The apparently contradictory evidence regarding the nature of the association between disinhibition and coherence suggests the possibility of an inverted U curve for the relationship. Computer modeling suggests inhibitory neurons may modulate cortical cells in either faster (disinhibited) or slower (inhibited) directions, but that GABA-A inhibition of neurons may reduce coherence (Golomb et al., 1994). This last finding is consistent with clinical observations that benzodiazepine drugs active at the GABA-A receptor reduce or block LSD hallucinations acutely, and the finding that intravenous midazolam reduces afterimages in HPPD (Abraham, unpublished data). The GABA antagonist, bicuculline, but not glutamate, restored visual input in cats deprived of vision at birth (Burchfiel and Duffy, 1981). The topographic localization of increased coherence in LSD hallucinators to posterior cortex in this study consensually validates our previous report of preponderant localization of deviant evoked potentials in the same regions in this sample of HPPD patients (Abraham and Duffy, 1996). Of particular interest is that the posterior localization of increased coherence in HPPD coincides with an increasing gradient of benzodiazepine receptors in the same cortical regions in normal subjects (Bremner et al., 1999).

In the EO state, especially outside of the occipital region, coherence was largely decreased (see Figs. 1 and 2). This pattern of broadly reduced coherence (see Fig. 2A) is not unlike the pattern of metabolic activity often delineated by PET scanning about an epileptic focus (Juhasz et al., 2000). Interictally, the epileptic focus is surrounded by a region of hypometabolism, thought

to represent a reactive and potentially protective interictal inhibitory influence. Perhaps the widespread reduced coherence in the less hallucinatory EO state in HPPD represents compensatory, background inhibition as well. During the very early phases of an actual epileptic seizure, the more restricted epileptic focus becomes hypermetabolic, as shown by ictal SPECT scanning (Lee et al., 2000). The epileptic focus is often associated with reduced benzodiazepine receptor binding in Flumazenil-PET studies (Arnold et al., 2000) and HPPD hallucinations appear to be modulated by benzodiazepines. Salant et al. have recently demonstrated that the EEGs in epileptic patients undergoing long-term monitoring show, just prior to the onset of a clinical seizure, 'increased preictal synchronization by calculation of coherence...' (Salant et al., 1998). Thus, the increased occipital coherence associated with eye closure in HPPD may, by analogy, also be signaling a more excitatory (less inhibited) state leading not to seizures but to hallucinations. No studies of PET or SPECT in HPPD have been published for comparison with the findings in epilepsy.

The gender difference between our predominantly male HPPD subjects and predominantly female control subjects requires comment. It is no surprise that a consecutive sampling of subjects with histories of HPPD would show males in the majority (Abraham, 1983). However, no female gender bias has ever shown up in our previous and extensive recruitments of subjects to serve as control subjects for qEEG studies (Duffy, unpublished observation). It may be that the very factors leading to a male preponderance among drug abusers serve to selectively discourage 'normal' male control subjects from participating in studies that involve drug testing. Fortunately, we found no evidence that this gender bias influenced our results to any significant degree. When forced into discriminant analysis, thereby serving as a covariate, the variable Gender failed to substantially alter either subsequent choices of discriminating variables or prospective estimates of classification success by jackknifing (see Tables 1 and 2). Moreover, by path analysis, group status (HPPD, control) predicted the discriminating variables better directly rather than through a

path where Gender served as an intermediate variable (see Table 3).

In summary, data from clinical, psychophysical and neurophysiologic sources all suggest that long-term hallucinations following LSD exposure result from physiological changes in visual system function. Even in the absence of active hallucinations, the occipital, visual regions of HPPD subjects show evidence of heightened but isolated neural synchrony, possibly serving as the platform to amplify minor aspects of visual stimulation, thereby facilitating production of the illusions and hallucinations that characterize HPPD. Whether the presumed changes in occipital neural synchrony by prior LSD exposure result from cortical-cortical influences, thalamocortical influence, or both remains an area for future investigation. Whether the pathophysiology of HPPD bears a functional similarity to epilepsy also bears investigation.

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