Spectral Analysis of Olfactory System Electrical Activity: Effects of Ketamine and Sodium Pentobarbital

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SPECTRAL ANALYSIS OF OLFACTOR Y SYSTEM ELECTRICAL ACTIVITY:
EFFECTS OF KETAMINE AND SODIUM PENTOBARBITAL

by

John Ludwig Orr

A Thesis
Submitted to the
Faculty of the Graduate College
in partial fulfillment
of the
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ACKNOWLEDGEMENTS

In the course of preparing this thesis I have benefited from advice and discussions with Drs. Fred Gault, Ronald Hutchinson and Arthur Snapper. My thanks go to them and especially the staff at the Western Michigan University Computer Center who gave patiently of their time. Of course, I assume the sole responsibility for what is written here.

John Ludwig Orr
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INTRODUCTION

Time domain displays of the electrical activity of the olfactory system are similar across a wide range of species (Adrian, 1950). The analysis of component frequencies in olfactory electrical activity by analog methods led Hughes and Hendrix (1967) to propose that the frequency components encode information concerning the nature of an olfactory stimulus. The purpose of this study was to implement digital frequency analysis techniques on a large digital computer to obtain the frequency components in olfactory system electrical activity and evaluate a potentially useful class of anesthetics for use in recording electrical activity in acute preparations.

Olfactory system electrical activity is intimately related to the activity of the midbrain reticular formation and is very sensitive to the effects of anesthetics. Electrical stimulation of the midbrain reticular formation increases the amplitude of olfactory spindle bursts (Pagano, 1966), and barbiturates, which depress the reticular system (Sharpless, 1970), reduce the frequency of olfactory spindle bursts (Hernandez-Peon, Lavin, Alcocer-Cuaron, & Marcelin, 1960; Gault & Coustan, 1965). Ether, an anesthetic frequently used in setting up acute preparations, disrupts the electrical activity of the olfactory bulb for up to six hours (Gault & Coustan, 1965). Thus for olfactory research with acute preparations, an anesthetic which did not depress the reticular system might prove useful.
"Ketamine has a stronger depressant effect on the diffuse thalamic projection system than on the midbrain reticular formation" (Miyasaka & Domino, 1968, p. 570). This conclusion, based on time domain displays, suggested that Ketamine would be a useful anesthetic for electrical recording in acute preparations. "Disassociative anesthesia" is the term introduced (Domino, Chodoff, & Corssen, 1965) to describe the state induced by Ketamine.

To evaluate Ketamine as an anesthetic for olfactory acute preparations, rats with chronically implanted olfactory system electrodes were used. This chronic preparation allows the recording of electrical activity before and after drug administration without the confounding effects of other drugs or surgical trauma. Sodium Pentobarbital, a barbiturate, was included in the evaluation for comparison.

The present research is closely related to that of Pagano (1966). Pagano's measure of olfactory system electrical activity was the integrated output of a bandpass filter centered at 40 Hz. The power spectrum, the dependent variable in the present research, may be considered the distribution of the integrated electrical activity by frequency.

The analysis of electrical activity into components may be performed with either analog or digital apparatus. At the present time, analog methods do not have all the advantages of digital methods implemented on a large digital computer. For example, multivariate spectra have been computed by digital methods and plots of phase and
coherence spectra used to describe the relationships between time series recorded from different electrodes (Walter & Adey, 1965). A major advantage of digital analysis is that the analysis bandwidth may be easily varied. This leads to the routine practice of conducting the analysis of a given time series at several bandwidths. Spectra obtained with the different bandwidths are then compared to judge the quality of the digital analysis for a given number of data points. This process is called window closing and allows after the fact selection of the most suitable bandwidth for a given record (Jenkins & Watts, 1968, pp. 280-281).

Spectral analysis is the term used to refer to adaptations of Fourier analysis to the analysis of nondeterminate stationary time series. Digital cross-spectral analysis was first applied to the electrical activity of the brain in studies of learning by Adey, Walter, and Hendrix (1961). Since that time a number of reports involving spectral analysis of brain electrical activity have appeared, including Walter (1963), Adey (1965), Elazar and Adey (1967) and Adey (1969).

Stationarity is a concept important to the evaluation of the appropriateness of spectral analysis because a stationary time series is completely described by the lower moments of its probability distribution (Jenkins & Watts, 1968, p. 3). The lower moments involved in the description of a stationary time series are the mean, standard deviation, autocovariance, and the power spectrum, which is the Fourier transform of the autocovariance (Jenkins & Watts, 1968, p. 3).
A stationary time series is one which exists in a state of statistical equilibrium with no trends (Jenkins & Watts, 1968, p. 4); in other words, the series is independent of clock time (Jenkins & Watts, 1968, p. 147). Even in cases where the empirical time series is non-stationary, spectral methods for stationary series are an appropriate starting point because nonstationarity in the mean will appear as a low frequency peak in the spectrum (Jenkins & Watts, 1968, p. 8).

A useful test for self-stationarity is the examination of more than one spectra obtained in a given experimental condition. If the variability is small, the process generating the spectra is self-stationary (Bendat & Piersol, 1966).

Spectral analysis has the property that the product of the bandwidth of the digital filters and the variance of the spectrum obtained is a constant (Jenkins & Watts, 1968, p. 257). This means that to obtain a high degree of spectral stability for a given length of record, one should use wide bandwidth digital filters. Fidelity, however, depends upon having digital filters on the same order of magnitude of bandwidth as the narrowest detail of interest in the spectrum (Jenkins & Watts, 1968, p. 279). The challenge of conducting an analysis which is stable enough to demonstrate spectral changes between experimental conditions and yet allows the display of as much spectral detail as possible is met by window closing.
METHODS AND MATERIALS

Four male Sprague-Dawley albino rats from the Upjohn Company colony were implanted with coaxial bipolar electrodes under Sodium Pentobarbital anesthesia in clean but not aseptic conditions. Atropine sulfate was administered to reduce respiratory system secretions. The electrodes were constructed from 26 gauge #303 stainless steel hypodermic tubing with 0.0063 inch diameter #303 stainless steel wire passing through the tubing and extending 0.5 to 1.0 mm. for the olfactory bulb electrodes and 2.0 to 3.0 mm. for the prepyriform electrodes. The electrodes were insulated with Formvar and the recording surfaces were exposed by scraping clear 0.5 mm. of the barrel and 0.5 mm. of the tip, leaving insulation between.

Olfactory bulb electrodes were implanted under visual control by observation of skull surface landmarks and subsequent histological examination confirmed that all olfactory bulb electrodes were appropriately placed. Three subjects were also implanted with concentric bipolar electrodes straddling the ipsilateral prepyriform cortex dipole generator layer by using the method of Freeman (1960). In this procedure, single pulses from a Grass S-4 stimulator and SIU-4 isolation unit were delivered across the olfactory bulb electrode. The prepyriform electrode surfaces were connected for monopolar recording from each surface by using Tektronix 122 pre-amplifiers, with the evoked response from each surface displayed.

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on a channel of a Tektronix 564B storage oscilloscope. As the dipole
generator layer is approached and crossed, the evoked potential
recorded from the prepyriform electrode tip flattens and then inverts
to form a mirror image of the evoked potential recorded from the
barrel. This gives the investigator positive evidence that he has
one recording surface on each side of the generator layer (Freeman,
1960). The stereotaxic target for the beginning of stimulation was
as follows: anterior, 9.0 mm.; lateral, 4.5 mm.; and depth, 0.0 mm.
(Pellegrino & Cushman, 1967). Various types of miniature plugs were
used for connecting the electrodes to the recording equipment and
were attached to the skull with dental acrylic. Bicillin was
administered post-operatively to minimize the likelihood of infection.

During recording sessions, which began at least a week following
surgery, the subject was in a 15 cm. by 15 cm. by 15 cm. Plexiglas
box with a grid floor. The box was located on a shelf in a
refrigerator cabinet which was equipped with a fan for ventilation.
Connections were made from the rat to a Grass Model 7 polygraph
equipped with capacitor coupled preamplifiers and interfaced with
a Sanborn model 2000 frequency modulated tape recorder. The
polygraph provided an ink written time domain display of the lower
75 Hz. of the data stored on magnetic tape. The recording system
was calibrated with a digital voltmeter before each session. Once
amplifier gain settings were determined for a given session, they
were not changed; therefore the spectra obtained are relative but
not absolute. Recording began after exploratory behavior by the
subject had decreased to a low level. Baseline recording was carried out until several sections of record with steady olfactory bulb slow wave activity were obtained. Ketamine (Vetalar from the Parke-Davis Co.) was administered by intraperitoneal injection in a dose of 50 mg/kg. At least five days intervened before Sodium Pentobarbital (Fort Dodge Laboratories) was administered by intraperitoneal injection in a dose of 60 mg/kg. Electrical activity from the olfactory bulb electrode was simultaneously displayed on two channels of the polygraph. One channel was set to display bulb slow wave activity with the polygraph filters set at 0.15 and 3.0 Hz. The second bulb channel was used to display fast activity with filter settings of 10 and 75 Hz. for chart write-out and 10 and 500 Hz. for the tape recorder. Prepyriform activity was displayed on another channel using the same filter settings as for bulb fast activity. Bipolar recording was done between the tip and barrel of the electrodes.

The abstracting of approximately six second sections of electrical activity for computer analysis was accomplished by selection of records which showed steady olfactory bulb slow wave activity. Once segments were selected for analysis, they were sampled and stored on computer compatible magnetic tape by a Massey-Dickenson data acquisition system.

Spectra are analyzed to a maximum frequency of one-half the rate of sampling of the analog signal. In order to avoid "aliasing" (interference from harmonics), it is necessary to have all significant
spectral power within the range analyzed (Blackman & Tukey, 1959; Walter, 1963; Jenkins & Watts, 1968, pp. 51-53). In this study, a preliminary sampling rate of 300 Hz. was selected on the basis of acute experiments in which the spectrum was analyzed to 350 Hz. After the effect of Ketamine was observed, most Ketamine records were resampled with a 420 Hz. sampling rate. The price one has to pay for a higher sampling rate is that less real time is analyzed for a given number of data points. Thus there is good reason for not using a higher rate of sampling than necessary.

Each digital magnetic tape contained a number of individual data records, and before the analysis began, certain sorting operations were performed. As the long file from the magnetic tape was converted into one-record files for data analysis, the number of "greater than full scale" codes, the number of blank characters, and the identifiers which were inserted manually at the time of analog to digital conversion were typed out on a teletype. This allowed monitoring of all parts of the digital system. For example, the occurrence of "blanks" on the tape indicated dirty tape heads and that cleaning and resampling were necessary.

Spectral analysis was carried out in the time sharing mode of the PDP-10 computer, using a locally modified version of program BMDX-92 "Time Series Spectral Estimation" from the Health Sciences Computing Facility (University of California, 1969). The same 2048 data points in each record were analyzed into 8, 16, 32, and 64 frequency bands for window closing. This particular program does
not compute the autocovariances as an intermediate step in computing the power spectrum. Since the covariances are not available, it was concluded that cross-spectral analysis would not be prudent (Jenkins & Watts, 1968, p. 396). With a sampling rate of 300 Hz., the digital filter bandwidth for 32 bands was 4.7 Hz., and for a 420 Hz. sampling rate, the filter bandwidth was 6.7 Hz. For a record of 2048 data points, resolving the spectrum into 8, 16, 32, or 64 bands results in 256, 128, 64, or 32 theoretical degrees of freedom respectively for the spectral estimate (University of California, 1969). Instead of accepting the theoretical degrees of freedom, window closing was performed. Since the ends of this study were best served by trading off high fidelity for high stability, the window closing procedure led to the selection of the 32 band estimates for comparison.
RESULTS

Differential spectral changes were observed following the administration of Ketamine and Sodium Pentobarbital. Ketamine injection was followed in three subjects at all electrode sites by a dramatic increase in power above 100 Hz. The high frequency peaks following Ketamine are centered at the same frequency within subjects and at different frequencies across subjects. One subject showed no change in the spectra obtained following Ketamine injection. It is possible that this lack of effect was due to an ineffective intra-peritoneal injection. Since Ketamine does not decrease muscle tone and the eyes remain open, it is not possible to determine by visual observation if the subject is anesthetized. Spectra obtained following Sodium Pentobarbital injection show a reduction of spectral power at frequencies below 100 Hz., with occasional increases at around 10 Hz.

Table 1 displays the changes observed following drug administration. Spectral overlays of three spectra obtained before and three spectra obtained 5 to 20 minutes after drug administration are presented for each subject, drug, and electrode site in Figures 1-14 and discussed individually in the figure captions.
### TABLE 1
SUMMARY OF SPECTRAL COMPARISONS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Site</th>
<th>Page</th>
<th>Frequency Range in Hertz</th>
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<tr>
<td></td>
<td></td>
<td>&lt;20</td>
<td>20-100</td>
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<td></td>
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</tr>
<tr>
<td>PO</td>
<td>B</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>32</td>
<td>†</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>J31</td>
<td>B</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>29</td>
<td>†</td>
</tr>
<tr>
<td>A3</td>
<td>B</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>25</td>
<td>-</td>
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<table>
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<th>SODIUM PENTOBARBITAL:</th>
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<th>20-100</th>
<th>&gt;100</th>
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<td>B</td>
<td>20</td>
<td>-</td>
<td>†</td>
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<tr>
<td>B</td>
<td>B</td>
<td>30</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>21</td>
<td>†</td>
<td>†</td>
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<tr>
<td>J31</td>
<td>B</td>
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<td>-</td>
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<tr>
<td>P</td>
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<td>A3</td>
<td>B</td>
<td>22</td>
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<td>†</td>
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<tr>
<td>P</td>
<td></td>
<td>23</td>
<td>†</td>
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Note.—B=olfactory bulb; P=prepyriform cortex; †=increase following drug administration; †=decrease following drug administration.

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Figure 1:

Subject PO, olfactory bulb spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). (The ordinate on all the spectra is in relative units of natural logarithm of power (microvolt^2/frequency band across an assumed one-ohm load).) Post-drug spectral power was reduced between the 53.8 Hz. and the 80.6 Hz. bands and increased in the 20.2 Hz. to 33.6 Hz. bands.
Figure 1
Figure 2:

Subject PO, olfactory bulb spectra before (dashed lines) and after Ketamine (solid lines). A large spectral increase occurred in these records between the 134.4 Hz. and the 201.6 Hz. frequency bands.
Figure 2
Subject A3, olfactory bulb spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). The decrease between 23.4 Hz. and 51.6 Hz. bands is associated with an increase between the 9.4 Hz. and 18.8 Hz. bands and is similar to the response observed for subject PO in Fig. 1.
Figure 3
Figure 4:

Subject A3, prepyriform cortex spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). The decrease between the 46.9 Hz. and 70.3 Hz. bands is associated with an increase in the range from the 0 Hz. to the 18.8 Hz. band. This change occurred at a higher frequency range than did the change observed at the olfactory bulb electrode shown in Fig. 3.
Figure 4
Subject A3, olfactory bulb spectra before (dashed lines) and after Ketamine (solid lines). It was stated in the text and Table 1 that Ketamine did not have an effect on the electrical activity of this subject and an ineffective intraperitoneal injection was suggested. This implies that at the time of recording, the drug dose was much smaller than for the other subjects. In light of the lower effective dose for this subject, the increase in the range of the 168 Hz. to 188.1 Hz. bands is suggestive of a change in the high frequency range. The large peak near 60.1 Hz. is a 60 Hz. artifact.
Figure 5
Figure 6:

Subject A3, prepyriform cortex spectra before (dashed lines) and after Ketamine (solid lines). No obvious change is observed for this electrode site.
Figure 6
Figure 7:

Subject J31, olfactory bulb spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). A broad decrease is observed from 46.9 Hz. to the 84.4 Hz. band but there is no low frequency increase as was seen in Fig. 1 and Fig. 3.
Figure 7

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Figure 8:

Subject J31, prepyriform cortex spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). A variable increase is suggested between the 4.7 Hz. and 14.1 Hz. bands but with only two records available after drug administration, this is not conclusive.
Figure 8

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Figure 9:

Subject J31, olfactory bulb spectra before (dashed lines) and after Ketamine (solid lines). The major feature of this comparison is the peak from 121 Hz. on up. It is possible that the 75 Hz. to 98.4 Hz. peak is an aliasing artifact. The center frequency of the peak at 131.3 Hz. is the same as observed at the prepyriform cortex electrode site shown in Fig. 10.
Figure 10:

Subject J31, prepyriform cortex spectra before (dashed lines) and after Ketamine (solid lines). The peak center at 131.3 Hz. is the same as for the olfactory bulb site shown in Fig. 9.
Figure 11:

Subject B, olfactory bulb spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). The spectral diminution between 65.6 Hz. and 75 Hz. is associated with an increase from 4.7 Hz. to 13.4 Hz., similar to the changes seen in Fig. 1 and Fig. 3.
Figure 12:

Subject B, prepyriform cortex spectra before (dashed lines) and after Sodium Pentobarbital (solid lines). The decrease from 51.6 Hz. to 79.7 Hz. is associated with an increase between 4.7 Hz. and 23.4 Hz., similar to Fig. 1, Fig. 3, and Fig. 11.
Figure 12
Figure 13:

Subject B, olfactory bulb spectra before (dashed lines) and after Ketamine (solid lines). The major peak centered at 134.4 Hz. and the minor peak between 80.6 Hz. and 100.8 Hz. correspond closely to the changes observed for the prepyriform cortex electrode in Fig. 14.
Figure 14:

Subject B, prepyriform cortex spectra before (dashed lines) and after Ketamine (solid lines). The spectra obtained are very similar to those obtained from the olfactory bulb site.
DISCUSSION

The application of digital spectral analysis to the electrical activity of the olfactory system of rats revealed differential changes following drug administration. The two drugs, Ketamine and Sodium Pentobarbital, are different in chemical class and are described as producing dissimilar anesthetic states in man (Domino, Chodoff, & Corssen, 1965).

The occasional increases in power around 10 Hz. following barbiturate administration are consistent with the report of Hernández-Peón et al. (1960). The decrease below 100 Hz. would be predicted (Pagano, 1966) if barbiturate administration was followed by more shallow respiration by the subject. Recordings of olfactory bulb slow wave activity, a known correlate of nasal air flow (Gault & Leaton, 1963; Gault & Coustan, 1965), support this interpretation. Figure 15 includes a section of bulb slow wave activity obtained before barbiturate administration and a section following administration. The post-barbiturate slow wave record indicates that respiration is more shallow than during the control period. Air flow cannot account for the entire barbiturate effect, however; air flow changes are correlated with amplitude changes, not waveform changes as are seen in the bulb fast activity in Figure 15. Since the reticular formation is depressed by barbiturates (Sharpless, 1970), perhaps reticular system depression is responsible for the waveform changes. If waveform changes as
Figure 15:

Subject J31, oscillographic displays before and after Sodium Pentobarbital administration. BSW is slow wave activity recorded from the same electrode as BULB (olfactory bulb). PPYR indicates the prepyriform cortex channel.
are seen for the fast activity in Figure 15 were observed in a system in forced vibration, the change would be described as an increase in the damping factor of the system.

Air flow arguments do not hold for the case of high frequency power increases following Ketamine administration; such changes were not observed following manipulation of nasal air flow in acute rat preparations initially anesthetized with Sodium Methohexital and maintained with artificial ventilation following spinal cord sectioning or Gallamine Triethiodide injection (Orr, Gault, & Stewart, 1971). The power increases below 100 Hz. following Ketamine injection for some subjects are correlated with an increase in nasal air flow. Figure 16 includes a pre-Ketamine slow wave record and a post-Ketamine slow wave record. The slow wave records show deeper respiration following drug administration, thus a low frequency spectral increase is consistent with Pagano's report (1966). Since Hughes and Hendrix (1967) have reported increases in spectral power between 100 and 150 Hz. following odor stimulation of rabbits, the possibility of olfactory stimulation must be considered. It seems unlikely that a long-term (at least 20 minutes) change in the olfactory environment would be correlated with the Ketamine injection. The possibility that Ketamine in the bloodstream is an effective olfactory stimulant would seem difficult to rule out.

A possible direction for future research would be to manipulate conditions of nasal air flow directly before and after drug administration. This would be possible in acute preparations where
Figure 16:

Subject J31, oscillographic displays before and after Ketamine administration. BSW is slow wave activity recorded from the same electrode as BULB (olfactory bulb). PPYR indicates the prepyriform cortex channel.
Figure 16

PRE

1 sec

50 μW/cm BSW

150 μW/cm BULB

75 μW/cm PPYR

POST

1 sec

50 μW/cm BSW

150 μW/cm BULB

75 μW/cm PPYR

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nasal air flow can be manipulated independently of respiration. This would show whether the drug was affecting the background activity or the olfactory spindle bursts. The development of a computer program which computed the appropriate covariances would make practical the investigation of multivariate spectra to determine frequencies shared between the time series arising from different electrodes.

Ketamine was found to be unsuitable as an anesthetic for olfactory research because of the high frequency spectral power increase but may prove useful in electropharmacologic analysis of olfactory system function.
REFERENCES


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