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Lateralized Effects of Diazepam on Frontal Brain Electrical Asymmetries in Rhesus Monkeys

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A growing body of literature has documented the differential role of the frontal regions of the two cerebral hemispheres in certain positive and negative affective processes. This corpus of evidence has led to the hypothesis of a possible differential effect of diazepam on asymmetry of frontal activation. To examine this question, nine infant rhesus monkeys were tested on two occasions during which brain electrical activity was recorded from left and right frontal and parietal scalp regions. During one session, recordings were obtained under a baseline restraint condition and then after an injection of diazepam (1 mg/kg). In the other session, following the same baseline restraint condition, a vehicle injection was given. In response to diazepam, the animals showed an asymmetrical decrease in power in the 4–8 Hz frequency band, which was most pronounced in the left frontal region. No change in electroencephalogram (EEG) activity was observed in response to vehicle. Asymmetry in parietal EEG activity was also unchanged by diazepam. Diazepam also produced overall reductions in power across different frequency bands in both frontal and parietal regions. Good test–retest stability of EEG measures of activation asymmetry was also found between the two testing sessions separated by three months. The possible proximal cause of the asymmetrical change in frontal brain electrical activity in response to diazepam, as well as the implications of these findings for understanding the mechanism of action of benzodiazepines are discussed.

Benzodiazepines typically decrease anxiety and increase reports of positive affect in humans when administered in small doses, while at larger doses, these drugs produce sedation (Rickels 1981). A growing body of literature has reported an association between asymmetrical frontal lobe activation and emotion (see Davidson, 1984; Davidson and Tomarken, 1989; Silberman and Weingartner, 1986 for reviews). In particular, the experimental arousal of certain forms of positive affect is associated with increased relative left-sided frontal activation, while the arousal of certain forms of negative affect is associated with increased relative right-sided frontal activation (Davidson and Tomarken, 1989; Davidson et al 1990b). The major purpose of this study was to determine if a single dose of diazepam produced an asymmetrical change in frontal brain activity, toward increased left-sided activation in rhesus monkeys. In addition to the literature on laterality

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and emotion, which clearly underscores the frontal specificity of the asymmetrical contributions, the distribution of benzodiazepine receptors in the brain also would lead us to expect frontal involvement. In a study of humans and cynomolgus monkeys using the positron-labeled benzodiazepine receptor antagonist, RO 15-1788, the frontal cortex was among the regions showing the highest degree of binding of all brain regions sampled (Persson et al 1985).

Most previous studies of the effects of benzodiazepines on regional brain activation assessed with either quantitative electroencephalography (EEG), positron emission tomography (PET), or procedures to measure regional cerebral blood flow have not focused on possible asymmetrical changes. For example, Buchsbaum and his colleagues (1987) reported decreases in glucose metabolism in some regions and increases in others after a 21-day trial of the benzodiazepine clorazepate, as compared with placebo. An important exception to this general trend is a study by Mathew, Wilson and Daniel (1985), in which they compared the effects of diazepam (0.1 mg/kg) to placebo in separate groups of subjects on regional cerebral blood flow measured with the ^{133}xenon inhalation technique. Diazepam was found to produce an asymmetrical shift in frontal blood flow, with a greater reduction on the right side than the left side. Unfortunately, separate groups of subjects were administered the drug and placebo. A repeated measures design is clearly preferable.

Previous EEG studies of benzodiazepines have not assessed lateralized changes. For example, in the squirrel monkey *Saimiri sciureus*, Ehlers and Reed (1987) found that oral administration of 2.5 mg/kg of diazepam reduced power in all frequency bands from 2 through 16 Hz. The only increase in power was found for the 16–32 Hz band. Although EEG was recorded from several anterior and posterior regions, only a single left hemisphere lead was chosen for analysis (F3–C3).

In rhesus monkeys, diazepam has been found to reduce certain fear-related behaviors. In particular, the pronounced freezing and crouching observed in response to a human intruder who is averting his gaze is dramatically reduced by the same dosage of diazepam used in the present study (Kalin and Shelton, 1989). In other words, in response to the drug the animals become much more behaviorally active when faced with a potential threat. In very shy human toddlers, who have a propensity to freeze in response to novelty, we have found decreased left frontal activation compared with a group of very sociable, outgoing children (Davidson et al 1992).

To assess lateralized electrophysiological changes produced by diazepam, we tested infant rhesus monkeys on two occasions, separated by three months. During each session, baseline measures of brain electrical activity were obtained while the animals were manually restrained. After the baseline recording period, diazepam was injected in the first session and vehicle was injected in the second session. On the basis of the previous EEG and behavioral data, we expected that diazepam, in the dosage used in the present study, would produce selective activation in the left frontal regional (indexed by desyncrhonization or reduction of power) compared with vehicle. We hypothesized that this lateralized effect would be restricted to the frontal region, since (a) previous electrophysiological studies have found emotion-related changes to be restricted to anterior brain regions, and (b) a high density of benzodiazepine receptors have been found in the frontal region. As the animals were tested on two occasions separated by three months, we also had an opportunity to examine the test–retest stability of EEG measures of frontal and parietal asymmetry taken during the same baseline restraint condition. Based upon our previous human data (Tomarken et al, in press) we predicted high test–retest correlations for

asymmetry in each region. We also predicted low correlations between frontal and parietal asymmetry, based upon our extensive series of human studies that have reported the same findings (see Davidson and Tomarken, 1989 for review).

Methods

Subjects

The subjects were four male and five female infant rhesus monkeys *(Macaca mulatta)*. They ranged in age from 1.08 to 1.24 yr and weighed 1.95–3.02 kg. The care and treatment of all animals was in accordance with institutional guidelines. The animals were housed with their mothers in a cage 71.5 cm wide by 71.5 cm high by 68 cm deep. Animals were maintained on a 12-hr light/dark cycle with lights on from 0600 to 1800. Infants were given water ad libitum and fed monkey biscuits as well as breast fed by their mothers except during the short experimental separation period. The animals had not been exposed to any other pharmacologic agents prior to this study.

Procedure

The experiment used a complete within-subjects design, with each animal tested on two separate occasions, three months apart. Animals were tested at the same time of day for each session, which occurred between 0830h and 1100h. Animals were separated from their mothers and brought to the electrophysiology laboratory. During each session, the animal was manually restrained while electrodes were attached (see below). Brain electrical activity was then recorded for approximately ten 15-sec trials prior to injection. In the first testing session, each animal was then injected i.m.[1] with 1 mg/kg of diazepam in a 5 mg/ml concentration. The injection occurred approximately 10 min after initial electrode application. Slight variations in time occurred as a function of the quality of the initial preinjection recordings (see below). After a period of 20 min after injection (during which the animals were continuously restrained), brain activity was recorded for approximately ten 15-sec trials. In the second testing session, after the initial baseline recording trials, the animals were injected i.m. with an equal volume of vehicle [each milliliter contained 0.4 ml propylene glycol, 0.1 ml alcohol, 0.015 ml benzyl alcohol, and sodium benzoate/benzoic acid (a total of 50 mg in water)] and following a 20-min period (during which the animals were again continuously restrained), a series of 15-sec recording trials were run. We determined the exact number of recording trials during each condition of the experiment on the basis of the quality of the recorded EEG. We wished to ensure that subjects had at least 20 artifact-free seconds of EEG across trials within each condition. We chose to use short trials (i.e., 15 seconds) so that we could monitor the quality of the EEG on-line and collect only as many trials as we needed to ensure a sufficient amount of artifact-free data. The interval between trials was usually about 2 sec, unless artifact was visibly present in the EEG. In such cases, the next trial began when the EEG normalized.

[1]Injections were given intramuscularly rather than intravenously to make this study comparable to other data from the Kalin laboratory on the behavioral effects of diazepam where i.m. injections have been used (Kalin and Shelton, 1989).

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Results

Electroencephalogram Recording and Data Reduction

Left and right frontal (F3 and F4) and left and right parietal (P3 and P4) electrodes were placed according to the standard 10/20 system. Silver/silver chloride electrodes were used, and the four active leads were referenced to linked mastoids.[2] The scalp surface was initially abraded with Omni-Prep (Boulder, CO) and then electrodes were attached with Grass EC-2 cream. All electrode impedances were below 10 kΩ. The EEG was amplified using Grass Model 12 EEG amplifiers, with a gain of 20,000 and a band-pass of 0.1–200 Hz. The EEG was passed through active, low-pass antialiasing filters set at 85 Hz with a 48 db/octave roll-off. The filtered output was sampled at 250 samples/sec on a PDP-11/34A computer. Prior to analysis, all EEG waveforms were visually edited to remove all portions of the record containing eye movement or other artifact. When artifact was detected in any channel, data from all channels were removed. A minimum of 20 artifact-free seconds of EEG was required per condition, per subject. All subjects met this criterion. There was a mean of 70.95 artifact-free seconds of EEG per condition.

A fast Fourier Transform (FFT) was performed on all artifact-free chunks of data 2 sec in duration. The 2-sec epochs were extracted with a Hamming window, overlapped by 50%. The FFT output was converted to power density (in $\mu V^2/Hz$); these values were then log-transformed to normalize the data (Gasser, Bacher and Mocks, 1982).

We expected that the most robust lateralized changes would occur in the 4–8 Hz band because most of the power in the EEG spectrum was in this band (Davidson et al 1990). Moreover, this band is consistent with that used in studies with young children in the 3–4 yr age range (Davidson et al 1992). In addition to assessing power in the 4–8 Hz band, we also examined power in two higher frequency bands: 8–13 Hz and 13–20 Hz. For each subject, we aggregated all artifact-free periods during the baseline (initial) recording period and during the period following the injection (either drug or vehicle). To express the direction and magnitude of asymmetry, a log difference was created (log right minus log left power). Assuming that decrements in power are associated with activation (see Davidson 1988 and Davidson and Tomarken 1989 for reviews), higher numbers on this difference score are associated with more relative left-sided activation. Sex was initially included as a factor in all of the overall analyses of power in each band. Neither the main effect for sex, nor any interaction with sex was obtained for any of the measures. It was therefore dropped from all subsequent analyses.

Results

Drug versus Vehicle Comparisons

4–8 Hz Band Power. We first examined differences in the asymmetry score between baseline and drug (versus baseline and vehicle conditions) separately for frontal and parietal region EEGs. A repeated-measures analysis of variance (ANOVA) was computed with test session (session 1/session 2) and condition (baseline/injection) as factors. During test session 1, the injection was always drug, while during test session 2 the injection

[2]Although an anecdotal observation reported in Nunez (1981) implied that physically linking the ears or mastoids might attenuate the magnitude of observed asymmetry, in a systematic study we have not found any evidence for this claim (Senulis and Davidson 1989). Two recent studies have also found no evidence of asymmetry attenuation as a function of linking the ears (Andino et al 1990; Miller et al 1991).

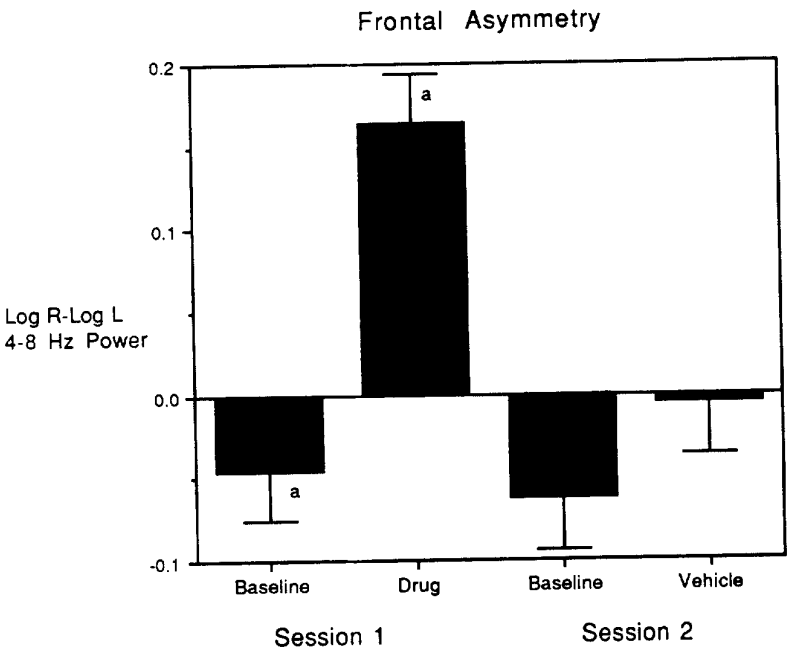

Figure 1. Mean frontal asymmetry scores (log right minus log left power in the 4–8 Hz band) during baseline restraint and in response to drug (diazepam) injection during session 1 and during baseline restraint and in response to vehicle injection during session 2. Note that higher numbers are indicative of greater relative left-sided activation. Error bars indicate standard error of the mean ($n = 9$). Bars that share common lower case letters indicate that they differ significantly from one another within session.

was always vehicle. The ANOVA on the frontal asymmetry scores revealed a significant test session × condition interaction ($F[1,8] = 7.00$, $p < 0.03$). As Figure 1 indicates, in the baseline recordings under restraint during both test sessions 1 and 2, the animals show right-sided frontal activation (denoted by the negative laterality scores). In response to diazepam, the animals show a dramatic increase in left frontal activation, as revealed by the change to a positive laterality score ($t[8] = 3.49$, $p = 0.008$). Little change is associated with vehicle injection ($t < 1$).

The ANOVA on the parietal asymmetry scores revealed no significant main effects or interaction. The clear lack of a test session × condition interaction ($F[1,7] = 0.39$) for parietal asymmetry[3] underscores the specificity of the asymmetrical effect of diazepam to the frontal region.

In order to decompose the asymmetry scores and determine the effects of diazepam on EEG power, separate repeated measures ANOVAs were run on frontal and parietal log power data with test session (session 1/session 2), condition (baseline/injection) and hemisphere (left/right) as factors. For both frontal and parietal EEGs (see Figures 2

[3]The reduced degrees of freedom for parietal EEG data is a function of unacceptably high impedances for recording parietal EEG in one animal. This animal was therefore dropped from all analyses of parietal EEG, so that these analyses are based upon eight animals.

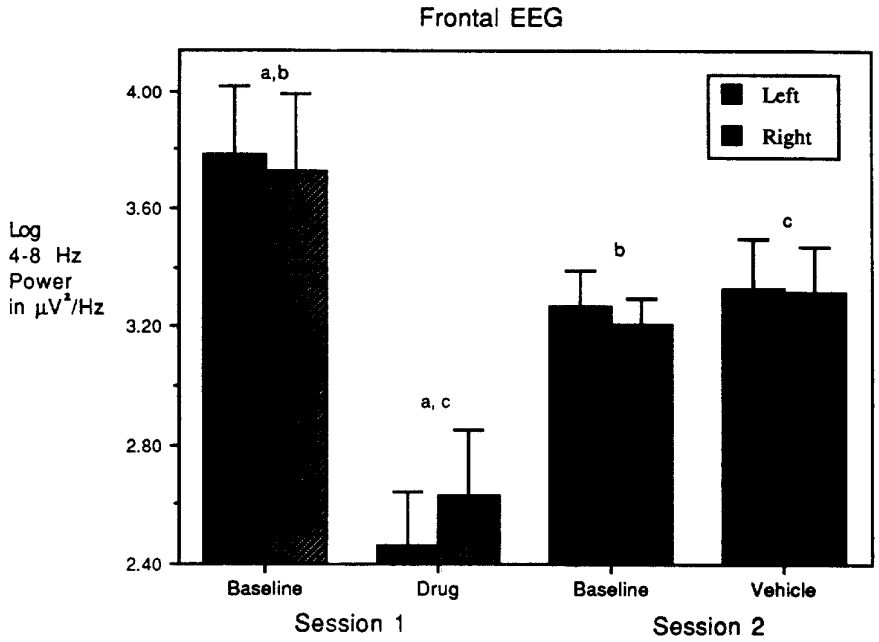

Figure 2. Mean log-transformed power density (in $\mu V^2/Hz$) in the 4–8 Hz frequency band for left and right frontal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 9$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

and 3), highly significant test session × condition interactions were obtained (frontal: $F[1,8] = 35.22$, $p = 0.0003$; parietal: $F[1,7] = 22.91$, $p = 0.002$). For both frontal and parietal EEGs, the administration of diazepam produced a significant reduction in the 4–8 Hz power bandwidth, while vehicle had no systematic effect. This was confirmed in separate ANOVAs on each session. For both frontal and parietal regions, highly significant main effect effects for condition (baseline/injection) were obtained for session 1 data only (frontal: $F[1,8] = 49.84$, $p < 0.0001$; parietal: $F[1,7] = 33.11$, $p < 0.001$). The main effect for condition was not significant for session 2. When the main effect for session was examined separately for the baseline and injection conditions, significant main effects were found for both frontal and parietal regions for the baseline condition (frontal: $F[1,8] = 8.93$, $p < 0.02$; parietal: $F[1,7] = 19.11$, $p < 0.005$). As can be seen from Figures 2 and 3, this main effect is a function of less power during baseline in the second test session compared with the first. However, when the main effect for session was examined for the injection conditions, a significant main effect was found for the frontal region in a direction opposite to the baseline data ($F[1,8] = 14.52$, $p = 0.005$). Diazepam produced greater suppression of power in the 4–8 Hz band as compared with vehicle. The main effect of injection condition for the parietal region was in the same direction, but was not significant ($F[1,7] = 4.28$, $p < 0.08$). In addition to these main effects, for the frontal leads only, there was a significant test session × condition × hemisphere interaction ($F[1,8] = 7.00$, $p < 0.03$). As can be seen from Figure 2,

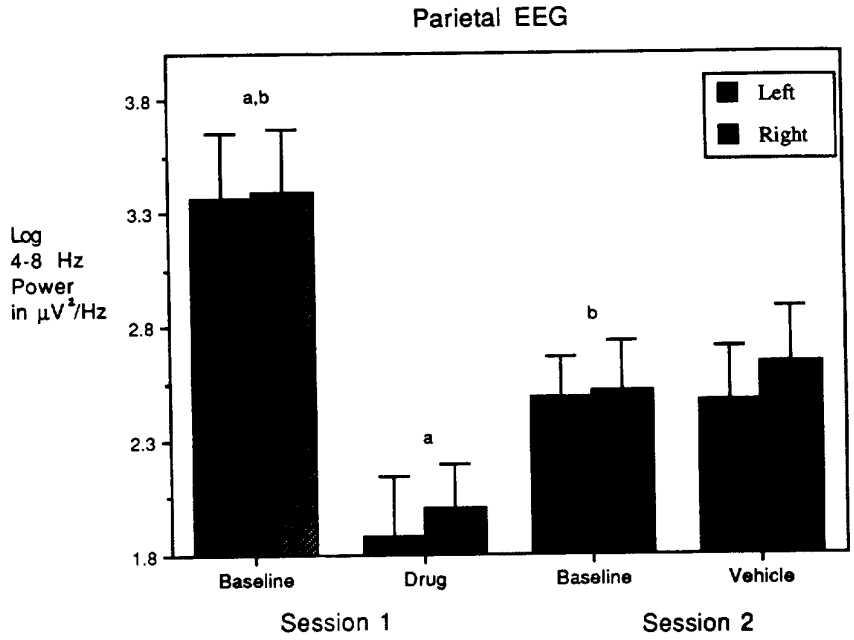

Figure 3. Mean log-transformed power density (in $\mu V^2/Hz$) in the 4–8 Hz frequency band for left and right parietal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 8$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

there was a clear reversal of asymmetry in response to diazepam compared with baseline. This was supported by the presence of a significant condition × hemisphere interaction for session 1 ($F[1,8] = 12.19$, $p < 0.01$). The absence of any interaction for session two indicated that vehicle had no systematic effect on asymmetry.

8–13 Hz Band Power. We computed ANOVAs on the power asymmetry metric for the 8–13 Hz band in the same manner as described above. A repeated measures ANOVA was computed with test session (session 1/session 2) and condition (baseline/injection) as factors. Neither the main effects, nor the interaction were significant for either frontal or parietal asymmetry. For the frontal region, the test session × condition interaction was $F[1,8] = 2.55$, $p = 0.15$; for the parietal region, this interaction was $F[1,7] = 0.13$, $p > 0.7$. We also examined individual hemisphere power values by computing ANOVAs with test session, condition, and hemisphere as factors. As we found for the 4–8 Hz band, a highly significant test session × condition interaction was obtained across hemisphere for both frontal and parietal region EEGs (frontal: $F[1,8] = 40.92$, $p < 0.001$; parietal: $F[1,7] = 26.51$, $p < 0.01$). In both the frontal and parietal regions, the main effect for condition was highly significant in session 1 and absent in session 2 (frontal: $F[1,8] = 61.30$, $p < 0.0001$; parietal: $F[1,7] = 44.36$, $p = 0.0003$). When the data for each of the two conditions were compared between the two sessions, it was found that the session 2 baselines contained significantly less power in this band than the

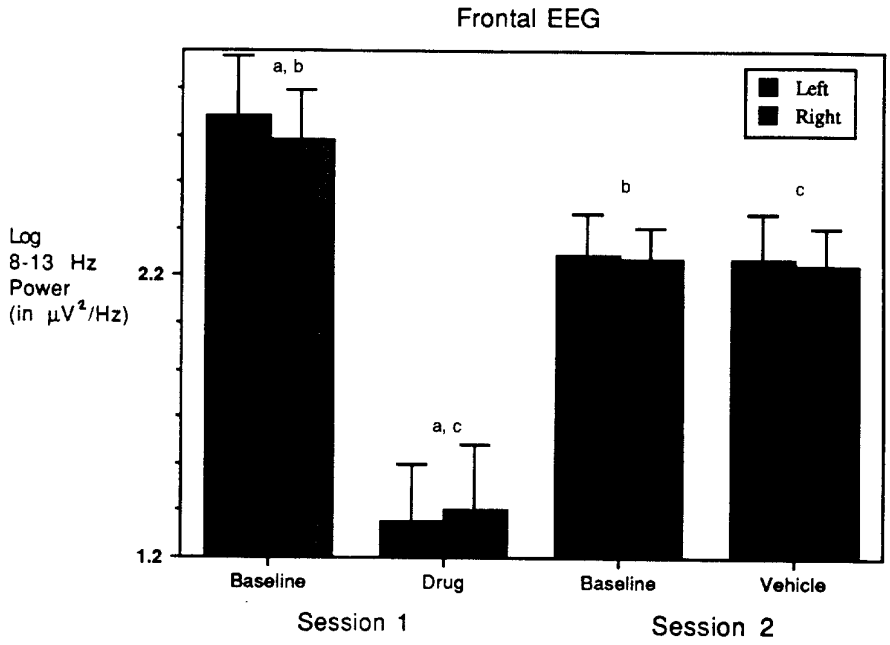

Figure 4. Mean log-transformed power density (in $\mu V^2/Hz$) in the 8–13 Hz frequency band for left and right frontal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 9$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

session 1 baselines (frontal: ($F[1,8] = 11.15$, $p = 0.01$); parietal: $F[1,7] = 19.69$, $p = 0.003$). During the injection conditions, however, significantly less power was present in response to diazepam (session 1) than in response to vehicle (session 2) for both frontal ($F[1,8] = 12.70$, $p < 0.01$) and parietal ($F[1,7] = 5.58$, $p = 0.05$) regions. The frontal and parietal 8–13 Hz data are presented in Figures 4 and 5.

13–20 Hz Band Power. ANOVAs computed on the power asymmetry scores for this band indicated no significant main effects or interactions (test session × condition) for either the frontal or parietal regions (test session × condition interaction for frontal region: $F[1,8] = 0.97$, $p > 0.35$; for parietal region: $F[1,7] = 0.06$, $p > 0.8$). When ANOVAs were performed on the power values, we found significant test session × condition interactions for both frontal and parietal power, as was found for all other bands. For the frontal region, $F[1,8] = 12.83$, $p < 0.01$. For the parietal region, $F[1,7] = 16.38$, $p < 0.005$. These interactions are illustrated in Figures 6 and 7. As can be seen from these figures, diazepam produces the lowest overall EEG power compared with the other conditions. To decompose this interaction, condition × hemisphere ANOVAs were performed on session 1 and session 2 data. As is apparent from Figures 6 and 7, significant main effects for condition were obtained in session 1 for both frontal ($F[1,8] = 12.91$, $p < 0.01$) and parietal ($F[1,7] = 12.00$, $p = 0.01$) EEGs with the diazepam condition associated with significant reductions in power compared with baseline for both

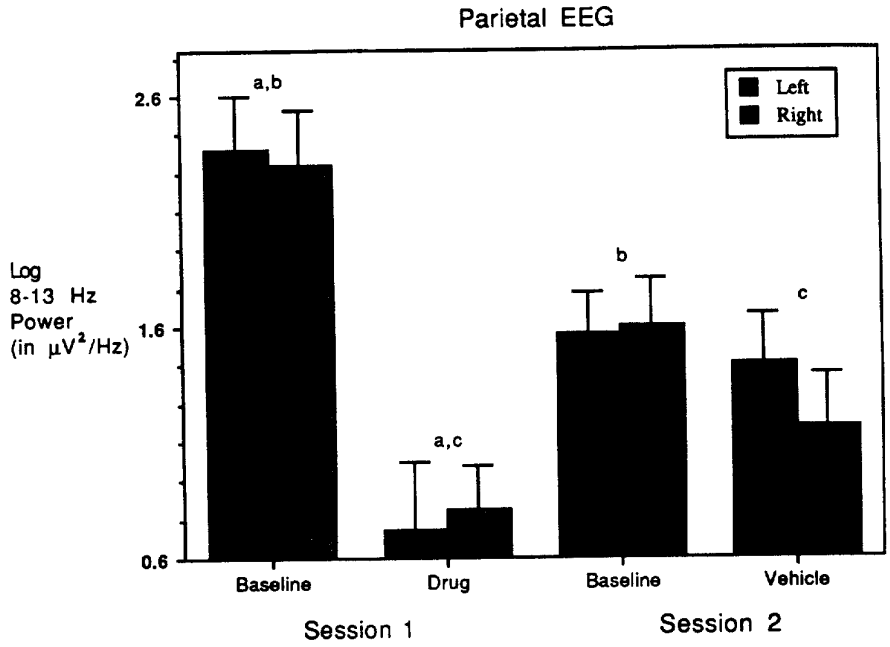

Figure 5. Mean log-transformed power density (in $\mu V^2/Hz$) in the 8–13 Hz frequency band for left and right parietal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 8$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

regions. No significant main effect for Condition was obtained for session 2 data in either frontal or parietal regions. When the two sessions were compared within each condition, we found that session 2 baseline was associated with less power in both frontal ($F[1,8] = 4.92$, $p < 0.06$) and parietal ($F[1,7] = 18.19$, $p < 0.005$) regions than session 1 baseline. In response to the injection conditions, diazepam produced less power when compared with vehicle in both frontal and parietal regions, although neither of these differences reached significance.

Stability of Electroencephalographic Measures of Asymmetry and Relations Between Frontal and Parietal Region Measures

To assess the stability of baseline EEG asymmetry, we examined the intraclass correlation (ICC) between test session 1 and test session 2 baseline asymmetry scores. The ICC is considered more appropriate than the Pearson correlation to assess test–retest stability (Shrout and Fleiss, 1979; see Tomarken et al, in press, for its application in a similar context in human research). There are several alternative versions of the ICC. The model adopted in the present study estimated the between-sessions component of variance as a fixed effect (Shrout and Fleiss' formula 3,1). We computed the ICCs separately for the baseline frontal and parietal asymmetry scores derived from band power in each of the three bands. For asymmetry in the 4–8 Hz band, the ICC for the frontal region was 0.77

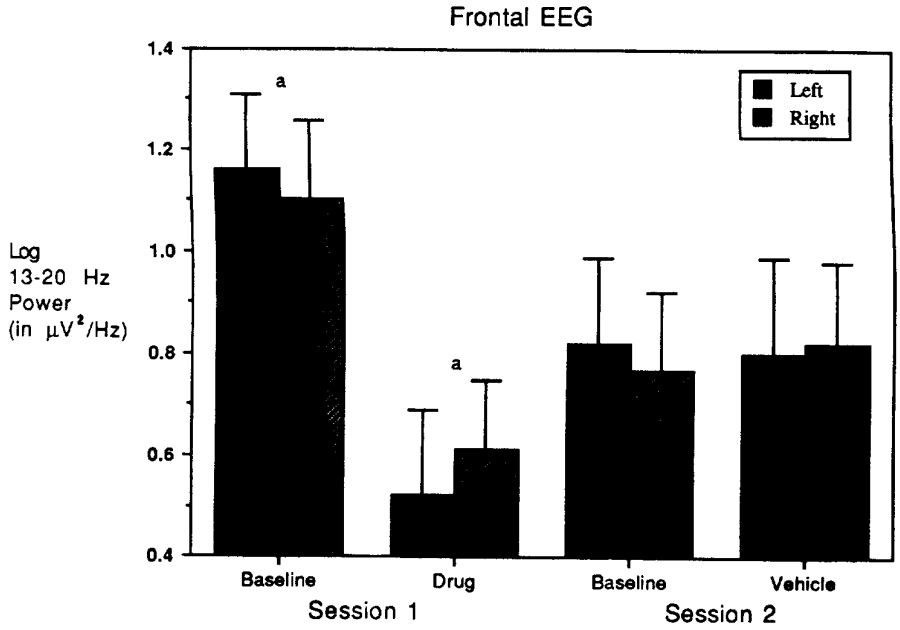

Figure 6. Mean log-transformed power density (in $\mu V^2/Hz$) in the 13–20 Hz frequency band for left and right frontal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 9$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

and for the parietal region it was 0.81. For the 8–13 Hz band, the ICC for the frontal region was 0.68 and for the parietal region it as 0.79. For the 13–20 Hz band, the ICC for the frontal region was 0.67 and for the parietal region, it was 0.88. All correlations were significant ($p < 0.05$) indicating moderate stability for EEG asymmetry measures in the frontal and parietal regions over a three month period.

We also computed the correlations between frontal and parietal baseline asymmetry scores, separately for test session 1 and test session 2 for each band. The correlations ranged from 0.47 to −0.32 and none were significant.

Discussion

The findings from this study supported the hypothesis that a single moderate dose of diazepam produced a significant change in frontal brain electrical asymmetry compared with vehicle injections. Diazepam resulted in greater relative suppression of power in the 4–8 Hz band in the left frontal region, as compared with the right. A wealth of evidence from human EEG studies suggests that reductions of power in this frequency band in age-comparable subjects is associated with activation (see Shagass, 1972 for a general overview; see Davidson 1988; Davidson et al 1990a for additional evidence). If the power reductions in the present study are interpreted in the same way, the data indicate that diazepam at moderate doses increases relative left frontal activation. This finding is

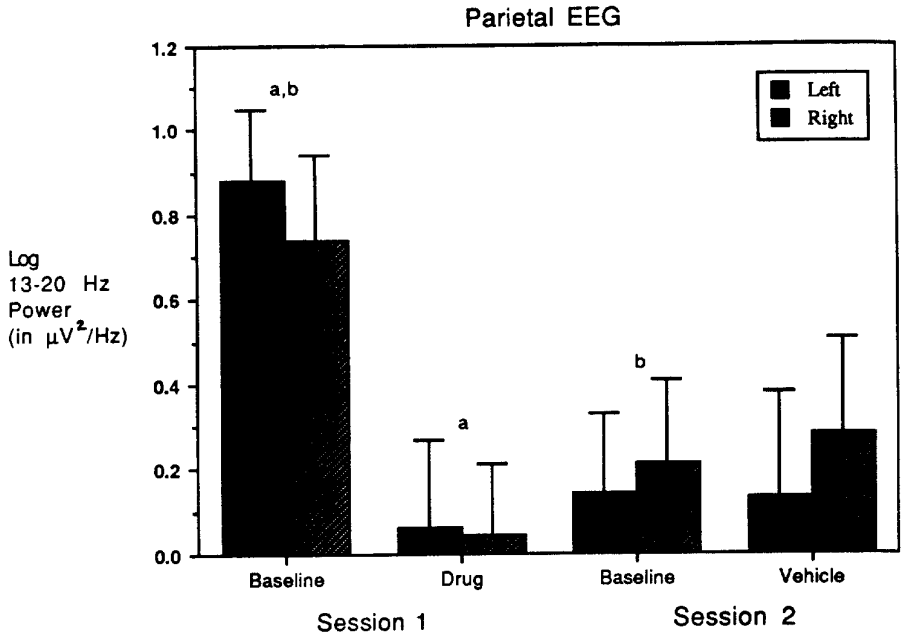

Figure 7. Mean log-transformed power density (in $\mu V^2/Hz$) in the 13–20 Hz frequency band for left and right parietal EEG during baseline restraint and injection conditions for sessions 1 and 2. Error bars indicate standard error of the mean ($n = 8$). Bars that share common lower case letters indicate that they differ significantly from one another across hemisphere.

consistent with the cerebral blood data of Mathew et al (1985) who found a change in frontal blood flow in the same general direction in response to a single dose of diazepam.

We also found that diazepam produced reductions in power in both frontal and parietal regions in each of the three frequency bands examined. That diazepam produced overall reductions in power (presumably associated with increased activation) is also consistent with other electrophysiological and behavioral observations. Ehlers and Reed (1987) have observed similar reductions in power in the squirrel monkey. Kalin and Shelton (1989) reported that diazepam given in the same dosage and by the same route as was used in the present study produced behavioral activation and decreased freezing in response to threat. Thus, we have reason to believe that if the animals in the present study were not restrained, they would likely show disinhibition and behavioral activation in the presence of novelty and/or threat.

The direction of the asymmetrical effect of diazepam on frontal brain electrical activity is consistent with the reported changes in mood induced by this drug. Experimentally aroused positive emotion is associated with an increase in relative left frontal activation (Davidson et al 1990b) and individuals with extreme relative left frontal activation report greater dispositional positive affect and less dispositional negative affect than their more right-frontally activated counterparts (Tomarken et al 1992). In future research with humans, it will be important to examine the relation between the magnitude of the frontal asymmetrical effect of diazepam and the change in intensity of reported mood. Alter-

natively, it might be the increase in behavioral activation per se that is associated with the increase in left-sided frontal activation. By obtaining self-report measures of mood and behavioral measures of activation in humans, it might be possible to determine which of these indices is most affected by benzodiazepine administration.

The proximal cause of the asymmetrical effect of diazepam is not known. In future research it will be of interest to systematically examine whether benzodiazepine receptors are asymmetrically distributed in the frontal cortex. This question can be addressed with currently available PET technology using a positron-labeled benzodiazepine receptor antagonist ([^{11}C] Ro 15-1788). In a preliminary study using this radio-labeled tracer with four subjects, Abadie et al (1991) found fewer benzodiazepine receptors in the right than left lateral frontal and lateral temporal regions. Such an asymmetry would presumably result in greater benzodiazepine effect in left, as compared with right hemisphere sites, although it will be important in future research to obtain such measures within the same subjects.

This study also established that measurements of frontal and parietal brain electrical asymmetries under conditions of restraint are moderately stable over a three month interval and comparable to those reported in humans (Tomarken et al, in press). It is also of interest to note that when tested under the condition of restraint, the monkeys show right-sided frontal activation during both test sessions 1 and 2, with virtually the same asymmetry score during each, despite changes from session 1 to session 2 in overall power during the baseline condition.

Several limitations of the present study should be noted. First, EEG was recorded from only four scalp locations. It is possible that the asymmetrical effects of diazepam would be observed in regions other than the frontal cortex. Relatively high receptor densities have been reported in the temporal cortex (Buchsbaum et al 1987) and we have observed asymmetrical brain electrical activity in the anterior temporal region that was similar to the patterns we have reported in the frontal region (Davidson et al 1990b; Tomarken et al 1992). A second limitation of the present study is that all animals received drug in session 1 and vehicle in session 2. We believe that this fixed order was inconsequential for two reasons: (a) the test sessions were separated by a three-month interval, which should be sufficiently long to counteract any order effects; (b) the frontal asymmetry was virtually identical during each test session under the initial restraint condition, with good test–retest correlations. It is also important to note, however, that although good test–retest stability was found across the three-month period for asymmetry during the baseline conditions, there was a significant change over time in overall power in both regions in this condition. Power at session 2 was always lower than power at session 1. It is likely that the primary contributor to this effect is a developmental change in skull thickness: the monkeys were approximately 1 yr old when they were first tested and therefore still undergoing major developmental changes in bone structure. A major contributor to overall EEG power recorded from the scalp surface is skull thickness (see Tomarken et al, in press, for discussion of this issue). As the animals mature and their skulls thicken, EEG power will be attenuated. In humans, EEG power among infants and children is consistently greater than power in adults (Davidson and Fox 1989). To more directly address this question, it will be of interest to compare adult versus infant monkeys across multiple sessions over a several-month interval. It is expected that there would be systematic variations in overall power as a function of age in the infant monkeys, but not in the already mature adult monkeys.

In future studies it will be of interest to examine dose–response effects. In the present

study, a single dose of diazepam was given (1 mg/kg). At higher and/or more prolonged doses, increased, rather than decreased power is likely to be observed in the slower frequency bands.

In subsequent studies, we intend to examine the relation between the behavioral and electrophysiological effects of diazepam. Some animals show very pronounced reductions in freezing to a novel challenge in response to diazepam, while others show less pronounced effects. It will be of interest to study whether the change in EEG asymmetry with diazepam predicts the behavioral change induced by the drug. Such data may have very important implications for predicting individual differences in response to diazepam as well as vulnerability to abuse of this class of drugs.

Finally, this study demonstrates the feasibility of measuring scalp electrophysiology noninvasively in the infant rhesus monkey. These procedures may prove useful in the investigation of brain–behavior relations in behaving monkeys where repeated testing and fast time resolution are required.

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