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Effect of unilateral ibotenate lesions of the ventral tegmental area on cortical and hippocampal EEG in freely behaving rats

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Short communication

Abstract. It was found previously that unilateral destruction of the ventral tegmental area (VTA) facilitated behavioral responses (exploration, eating) induced by electrical stimulation of the contralateral VTA. The same effect occurred after unilateral injections of pharmacological agents, which led to a decrease in dopaminergic transmission in the VTA. While trying to explain the mechanism behind this "contralateral facilitation effect" in the present experiment we examined whether augmentation of function of the contralateral hemisphere would be reflected in cortical and hippocampal EEG changes in conscious rats. Unilateral, cytotoxic lesion of the VTA caused a bilateral decrease in neocortical and hippocampal EEG power during both exploratory sniffing and eating. Depression involved all the frequency bands in the prefrontal cortex, mainly in the hemisphere contralateral to the VTA lesion. In the hippocampus the depression was slightly more intense ipsilaterally, also involving all the frequency bands although to different degrees. The results indicate that the VTA is involved in the regulation of cortical and hippocampal activity during VTA-dependent behavioral activation, and that the "contralateral facilitation effect" is concomitant with lateralized changes in EEG activity.

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The midbrain ventral tegmental area (VTA) is a key structure of the dopaminergic mesolimbic-mesocortical system, which is involved in the regulation of various appetitive behaviors, stress responses and reward, including that produced by drugs of abuse (e.g., Le Moal and Simon 1991, Wise and Rompre 1989). Stimulation of the VTA results in general activation expressed as an increase in locomotor activity, especially exploratory activity which frequently leads to an eating response (e.g., Maliszewska-Ścisło and Trojniar 1999, 2000, Trojniar and Klejbor 1999, Trojniar and Staszewska 1994). In the rat such behavioral activation is usually accompanied by synchronization of hippocampal field activity at theta frequency (Vanderwolf 1969) and cortical desynchronization.

In the present study we were interested in whether the VTA participates in the regulation of hippocampal and cortical EEG in rats performing VTA-dependent behaviors. The following facts suggest such a possibility: (i) the hippocampal formation receives dopaminergic afferents from the VTA (Gasbarri et al. 1997, Scatton et al. 1980); (ii) there are dopamine-binding receptors within the hippocampus (Goldsmith and Joyce 1994, Verney et al. 1985); (iii) prefrontal cortex is innervated by both dopaminergic (Oades and Halliday 1987) and GABA-ergic (Carr and Sesack 2000) afferents from the VTA; (iv) bilateral suppression of synaptic dopamine release evokes behavioral sleep and an increase in cortical EEG total power (Bagetta et al. 1988, 1989, Sebban et al. 1999b); but (v) activation of the mesocortical dopaminergic system results in suppression of the activity of the prefrontal cortex (Gotbout et al. 1991, Jay et al. 1995); (vi) discharge rates of VTA GABA-ergic neurons correlate with psychomotor behavior and the sleep-wake cycle (Lee et al. 2001). Dopaminergic activation also exerts a frequency-dependent effect on hippocampal-prefrontal cortex transmission (Gurden et al. 1999); (vii) 6-OHDA lesions of the VTA in the rat decrease the frequency of the cortical theta rhythm during waking and paradoxical sleep (Sei et al. 1999).

Previously we found that unilateral inactivation of the VTA by either electrolytic lesions or 6-OHDA administration enhance the reactivity of the contralateral VTA to electrical stimulation (Klejbor and Trojniar 1997, Maliszewska-Ścisło and Trojniar 1999, Trojniar and Klejbor 1999, Trojniar and Staszewska 1994). Unilateral VTA stimulation-elicited behaviors (feeding, exploratory locomotion) are sensitized after contralateral VTA lesion. The same effect occurs after unilateral intra-VTA application of $GABA_A$, DA1, DA2 (Klejbor and Trojniar 1997, Trojniar and Klejbor 1999) and NMDA (Maliszewska-Ścisło and Trojniar 2000) receptor antagonists. The mechanism of such "contralateral facilitation" is unclear. It undoubtedly depends on the VTA dopamine transmission and the factors which regulate the activity of the dopaminergic cells. In the present experiment we tested whether the facilitatory effect of unilateral lesions of the VTA on the function of the intact hemisphere is reflected in changes in EEG activity of the prefrontal cortex and dorsal hippocampus.

The experiment was performed on 6 male, well-handled, Wistar rats implanted with bilateral, chronic electrodes for EEG recording (monopolar) over the frontal cortex (area FR 2 according to the atlas by Paxinos and Watson 1998) and in the dorsal hippocampus. A reference electrode (jeweler screw) was screwed into the skull over the olfactory bulbs. Unilateral cannula for the ibotenic acid injection was implanted in the left VTA. Stereotaxic coordinates were as follows: cortex, AP (bregma) = -3.5 mm, L = 1.0 mm, D = 1.0 mm (skull surface); hippocampus, AP = 3.8 mm, L = 2.4 mm, D = 3.2 mm; VTA, AP = 4.8 mm, L = 1.0 mm, D = 8.2 mm.

After the rats recovered from surgery, cortical and hippocampal EEG was recorded using a Medicor electroencephalograph as a preamplifier (bandpass 0.3-70 Hz) and a EEG Digi Track system (ELMIKO, Poland) to register the signal (sampling rate 240 Hz) on the computer's hard drive. The recordings were made in 260 × 260 × 400 mm glass cages placed in a sound attenuating chamber in which the rats could move freely and had access to food pellets covering the floor. Recording sessions lasted about 1 hour in the morning. In each rat the EEG was analyzed during two behavioral reactions in separate experimental sessions: exploratory sniffing (exploration of the experimental cage) and a more automatic reaction – eating induced by 24 h food deprivation. EEG recordings were conducted in 3 experimental states: the control drug-free state, one week after phosphate buffer injection (ibotenate solvent, pH 7.4, 0.5 μl) and one week after ibotenic acid injection (4μg/0.5μl, dissolved in phosphate buffer) to the VTA. All injections were made to the left VTA and were separated by a 7-day period.

For each behavior the spectral EEG analysis was performed off-line by fast Fourier transformation (FFT) on nine 5-s artifact-free epochs of the cortical and the hippocampal records (chosen randomly). Assessed were: the total power and power in the standard EEG

bands: delta (0.3-3.9 Hz), theta (4.0-8.0 Hz), alpha (8.1-12.0 Hz), beta (12.1-30.0 Hz) and gamma (30.1-65.0 Hz).

After completion of the experiment the brains were subjected to the standard histological procedures to reconstruct the extent of the ibotenic lesions, and localization of the recording electrodes.

No major behavioral changes (food and water intake, general motility) were observed after the lesions. In 4 rats necrosis and cell loss was found in the anterior VTA area; in the other two rats lesions were situated above and rostral to the VTA, at the level of the zona incerta or the posterior thalamus. These rats were used as a control for anatomical specificity of the results obtained. Hippocampal electrodes were localized within the dorsal blade of the dentate gyrus.

Cortical and hippocampal EEG and the corresponding power spectra in an example rats before and after VTA lesion are presented in Fig. 1 (exploratory sniffing) and Fig. 2 (eating), and lesion-induced changes in power at distinguished frequency bands in Fig. 3 and Fig. 4, respectively.

Lesions of the VTA resulted in a bilateral decrease in the total power of the EEG signal recorded from the neocortex and the hippocampus both during exploratory sniffing and eating. Due to the inter-individual variability in the power values all results were expressed as a percentage change in comparison to the control, phosphate buffer (solvent) injections. During sniffing in the prefrontal cortex the total power was reduced by 25.6 ± 5.7% (mean ± SE) ($P<0.001$) on the ipsilateral side and by 45.6 ± 4.1% ($P<0.001$) on the contralateral side in comparison to the buffer injection. During eating the reduction of power was 44.1 ± 4.7% ($P<0.001$) ipsi- and 60.1 ± 3.2% ($P<0.001$) contralaterally. In the hippocampus the analogous values were: 32.2 ± 5.1% ($P<0.001$) and 26.2 ± 3.5% ($P<0.001$) for sniffing, and 27.3 ± 5.9% ($P<0.001$) and 27.0 ± 3.6% ($P<0.001$) for eating. The mean reduction of power was significantly greater contralateral to the lesion in the cortex during eating and sniffing ($P<0.01$). Decrease in the total power seems to be structure-specific, because in the rats with misplaced lesions the total power was either several times higher in comparison to the control or no different (not shown).

In the cortex depression of EEG power occurred in almost all frequency bands bilaterally both during sniffing (Fig. 3) and eating (Fig. 4) except in the delta band in the ipsilateral hemisphere during sniffing. The hemisphere contralateral to the lesion was more profoundly affected. Significant interhemispheric differences were found at all frequency bands during eating and at delta, beta and gamma bands during sniffing. In the hippocampus all frequency bands were affected bilaterally during sniffing with a slightly higher effect on the ipsilateral hemisphere (Fig. 3). During eating (Fig. 4) there was a bilateral decrease of power in the lower frequency bands (delta and theta). The higher frequency bands (alpha, beta, gamma) were affected ipsilaterally.

Decrease in the power spectra is frequently taken as an index of EEG desynchronization, whereas an increase in power is seen as a sign of EEG synchronization. For example, in pharmacological studies (Sebban et al. 1999a,b) on cortical EEG profiles elicited by psychotropic drugs, the synchronizing action of low doses of dopamine receptor agonists (inhibition of synaptic dopamine release by selective activation of autoreceptors) was postulated on the ground that they caused an increase of EEG power at higher frequencies and its reduction at low frequencies. The opposite effect i.e., a reduction of power at higher frequencies and its enhancement at low frequencies found after higher doses of dopaminergic agonists was regarded as an expression of their desynchronizing action. The DA antagonist haloperidol which caused an increase in power over almost the entire range of EEG frequencies was regarded as a synchronizing drug.

In the present study decreases in the prefrontal cortex EEG power were uniform across frequency bands but it is not certain whether they really reflected increased desynchronization, as no marked displacement in the FFT power peaks (at delta and theta band) occurred after the lesions (Figs. 1 and 2, particularly the contralateral hemisphere).

The EEG effects of unilateral VTA destruction in the present study are not compatible with those of pharmacological suppression of the postsynaptic dopaminergic activity (Bagetta et al. 1988, 1989, Sebban et al. 1999a,b). In fact they are opposite. This inconsistency may result from various compensatory adaptations in the dopaminergic and other neurotransmitter systems after their incomplete destruction (Kostrzewa 1995, Robinson et al. 1990). It is worth mentioning that unilateral VTA damage affected cortical and hippocampal activity bilaterally. However, clear lateralization of the observed effects, a more profound drop in power contralaterally in the prefrontal cortex was observed. Only further experiments may disclose whether these interhemispheric difference are of relevance for the

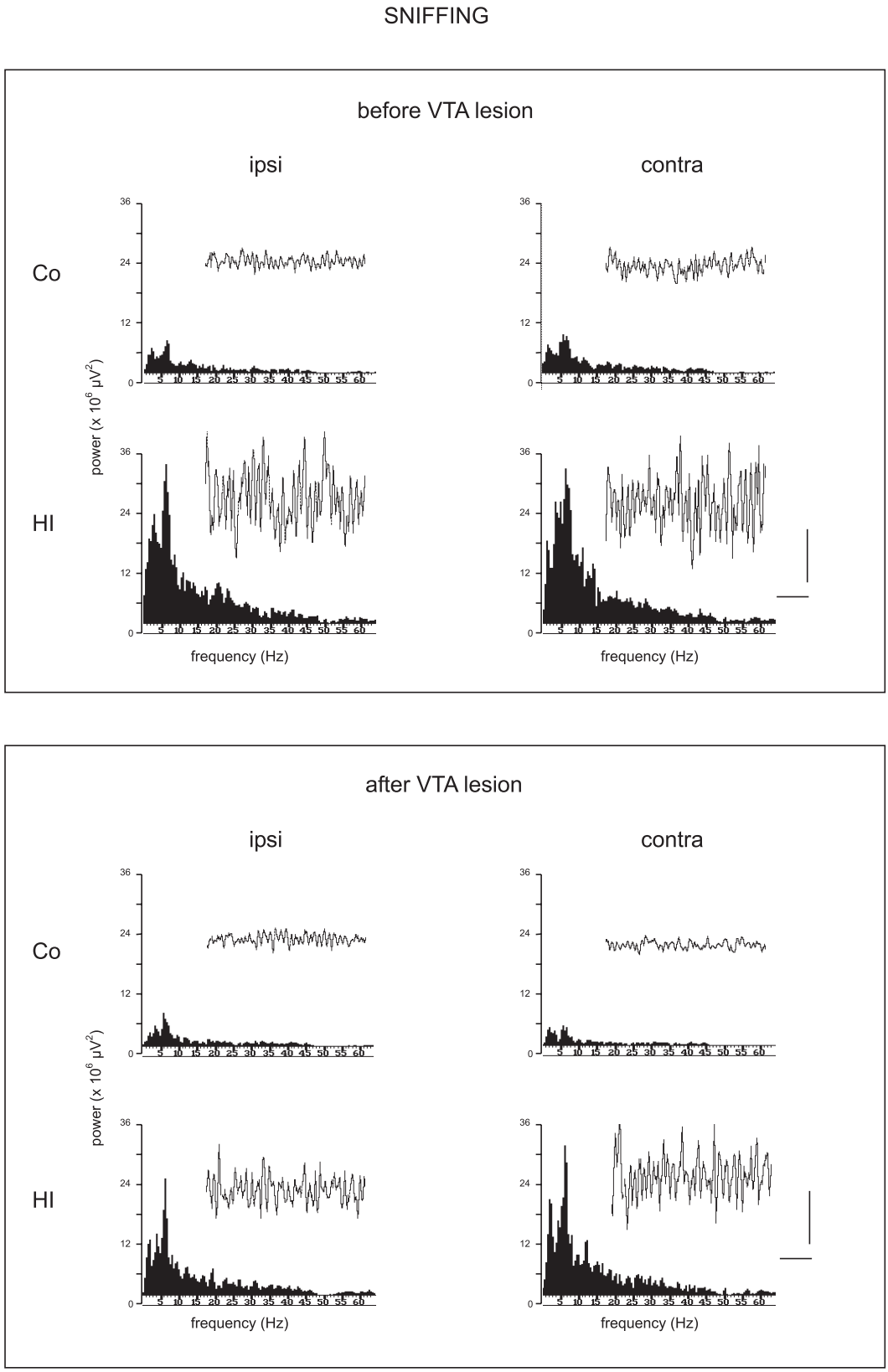

Fig. 1. EEG power spectra and corresponding cortical (Co) and hippocampal (HI) EEG traces in an example rat performing exploratory sniffing before and after unilateral VTA lesion. Calibration: 1 s and 250 µV.

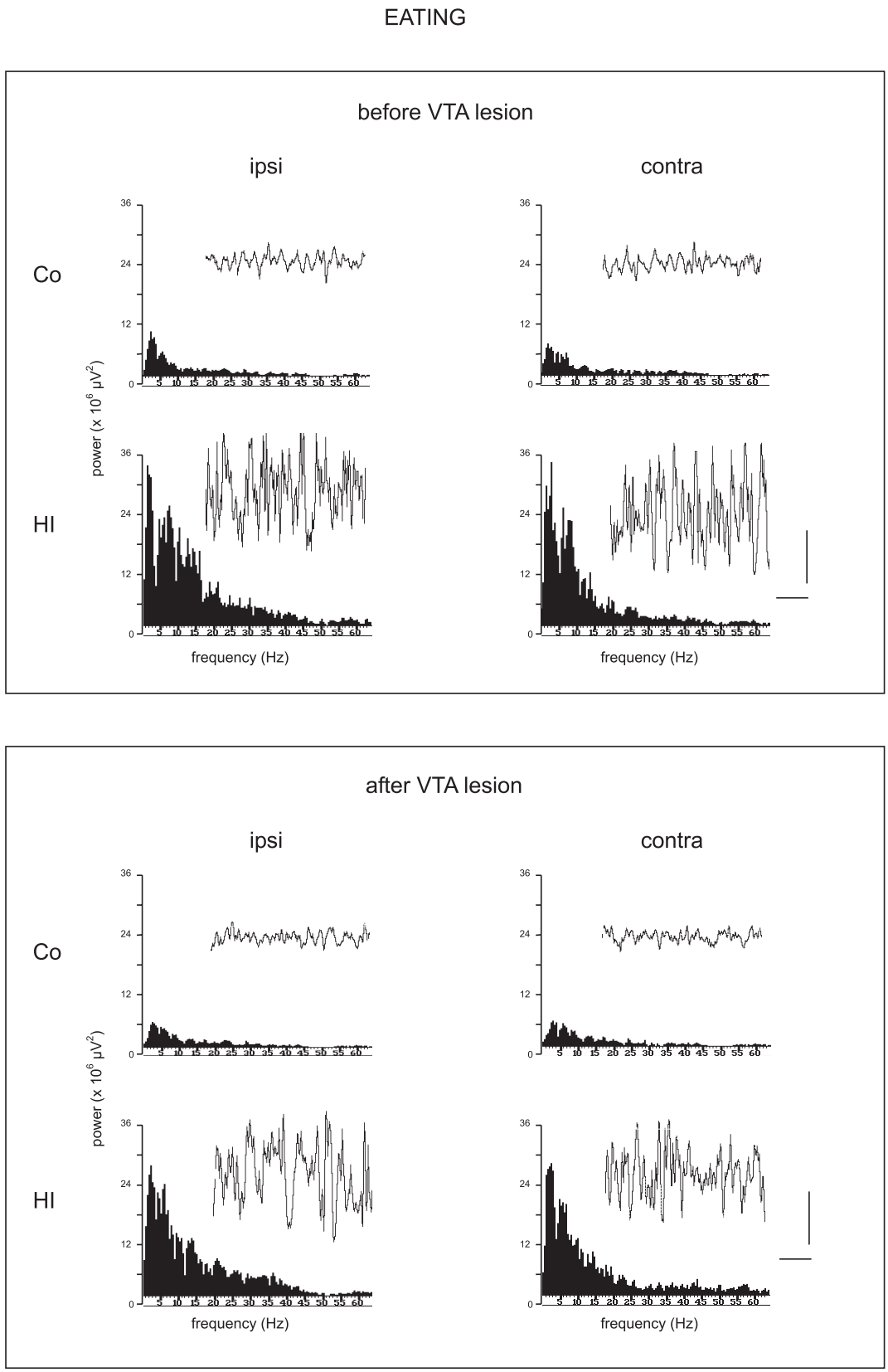

Fig. 2. EEG power spectra and corresponding cortical (Co) and hippocampal (HI) EEG traces in an example rat performing eating reaction before and after unilateral VTA lesion. Calibration: 1 s and 250 μV.

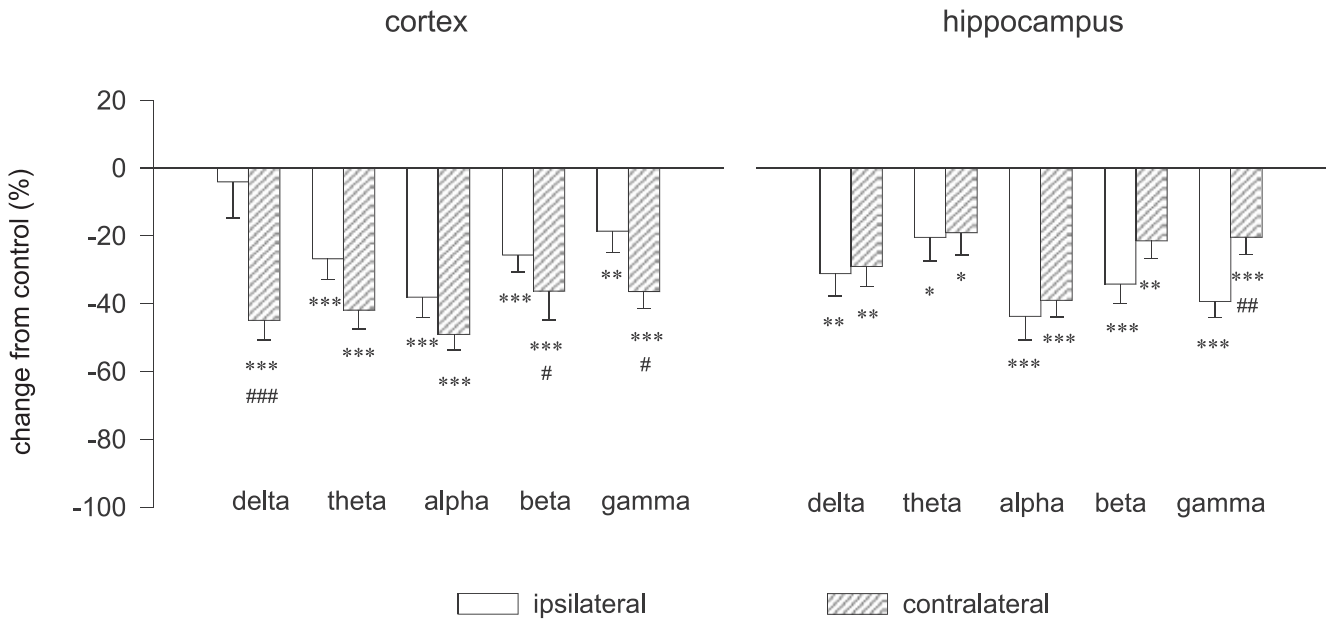

Fig. 3. Lesion-induced changes in power at the standard frequency bands (delta, theta, alpha, beta and gamma) of the neocortical and hippocampal EEG signal recorded during sniffing (n = 4). All values are expressed as the percentage change from the control, buffer injection. Explanations: (*) P<0.05; (**) P<0.01; (***) P<0.001: differences in comparison to the control; (#) P<0.05; (##) P<0.01, (###) P<0.001: interhemispheric differences (Student's t-test for independent samples).

effect of "contralateral facilitation of function". Nevertheless, the present data indicate that the VTA is indeed involved in the regulation of cortical and hippocampal activity during VTA-dependent behavioral activation and that facilitation of behavioral responses after unilateral VTA lesion (Klejbor and Trojniar 1997, Maliszewska-Ścisło and Trojniar 1999, 2000, Trojniar and Klejbor 1999, Trojniar and Staszewska 1994) is concomitant with lateralized changes in the EEG.

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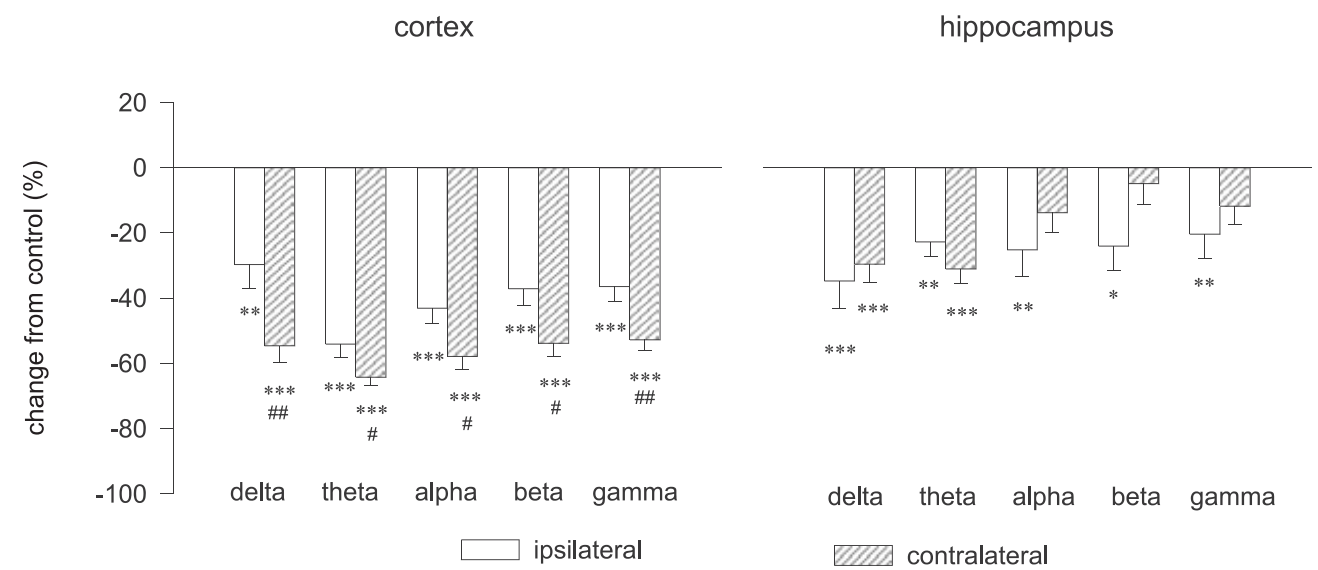

Fig. 4. Lesion-induced changes in power at the standard frequency bands (delta, theta, alpha, beta and gamma) of the neocortical and hippocampal EEG signal recorded during eating (n = 4). Explanations as in Fig. 3.

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