

The Effects of Electrical Stimulation of the Nucleus Basalis on the Electroencephalogram, Heart Rate, and Respiration

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The nucleus basalis (NB) mediates cortical electroencephalograph (EEG) activation; NB stimulation also modulates cortical responses to sensory stimuli and can induce learning-related receptive field plasticity. However, little is known about the behavioral effects of NB stimulation. This study concerns the effects of NB stimulation on cardiac and respiratory behavior and quantifies its EEG effects in freely moving rats. The EEG exhibited stimulation-induced decreases in theta and alpha power and increases in gamma power. NB stimulation elicited biphasic heart rate changes and disrupted ongoing respiration patterns. Neither EEG nor behavioral effects exhibited habituation or facilitation. These results indicate that the NB may serve not only as a cortical, but also as a behavioral, activation system that is normally engaged during learning.

The nucleus basalis (NB) is the major source of acetylcholine for the cerebral cortex (Lehmann, Nagy, Atmadja, & Fibiger, 1980; Mesulam, Mufson, Wainer, & Levey, 1983). Its cholinergic projection is believed to play an important role in regulating cortical activity. For example, the rate of discharge of cholinergic cortically projecting NB cells varies directly with the level of cortical activation, being highest during waking and REM sleep and lowest during slow-wave sleep (Buzsaki et al., 1988, Détári, 2000; Détári & Vanderwolf, 1987). Stimulation of the NB also causes cortical activation and a concomitant release of cortical acetylcholine (Buzsaki et al., 1988; Casamenti, Deffenu, Abamondi, & Pepeu, 1986; Jiménez-Capdeville, Dykes, & Miasnikov, 1997; Kleiner & Bringmann, 1996; Kurosawa, Sato, & Sato, 1989; Metherate, Cox, & Ashe, 1992; Rasmusson, Clow, & Szerb, 1994). Lesions of the NB impair cortical activation (Buzsaki et al., 1988; Riekkinen, Sirviö, Hannila, Miettinen, & Riekkinen, 1990).

The NB also has been implicated in cognitive functions such as memory and attention. Ibotenic acid, *N*-methyl-D-aspartate, and other excitotoxic lesions of the NB produce deficits in memory (e.g., Connor, Langlais, & Thal, 1991; Santucci & Haroutunian, 1989; Turner, Hodges, Sinden, & Gray, 1992). However, such lesions are not selective for cholinergic NB cells. Selective immunotoxic destruction of cholinergic neurons in the NB supports the conclusion that these cells are involved in selective attention rather than memory (reviewed in Everitt & Robbins, 1997; Wenk, 1997). Therefore, NB lesions affecting memory may involve noncholinergic neurons. However, other studies have reported that selective destruction of cholinergic NB cells apparently can produce mem-

ory deficits (e.g., Gutiérrez et al., 1999; Leanza et al., 1996). Therefore, it is possible that cholinergic NB cells are involved in both attention and memory, although the issue remains in doubt.

Complementary to lesion studies are studies of electrical stimulation of the NB. These studies have the advantage of affecting its cholinergic and noncholinergic neurons, both of which normally participate in NB responses to sensory stimuli (Nadal, Armario, Gill, & Janak, 2001). Electrical stimulation of the NB has been used to study learning and memory, but not to study attention. For example, posttraining stimulation of the NB has been reported to improve memory consolidation (Montero-Pastor et al., 2001). Stimulation of the NB can also facilitate responses to sensory stimuli, an effect that may be involved in the storage of sensory information (e.g., Edeline, Maho, Hars, & Hennevin, 1994; Hars, Maho, Edeline, & Hennevin, 1993). In addition, the NB has been directly implicated in learning-related cortical plasticity. Receptive fields and tonotopic maps in the auditory cortex (ACx) are modified to emphasize a particular signal frequency when it gains behavioral significance during learning (reviewed in Weinberger, 1995, 1998). Substitution of NB stimulation for a standard sensory reinforcer (e.g., food or shock) induces the same receptive field plasticity as that induced during standard conditioning (Bakin & Weinberger, 1996; Bjordahl, Dimyan, & Weinberger, 1998; Dimyan & Weinberger, 1999; Kilgard et al., 2001; Kilgard & Merzenich, 1998; Miasnikov, McLin, & Weinberger, 2001). These findings support the hypothesis that the NB enables such cortical reorganization by signaling stimulus importance, a view consistent with the fact that the NB is normally engaged by behaviorally important stimuli, for example, conditioned and unconditioned stimuli (Maho, Hars, Edeline, & Hennevin, 1995; Pirch, 1993; Richardson & DeLong, 1991; Whalen, Kapp, & Pascoe, 1994).

Although stimulation of the NB is becoming increasingly useful as a technique for studying cortical plasticity and learning, greater knowledge of both its neurophysiological and behavioral consequences is required. Regarding neurophysiology, electroencephalograph (EEG) activation that accompanies spontaneous changes in state has been evaluated quantitatively by power spectral analysis of the several EEG frequency bands (Maloney, Cape, Gotman, & Jones, 1997), some of which have been associated with specific

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This study was supported by National Institute of Deafness and Other Communication Disorders Grants DC 02346 and DC 02938 and National Institute of Mental Health Grant MH 57235 to Norman M. Weinberger.

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cognitive processes (e.g., Krause, Pörn, Lang, & Laine, 1997). However, the effects of NB stimulation on the EEG have not been investigated in detail. Thus, the present study includes a power spectral analysis of NB-induced EEG activation.

Even less is known about the behavioral consequences of NB stimulation. It has been reported that NB stimulation that produces cortical EEG activation (desynchronization) elicits no visible movements in animals (Bakin & Weinberger, 1996; Bjordahl et al., 1998; Dimyan & Weinberger, 1999; Kilgard et al., 2001; Kilgard & Merzenich, 1998; but see Bringmann & Klingberg, 1989). In addition, NB stimulation reportedly elicits no movements when applied to the human brain (Turnbull, McGeer, Beattie, Calne, & Pate, 1985).

Although NB stimulation can modulate cortical state without producing movements, it might elicit changes in autonomic behaviors, which have a higher degree of sensitivity. For example, conditioned cardiac, respiratory, pupillary, galvanic skin response, and blood pressure responses develop within a few trials, although conditioned somatic movements in the same subjects (e.g., eyeblink, nictitating membrane/eyeball withdrawal, limb flexion) are not evident for tens of trials (reviewed in Lennartz & Weinberger, 1992). Thus, the autonomic response systems indexing rapidly acquired associative learning are good candidates for the detection of behavioral NB effects. In the present study, we investigated the effects of NB stimulation on heart rate and respiration in unrestrained rats. Previously, Bringmann and Klingberg (1989) reported that NB stimulation can alter respiration.

Method

Surgery

The subjects were male Sprague-Dawley rats ($n = 7$, 350–690 g) housed in individual rat cages, with ad-lib food and water and a 12-hr light–dark cycle (lights on at 7:00 a.m.). They were studied during the light portion of the cycle. Under sodium pentobarbital anesthesia (35–40 mg/kg ip), the rats were implanted with an epidural stainless steel screw recording electrode over the right ACx, a thoracic electrocardiogram (EKG) electrode inserted subcutaneously, and a reference screw overlying the frontal sinus. The location of ACx was first determined by mapping click-evoked responses (100 μ s) from the temporal bone with a roving stainless steel electrode. The recording electrode was placed over the site with maximal response to a click delivered to the contralateral ear, minimally consisting of a high-amplitude (200–400 μ V) reproducible waveform with a short-latency (8–15 ms) positive component followed by a long-latency (80–120 ms) negative component. The EKG electrode consisted of a 30-cm-long, Teflon-insulated, seven-strand stainless steel wire (140- μ m diameter [0.0055 in.], #7932; A-M Systems, Carlsborg, WA) with 5 mm of insulation removed from the middle. A guide probe was used to manually direct the wire around the circumference of the rib cage, so that the exposed central (recording) portion of the wire rested in the medial ventral region of the chest, close to the heart. To ensure sterility during implantation, the extent of the wire not in the guide probe was inserted into flexible polypropylene tubing coupled with a 50-ml syringe filled with 70% (vol/vol) alcohol.

Because successful elicitation of cortical desynchronization served as an important guide for proper positioning of the NB electrode, at least 3 days separated cortical electrode placement from NB electrode implantation, to help ensure recovery of the cortex and stability of the cortical response. For the NB electrode implantation, the rats were again anesthetized, and a 13-mm concentric bipolar stimulating electrode (#SNEX-100x; David Kopf Instruments, Tujunga, CA) was lowered through the contralateral hemisphere at a 45° angle in the frontal plane at AP -2.3 , L 4.2, entering

laterally and passing medially to the target NB, which was ipsilateral to the ACx electrode. Beginning 8 mm from the cortical surface, bipolar electrical stimuli (0.2 ms, 20–150 μ A, 200–300-ms-long trains, 100 Hz) were delivered via stimulus isolation units (PSIU6, Grass S88 stimulator; Grass Instruments, Quincy, MA). The electrode was advanced in 0.2–0.3-mm steps with a manually driven microdrive (Kopf 1460, David Kopf Instruments) until EEG activation lasting 1–5 s, as recorded from the epidural ACx electrode, could be consistently elicited in ACx.

All electrode leads were attached to a multichannel connector that could be connected to a cable from a commutator. The connector was embedded in a dental acrylic pedestal that contained threaded spacers for the attachment of a respiration recording assembly. All procedures were performed in accordance with University of California, Irvine Animal Research Committee and National Institutes of Health animal welfare guidelines.

Testing

After a minimum of 2 weeks of recovery, the rats were individually placed in a plastic container (25 cm long \times 22 cm wide \times 26 cm high; Sterilite, Townsend, MA) within a sound-attenuating acoustic chamber. After 20–30 min of adaptation, they assumed a resting posture. Next, we determined the minimal NB stimulation current level (biphasic 0.2-ms pulses, 100 Hz, 200 ms, 50–100 μ A) required to elicit approximately 4 s of consistent, visually identifiable EEG activation. Minimal current levels averaged $71.14 \pm 5.44 \mu$ A. Determination of the effects of NB stimulation was performed in a single session the next day. Each rat received 20 trials of stimulation, during which the EEG, respiration, and heart rate were recorded (see below for details).

Although all 7 subjects yielded EEG data, technical failures limited the number of subjects for heart rate ($n = 4$) and respiration ($n = 5$) data. The thoracic EKG electrode failed in 2 cases, and amplifier malfunction precluded recording of EKG in 1 case and respiration in 2 cases. To minimize response variability that might arise from a wide range of background states, we presented trials only when the respiration pattern (monitored on a computer screen) was visually assessed to be stable for at least 2 s after a minimal intertrial interval of 30 s (maximum \sim 300 s). All subjects were videotaped throughout testing.

After testing, electrolytic marking lesions were made with the NB stimulation electrode. The rats received an overdose of Nembutal (100 mg/kg ip) and were perfused intracardially with 0.9% (wt/vol) saline followed by 10% (wt/vol) Formalin. The brains were removed and stored in 10% Formalin for 2–10 days, then placed in 30% (wt/vol) sucrose–Formalin until they sank. Subsequent histological verification of electrode placement was performed on Nissl-stained frozen sections (40 μ m).

Recording and Analysis of EEG

The signal from the EEG recording electrode was amplified and filtered with a DAM 50H amplifier (1,000 \times , 0.1–100.0 Hz; World Precision Instruments, Sarasota, FL) and Frequency Devices 9002 filter (Frequency Devices, Haverhill, MA; bandpass eight-pole filter set at 1–100 Hz), digitized at 500 samples per second with the CED Power-1401/Spike-3 interface/software (Cambridge Electronic Design, Cambridge, UK), and stored on a Pentium computer.

To determine the effects of NB stimulation on the EEG, we analyzed the digitized record in consecutive 1-s epochs: two epochs immediately preceding stimulation and nine epochs beginning 200 ms after stimulation. Fast Fourier transformations were performed on each of these epochs to determine the power in the following EEG bands: delta (1.09–3.26 Hz), theta (3.27–8.68 Hz), alpha (8.69–15.19 Hz), beta 1 (15.20–19.53 Hz), beta 2 (19.54–32.55 Hz), and gamma (32.56–59.68 Hz). To normalize the responses, thus permitting pooling of data across trials and subjects, we quantified the effect of NB stimulation on each EEG band for each trial on a second-by-second basis as the ratio of power after stimulation to the average power during the 2 s immediately preceding stimulation (post/pre

mean). The resultant values were used to quantify the magnitude, duration, and dynamics of the changes in each band across time, trials, and subjects.

Recording and Analysis of EKG

The output signal from the EKG electrode was recorded via the differential input of a DAM 50H amplifier ($\times 1,000$, 1.0–100 Hz) and stored in the computer. Heart rate was calculated offline on the basis of interbeat intervals; rate values were determined for consecutive 200-ms bins. Responses to NB stimulation were characterized by a bradycardia followed by a tachycardia. To normalize for changes in the baseline heart rate between trials and subjects, we subtracted the mean heart rate in the 2 s preceding the trial from the heart rate in each post-stimulation bin. These difference values were used to quantify the magnitude, duration, and dynamics of response across time and trial. To compare heart rate response with respiration response on individual trials, and to detect possible trends in magnitude across time, we used an individual quantitative value (maximal response) for each trial. *Maximal response* was defined as the maximal difference in heart rate during the 8 s after NB stimulation (i.e., the value attained by subtracting the nadir of the bradycardia from the peak of the tachycardia).

Recording and Analysis of Respiration

Respiration was determined by continuous recording of the air temperature fluctuations immediately adjacent to the rats' nares. This was achieved by using a lightweight head-mounted assembly of our own design, consisting of three adjustable brackets connected to a 3-s time constant, glass-encapsulated, 250 Ω (at 25 $^{\circ}\text{C}$) Style-1 thermistor (#837-5170, Allied Electronics, Fort Worth, TX). To maximize sensitivity, we placed the thermistor as close as possible to the nostril without touching or blocking it. The thermistor served as one of the arms in a resistor bridge circuit, making it sensitive to the local temperature fluctuations caused by the rat's respiration. The output signal from the bridge was recorded via the differential input of a DAM 50H amplifier, digitized at 2,000 samples per second, and stored on the computer.

Fast Fourier transformations were performed on eleven 1,024-ms-long epochs (two prestimulus and nine post-stimulus) of digitized respiratory recordings, resulting in power spectra for each epoch. We extracted data in the smallest time bins possible for maximum frequency resolution; given a 2000-Hz sampling rate, this yielded 1.63-Hz bins. To eliminate artifacts that might have resulted from increased power due to DC offset, the 0–1.63-Hz bin was removed from these analyses. Analysis of spectrograms derived from epochs of spontaneous respiration in the absence of NB stimulation revealed that 99% of the power was below 4.88 Hz, consistent with respiration rates we observed, ranging from approximately 1.5 to 2.5 Hz. Consequently, we restricted analysis to the power spectrum between 1.63 and 4.88 Hz, ensuring that frequencies relevant to the respiration were captured while minimizing noise introduced by unrelated frequencies.

To achieve maximal sensitivity in detecting respiration changes, a measure that is sensitive to both increases and decreases in both rate and amplitude is required. To this end, respiration was quantified by means of a respiration change index (RCI) that (a) reflects changes in respiration rate and magnitude, regardless of the direction of that change, (b) is sensitive to changes across the frequency spectrum and time, and (c) mitigates against artificial inflation due to the maximal percentage decrease being 100% but the maximal percentage increase being unconstrained. This was achieved by using the following formula: $\text{RCI} = [|\text{Post} - \text{Pre}| \div (\text{Pre} + \text{Post})]$, averaged for the frequency bands 1.63–3.25 and 3.26–4.88 Hz. The RCI measure can range from 0.0, indicating no change, to 1.0, indicating complete cessation of respiration, that is, a post value of 0.0. To maximize temporal sensitivity, we calculated RCIs on a second-by-second basis. To normalize for the variable degree of respiration stability across trials and subjects, we subtracted the spontaneous variability (the RCI for the two 1-

epochs immediately preceding stimulation) from each post-stimulation epoch on a trial-by-trial basis. These values were used to quantify the magnitude, duration, and dynamics across time and trial. Two other values were used for comparing respiration responses on individual trials with the heart rate responses and for determining possible trends in magnitude across trials. The first, mean RCI, was calculated as the average RCI across 9 s post-stimulation. This measure encompasses the total response to stimulation, but it is relatively insensitive to large transient responses, which could be concealed by averaging. To ensure that such responses were not overlooked, we also performed each analysis using the maximal RCI, or the largest 1-s RCI value for each trial.

Results

The locations of the stimulation sites are shown in Figure 1. These loci lie within the caudal globus pallidus, substantia innominata, and adjacent internal capsule. These sites are consistent with the known location of the NB that projects to the ACx (Mesulam et al., 1983), the stimulation of which induces cortical desynchronization in the ACx (Metherate et al., 1992).

Stimulation of the NB did not elicit discernible muscle twitches or movements of the body, limbs, head, or ears. Online observations of the subjects were supplemented by analysis of videotapes

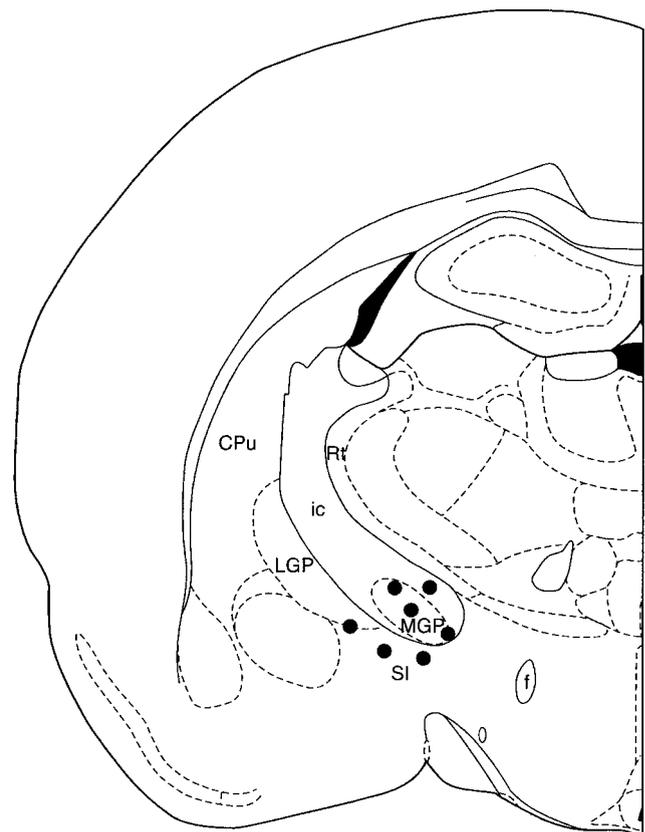


Figure 1. The location of nucleus basalitis stimulation in all subjects. Electrode placements are ± 0.25 mm in the anterior–posterior plane. CPU = caudate-putamen; Rt = reticular nucleus of the thalamus; ic = internal capsule; LGP = lateral globus pallidus; MGP = medial globus pallidus; SI = substantia innominata; f = fornix. From *The Rat Brain in Stereotaxic Coordinates* (4th ed., Figure 24), by G. Paxinos and C. Watson, 1998, San Diego, CA: Academic Press. Copyright 1998 by Academic Press. Adapted with permission.

by two observers who were unaware of the time of NB stimulation. Observers separately viewed 30-min segments of randomly selected training session tapes from 4 subjects and were instructed to identify the onset time of all movements, such as twitching, stretching, head lifting, and grooming. Of the 84 movements identified, only 1 (1.14%) occurred to NB stimulation or within the next 2 s. Therefore, NB stimulation did not produce detectable movements in this study.

Effects of NB Stimulation on the EEG

Stimulation of the NB elicited changes in the EEG of all subjects ($n = 7$). These were indicative of cortical activation. Figure 2A shows an example of the EEG, characterized by slower waves preceding NB stimulation. After stimulation, the slow waves were reduced and faster waves were increased. The spectra representing the power in each EEG band are shown in Figure 2B, and change in power for each band (post \div mean pre) is given in Figure 2C. Consistent with the visual impression of the example, the power spectra show a decrease of power in the lower frequency bands of delta, theta, alpha, and beta 1, and an increase of power in the beta 2 and gamma bands.

We evaluated the EEG for three effects: (a) the persistence of any increase or decrease in power during the 9-s period of analysis after each trial (post period), (b) the magnitude of change for each 1-s epoch during the post period, and (c) an interaction between the cardinal order of the 20 repeated trials and effects during the 9-s post-stimulation period.

Group results are presented in Figure 3. A binomial runs test was used to evaluate whether each band exhibited a persistent increase or decrease across the 9-s post period. One-tailed runs tests were performed, using the direction of change predicted on the basis of spectral analysis of the EEG during the normal

sleep-wake cycle of the rat (Maloney et al., 1997). There was no persistent decrease in delta ($p = .254$). Both the theta and alpha bands exhibited persistent decreases ($p = .002$). Beta 2 did not show the decrease expected on the basis of change previously reported between slow-wave sleep and wakefulness (Maloney et al., 1997; $p > .05$) but rather showed a significant increase ($p = .002$). The power within the gamma band increased significantly ($p = .002$), as expected from prior reports of spontaneous activation (Franken, Dijk, Tobler, & Borbély, 1994; Maloney et al., 1997).

To determine the magnitude of changes in relative power, we performed one-group t tests (two-tailed) against a hypothesized post/pre mean of 1.0 (i.e., no change) on each 1-s epoch for each EEG band. The change in delta power was not significant for any of the 9 s. For both the theta and alpha bands, power was significantly reduced for each of the 9 s after stimulation ($ps < .05$). Beta 1 power showed a transient decrease that was significant 2 and 3 s post-stimulation ($p < .05$). Beta 2 power exhibited a transient significant increase for 2 s after stimulation, and once again at 9 s ($ps < .05$). Power in the gamma band was significantly increased for every epoch during the 9 s analyzed ($ps < .05$).

To determine whether there was an interaction between time during the 9 s after stimulation and trial number, or whether changes in EEG power exhibited a decrement (i.e., habituation) or an increment (i.e., facilitation) with repeated stimulation, we applied a two-factor (time and trial) analysis of variance (ANOVA) to each band. (It should be noted that results from the time factor are potentially less informative than those from the trial factor because of the necessary normalization of the data. For example, if the power in a band were reduced by 50% and that effect were maintained for more than 9 s without returning to baseline, then the time factor would not be significant, despite the large change in

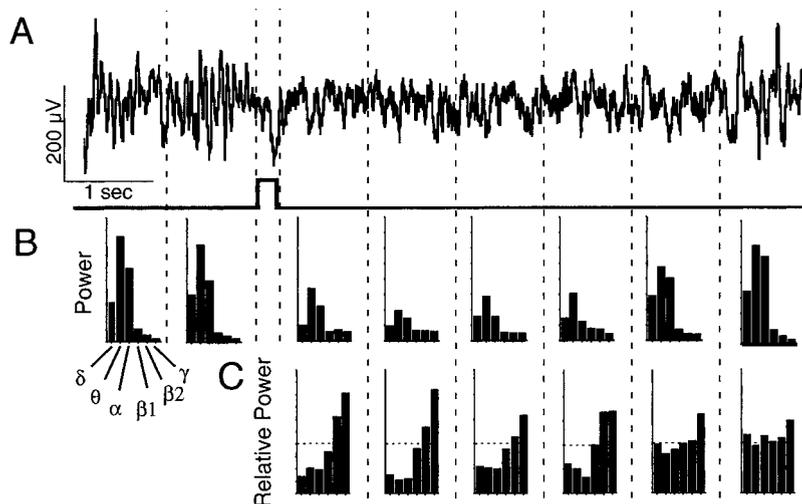


Figure 2. A: An example of the electroencephalogram (EEG) showing desynchronization elicited by nucleus basalis (NB) stimulation. Time of NB stimulation is indicated by the notch in the baseline. B: Spectra histogram showing the power on a second-by-second basis for each EEG band. Vertical dashed lines demarcate the 1-s epochs of recording, 2 s preceding stimulation, and the 6 s required for the EEG to return to baseline in this example. C: Spectra histogram showing relative power in each EEG band. The histogram bars are arranged from lowest to highest frequency band (delta, theta, alpha, beta 1, beta 2, gamma). Stimulation causes a decrease of power in the lower frequencies (delta, theta, alpha, and beta 1) and an increase of power in the higher frequencies (beta 2 and gamma). Dashed horizontal lines indicate a value of 1.0, or no change from average baseline.

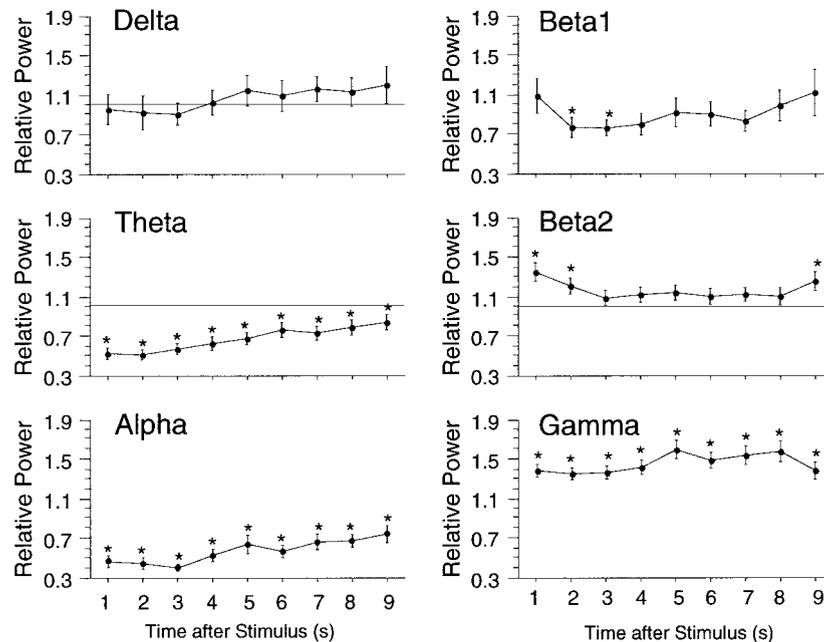


Figure 3. Group mean (\pm SEM) relative change in power after nucleus basalis stimulation. Asterisks indicate significant changes ($p < .05$; value at that time period represents a significant change from prestimulus level, no change = 1.0). Power was significantly reduced in the theta and alpha bands for all time periods. Power was significantly increased in the gamma band for all time periods.

power. However, inclusion of the time factor does provide for addressing the issue of possible interaction between the cardinal order of the trials and time within trials.)

The delta, theta, alpha, and gamma EEG bands exhibited a significant change over the 9-s post-stimulation period: time factor for ANOVA, $F(8, 688) = 2.07$, $F(8, 728) = 5.05$, $F(8, 664) = 4.20$, and $F(8, 768) = 2.45$, respectively, $ps < .05$. Visual inspection of Figure 3 shows that, after an initial decline, the power in low-frequency bands, especially in the theta and alpha bands, approached a recovery to baseline levels by 9 s post-stimulation. The changes for gamma indicate an increased response after 3 s, rather than a decay.

Of particular interest, no EEG band had a significant trial effect (ANOVA, $ps > .05$). In addition, no band showed an interaction between trial order and time after stimulation (ANOVA, $ps > .05$). The lack of trial effect indicates a lack of habituation or facilitation to the NB stimulation. The lack of interaction further supports the stability of the EEG changes across trials, indicating that the within-trial temporal dynamics did not change with repeated stimulation. In other words, neither the change in power nor its duration changed significantly across trials.

Effects of NB Stimulation on Heart Rate

Stimulation to the NB changed cardiac activity. Specifically, it produced a biphasic response, a brief bradycardia followed by a longer duration tachycardia. Figure 4A provides an example of the change in heart rate from 1 subject for a single trial. The baseline heart rate was 292 beats per minute (bpm); it decreased to 282 bpm, reaching its nadir at 1.4 s after stimulation. Heart rate then increased to 337 bpm, reaching its peak at 4.6 s after stimulation. Figure 4B shows the change in rate for this individual trial nor-

malized to the baseline heart rate (i.e., subtracting the baseline rate from the rate after stimulation). The result is a maximal bradycardia of -10 bpm and a maximal tachycardia of $+45$ bpm.

All subjects exhibited this pattern of change. Group results are presented in Figure 4C. The mean baseline heart rate was 304.17 ± 1.95 SE ($n = 80$). The direction, time course, and magnitude of change were analyzed by assessing whether each time bin differed from the baseline heart rate. This was accomplished with one-sample t tests (two-tailed) against a mean of zero (no change) for each 200-ms heart rate bin. Heart rate was significantly slowed between 0.8 and 2.4 s after NB stimulation ($ps < .05$). It then returned to baseline and continued increasing. The increase over baseline became significant from 3.2 s after NB stimulation to the longest time point recorded, 9 s ($ps < .05$). Although data were analyzed for only 9 s, observation of an online rate meter suggested that heart rate usually returned to baseline rate by 12–15 s after stimulation.

To determine whether repetition of stimulation affected the response, we quantified the change in heart rate induced by each NB stimulation by calculating the maximal (base to peak) response (see the Method section). The average maximal response on each trial is shown in Figure 4D. A one-factor ANOVA for trial order was not significant, $F(19, 60) = 0.62$, $p > .05$. This indicates that the heart rate response did not habituate or facilitate with repeated stimulation.

Effects of NB Stimulation on Respiration

Stimulation to the NB disrupted ongoing respiration patterns. Figure 5A provides an example of respiration before and after NB stimulation. The sinusoidal waveform corresponding to the respiration pattern present during the 2 s preceding stimulation is

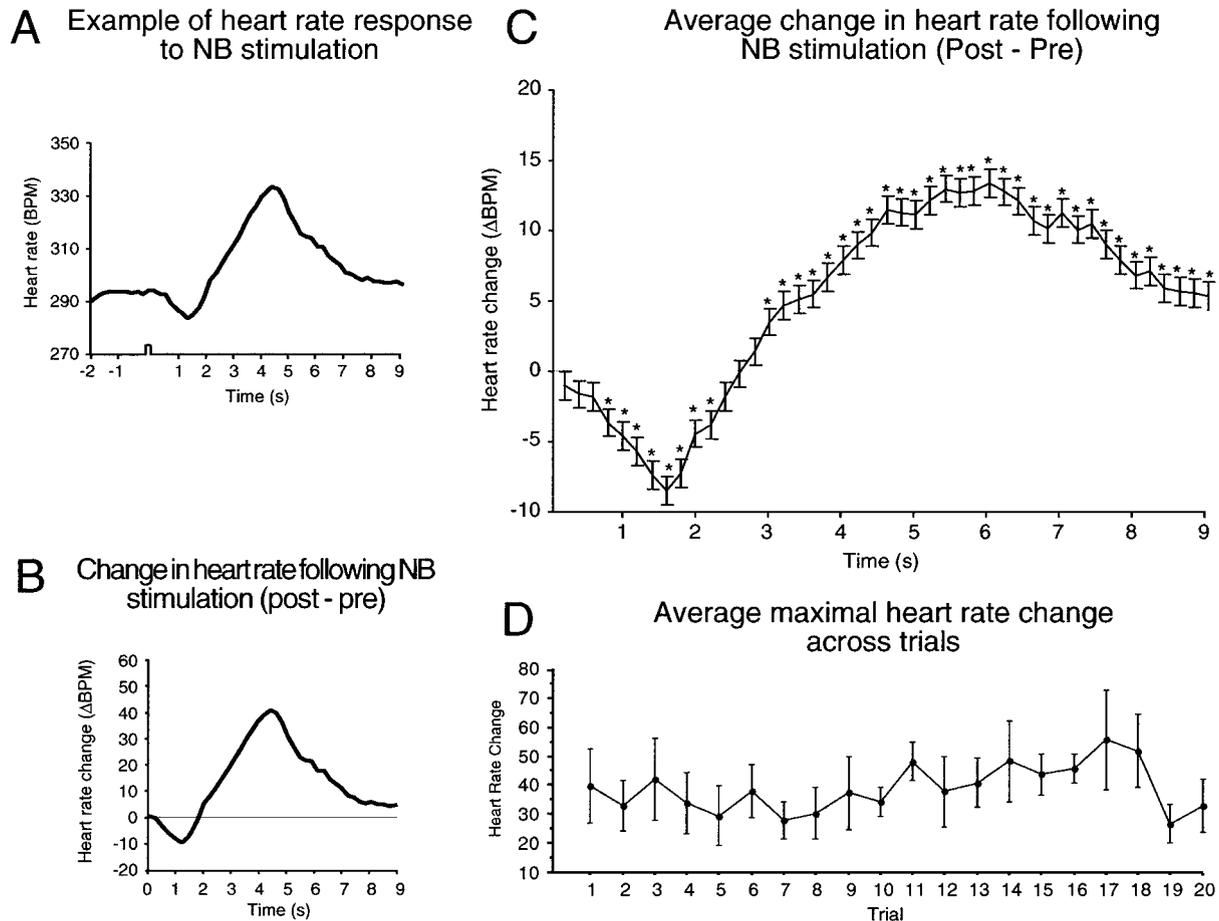


Figure 4. A: Example of an individual heart rate response to nucleus basalis (NB) stimulation. After stimulation (indicated by the notch in the x -axis), the heart rate undergoes a brief, short-latency bradycardia, followed by a longer duration and latency tachycardia. The waveform has been smoothed with a running average of three 200-ms bins. BPM = beats per minute. B: Example of a normalized individual heart rate response. The average baseline heart rate from the above response was subtracted from each 200-ms bin to yield the change in heart rate. post = post-stimulation; pre = prestimulation. C: Mean (\pm SEM) change in heart rate for all subjects. The response is characterized by a bradycardia reaching its nadir approximately 1.5 s after stimulation, followed by a prolonged tachycardia reaching its peak about 5.5 s after NB stimulation. The heart rate has not returned to baseline after 9 s. Asterisks indicate a significant difference from baseline ($p < .05$). D: Mean (\pm SEM) maximum change in heart rate across trials for all subjects. There was no significant effect of trial order, indicating a lack of habituation or facilitation.

altered, with amount of change increasing over the 9-s analysis period of the trial. The RCI values (see the Method section) for each 1-s epoch after stimulation for this trial are shown below the waveform in Figure 5A. In this example, respiration is immediately disrupted for the first few seconds after stimulation, and the magnitude of disruption increases over the duration of the recording period. The spontaneous variation is the value resulting from calculating the RCI between the 2 s of spontaneous respiration preceding NB stimulation. It should be noted that, although the respiration pattern present before stimulation appears to be a sinusoid with little variation, the RCI is highly sensitive to small changes, yielding a value of 0.25 for this particular example. Subtraction of the pretrial spontaneous variation from the post-stimulation RCI values, to normalize for the respiration state preceding each trial, yields the change in RCI, shown in Figure 5B.

The average normalized RCIs for all subjects at each of the nine epochs after stimulation are shown in Figure 5C. Stimulation of the NB elicited a response in respiration consisting of a relatively small immediate disruption that tended to increase throughout the 9 s recorded. To determine the magnitude and duration of effect, we analyzed the change in RCI value for each 1-s bin with a one-group t test against a mean of zero (no change). Respiration was significantly disrupted beginning 4 s after NB stimulation, and the magnitude increased throughout the duration of the 9 s of recorded data ($ps < .05$).

The effects of NB stimulation across trials were assessed by calculating the average response across the 9 s post-stimulation for each trial ($n = 100$, see Figure 6A). A one-factor ANOVA for trial order was not significant, $F(19, 100) = 0.46$, $p > .05$. Because averaging the respiration change over 9 s may be insensitive to

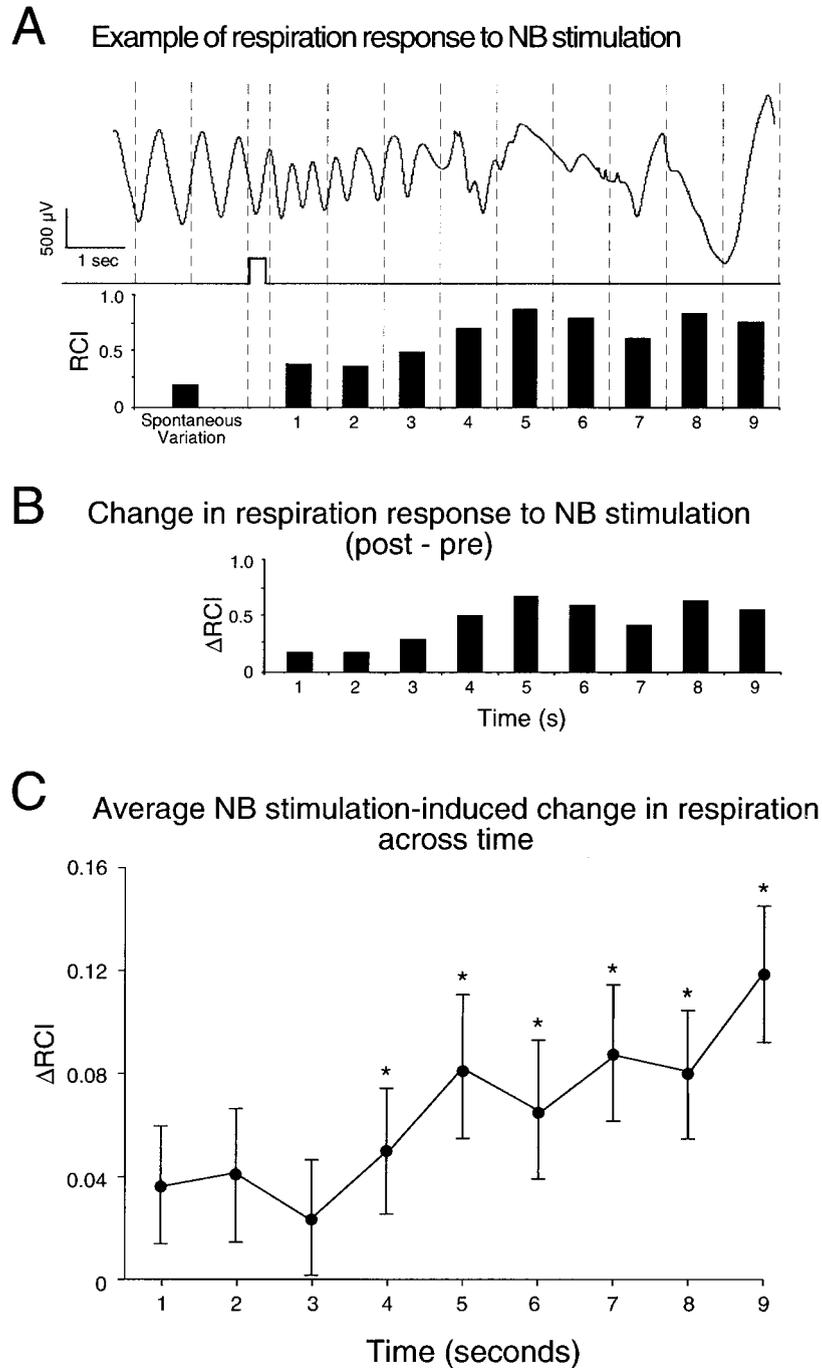


Figure 5. A: An individual example of the effects of nucleus basalis (NB) stimulation on respiration. The ongoing pattern is mildly disrupted immediately after stimulation. The disruption increases over several seconds before reaching asymptote. The bars below the waveform represent the value of the respiration change index (RCI) on a second-by-second basis after the stimulation. B: RCI for each second of this example, normalized for the variability of spontaneous respiration. post = post-stimulation; pre = pre-stimulation. C: Group mean (\pm SEM) change in respiration for all subjects. Asterisks indicate time periods with significant changes (i.e., values significantly greater than zero, $p < .05$). There is a small immediate disruption that reaches significance 3 s after stimulation and remains significant throughout the 9 s analyzed.

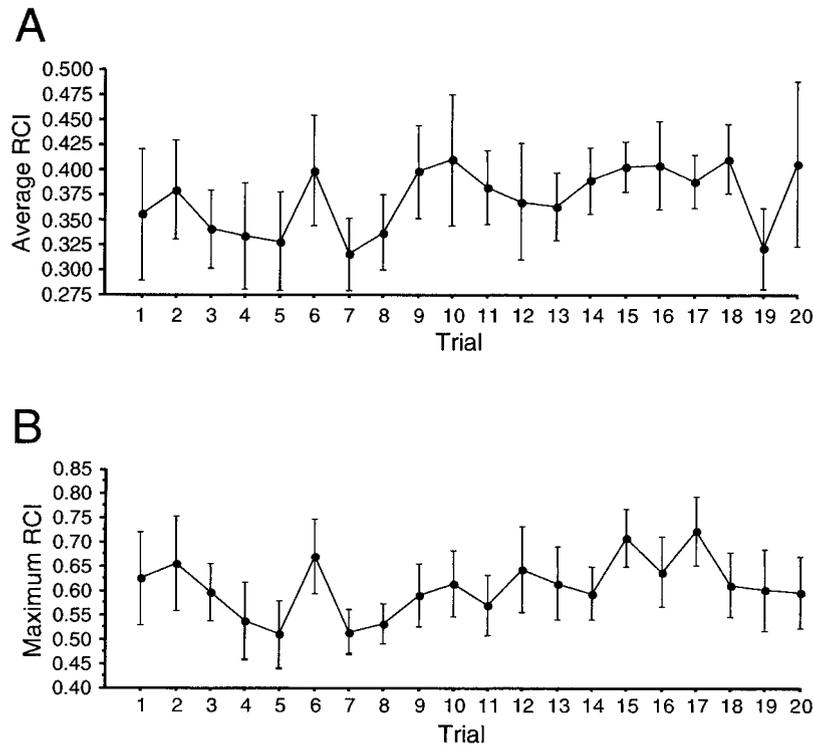


Figure 6. A: Group mean (\pm SEM) respiration change index (RCI) across 9 s post-stimulation. B: Group mean (\pm SEM) maximum change. Data include all trials for all subjects. There was no significant effect of trial order for either measure, indicating a lack of habituation or facilitation of the behavioral response.

large, transient changes lasting fewer than 9 s, the respiration response was also quantified in terms of the maximal RCI occurring in response to NB stimulation on each trial (see Figure 6B). This analysis also yielded no significant effect of trial order, $F(19, 100) = 0.65$, $p > .05$. Therefore, neither measure of respiration response yielded an effect of trial order, indicating that the magnitude of response does not change with repeated NB stimulation.

Correlation of Heart Rate and Respiration Responses

The magnitudes of heart rate change and respiration change are related. Figure 7A shows a scattergram of maximal heart rate change versus the average RCI for each trial across subjects ($n = 80$). The correlation coefficient is $.39$ ($p < .01$, $df = 79$; Brownlee, 1953), indicating that 15% of the variance can be accounted for by the relationship between the two variables. In addition to the RCI averaged across the 9-s analysis period for each trial, heart rate was also compared with the maximal RCI during each trial (see Figure 7B). The measures are again related; the correlation coefficient is $.46$ ($p < .001$, $df = 79$), accounting for 21% of the variance. This suggests that the NB stimulation-elicited changes in heart rate and respiration are related, but not redundant, measures.

Discussion

EEG Activation

The present observations, that stimulation of the NB elicits EEG activation, are not novel, as this effect has been demonstrated repeatedly in vivo (e.g., Belardetti, Borgia, & Mancia, 1977; Cape

& Jones, 1998; Metherate et al., 1992). Although this study did not include analysis of cholinergic involvement, it is known that NB-induced EEG activation is blocked by atropine applied to the cortex (Bakin & Weinberger, 1996).

The observation of EEG activation served two purposes in this study. First, it provides an independent indication that NB stimulation was physiologically effective. Had there been neither heart rate nor respiration effects, this negative behavioral outcome would not have been interpretable in the absence of independent verification that the stimulation parameters used were adequate to affect the cerebral cortex. As it happens, this safeguard proved unnecessary. Second, the EEG data provided an opportunity to perform a spectral analysis and to compare the profile of EEG changes with that obtained during spontaneous cortical activation, such as occurs in the transition from a sleeping or drowsy state to a state of wakefulness.

Previous studies have indicated that shifts from sleep to waking are normally accompanied by a decrease in power of the low-frequency bands: delta, theta, and alpha. Whereas beta activity had usually been thought to increase during arousal, both beta 1 (15–19 Hz) and beta 2 (19–32 Hz) power are lower in waking than in sleep. The major increase in power during EEG activation is within the gamma band (Franken et al., 1994; Maloney et al., 1997). The present effects of NB stimulation are not identical to these findings. A major difference is that delta showed no persistent decrease (binomial runs test) or a significant decrement at any time point (t tests). The ANOVA did indicate that delta power was altered by NB stimulation. Beta 2 exhibited a significant increase in power. However, other changes in the EEG were the same as previously

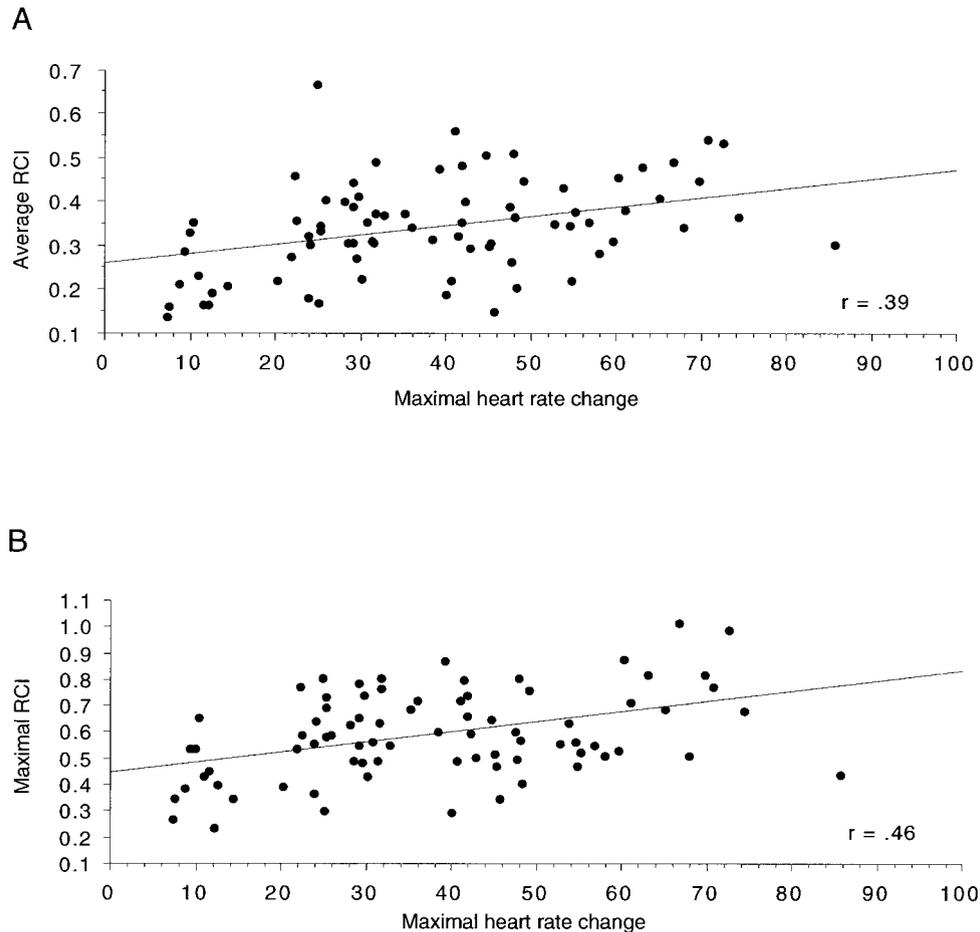


Figure 7. The relationship between nucleus basalis stimulation-elicited heart rate and respiration responses. A: Scattergram between the maximal heart rate change and average respiration change index (RCI). B: Scattergram between the maximal heart rate change and the maximal RCI.

reported, that is, a decrease in theta and alpha power (and beta 1 to a lesser extent) and an increase in gamma power.

The increased power in the gamma band may be of particular interest, as this component of the EEG has been linked to increased synchronized discharge between neurons (Bressler, 1990; Gray & Singer, 1989; Murthy & Fetz, 1992) and to several cognitive processes, including focused attention (Bouyer, Montaron, & Rougeul, 1981), perception of sensory stimuli (Gray, König, Engel, & Singer, 1989), and the binding of stimulus components into perceptual objects (Joliot, Ribary, & Llinás, 1994; Jones & Barth, 1997). Therefore, the NB may be involved in promoting such processes by enhancing the gamma rhythms in a manner similar to the effects of stimulating the reticular formation (Munk, Roelfsema, König, Engel, & Singer, 1996).

There are many possible explanations for the lack of identical EEG profiles between spontaneous and NB-elicited cortical activation, particularly the failure of NB stimulation to significantly reduce delta power. First, the EEG was seldom dominated by delta waves. Our rats generally rested quietly but did not display normal sleep-waking cycles. This may have been due to the fact that they were not extensively habituated to the testing environment, having experienced it only for a few hours the preceding day. Also, they were subjected to NB-elicited EEG arousal every few minutes,

which possibly interfered with achievement of slow-wave sleep. In addition, one should not assume that the NB is the only neural system that modifies EEG state and induces EEG activation. It is well established that there are parallel ascending influences. For example, the cholinergic brainstem nuclei in the rostral pons are capable of activating effects via the thalamus in NB-lesioned subjects (reviewed in Steriade & Buzsáki, 1990).

The magnitude of NB-induced EEG activation did not change over repeated trials, that is, it exhibited neither habituation nor facilitation. The lack of these effects suggests that the stimulation used in this study did not act as a sensory stimulus, either weak or strong, because habituation or facilitation (e.g., sensitization), respectively, result from the repeated application of such sensory stimuli (Thompson & Spencer, 1966; see also Glaser, 1966). This is not surprising, as the NB is not part of any sensory system. However, it projects to sensory (and other) cortical areas, but the effects of stimulation appear not to act as sensory stimuli within these areas. One possibility is that the lack of habituation or facilitation indicates that the NB modulates cortical state directly, without engaging mechanisms that are involved in the serial analysis of stimuli.

Stimulation of the NB has previously been shown to increase EEG and cortical intracellular oscillations in the range of 20–40

Hz, which includes the beta 2 and part of the gamma bands in the anesthetized rat (Metherate et al., 1992). The present study supports and extends these findings to unanesthetized animals. It also provides a more detailed characterization of the increase in high-frequency oscillatory activity by indicating that the major effect is an increase in gamma, rather than in beta 2.

Activation of the NB by direct application of pharmacological agents produces increased gamma power and decreased delta power (Cape & Jones, 2000; Cape, Manns, Alonso, Beaudet, & Jones, 2000). Our results are in agreement for gamma, but not for delta. As noted above, the absence of significant decreases in delta power may reflect the relatively lower level of delta activity in the present study.

It should be noted that not all investigators have observed increased cortical gamma oscillations after NB stimulation (Brett & Barth, 1997). The failure to detect an increase in gamma, however, may be attributable to a difference in experimental design. As noted by the authors themselves, they used a current level of 15 μ A, much lower than that used by other investigators; generally, currents of 50–100 μ A have been used to induce EEG activation (e.g., Bjordahl et al., 1998; Metherate et al., 1992) or significant increases in cortical acetylcholine release (Kurosawa et al., 1989). Also, the NB is a diffuse structure with a rough topography such that (a) very low currents might not activate enough cortically projecting cells and (b) stimulation sites within the NB might not project to the sites of cortical recording electrodes (Price & Stern, 1983).

Changes in Behavior: Heart Rate and Respiration

The present findings indicate that stimulation of the NB elicits aspects of behavioral, as well as cortical, activation. The current study may be viewed as complementary to the classic literature on the cortical and behavioral activating effects of the reticular formation (reviewed in Lindsley, 1951), further consideration of which lies beyond the scope of this article.

The present findings appear to be the first systematic report that stimulation of the NB alters heart rate. Prior studies in unanesthetized animals made incidental observations on heart rate and generally failed to detect NB-elicited effects (Bakin & Weinberger, 1996; Bjordahl et al., 1998; Dimyan & Weinberger, 1999). However, the current findings are reconcilable with these failures because of differential sensitivity of methods. Detection of heart rate changes in those experiments was based on visual inspection of polygraph records of heart rate that was integrated over several seconds. This was less sensitive than the quantitative beat-by-beat analysis used in this study, particularly as the biphasic changes in heart rate would be partially cancelled by using a measure that was integrated over seconds.

Bringmann and Klingberg (1989) reported that NB stimulation increases the rate of respiration, whereas we observed both increased and decreased rates and amplitudes within a single trial (e.g., see Figure 5A), and therefore used a measure that was sensitive to both types of change. Comparisons are also problematic because Bringmann and Klingberg stimulated in the rostral forebrain and did not specify the levels of current used, both of which methods differ from those of the present study. Also in contrast to the current experiment, Bringmann and Klingberg's stimulation elicited gross motor activity, including head movements and chewing, so it is unclear whether their respiration

effects preceded or were secondary to such movements. We do agree with Bringmann and Klingberg that the NB is involved in behavioral activation, as well as electrographic activation, although on somewhat different grounds.

The magnitudes of change in heart rate and respiration were significantly correlated on a trial-by-trial basis. The correlation coefficients were .39 for average respiration change and .46 for maximal respiration change. These values, although statistically significant, nonetheless account for no more than 21% of the variance. Therefore, the effects of NB stimulation on one behavior do not provide a high degree of information about the magnitude of change on the other behavior. It seems prudent to determine the effects of NB stimulation simultaneously on multiple behavioral measures.

The circuitry underlying NB elicitation of cardiac and respiratory responses needs to be elucidated, including the extent to which they are mediated by cholinergic cells. Changes in heart rate and respiration might be mediated indirectly via the cerebral cortex. For example, NB stimulation is known to increase cerebral blood flow (CBF) and to do so through a cholinergic mechanism (e.g., Biesold, Inanami, Sato, & Sato, 1989; Lacombe et al., 1989). Therefore, it might be thought that heart rate and respiratory changes are secondary to changes in CBF that might have been detected by the rats. However, the minimal stimulus duration previously used to elicit CBF effects has been 10 s (reviewed in Sato, Sato, & Uchida, 2001). We used a 200-ms train of stimulation, which is 1/50th the duration of the briefest stimulation used in CBF studies. Therefore, this brief stimulus may not have elicited CBF effects; this remains to be determined.

An alternative is that the behavioral effects directly involve subcortical mechanisms, including those concerned with hedonic value, for example, appetitive or aversive motivational factors. This is consistent with the present finding that the behavioral responses to NB stimulation do not habituate. However, the NB is not a part of any known motivational system. The NB could be downstream of neurons involved in the determination of hedonic value. Consistent with this possibility, nonhabituating behavioral arousal can be produced by repeated electrical stimulation that is neither appetitive nor aversive. For example, Wester (1972) found that repeated stimulation of nonspecific midline and intralaminar nuclei elicited nonhabituating orienting responses in the cat. Nonetheless, the possible motivational effects of NB stimulation require direct investigation.

It might be argued that the present behavioral findings do not reflect effects of stimulating the NB itself, because this structure is organized in a somewhat diffuse manner; hence, stimulation may affect other cells, fibers of passage, or both. This possibility cannot be discounted and requires further inquiry. Electrical stimulation has proven advantageous throughout the history of neuroscience as a method that provides, among other advantages, controlled timing of action and engagement of normal circuitry (e.g., Rasmussen, 2000). The stimulation levels used in this study were minimal for inducing EEG activation, and the loci of stimulation overlapped with those used by previous researchers. For example, the present sites involve the location of NB neurons within the ventral globus pallidus, substantia innominata, and adjacent internal capsule of the rat that are the sites of activation of the EEG (e.g., see Figure 2A in Metherate et al., 1992), increase in CBF (e.g., see Figure 1 in Lacombe et al., 1989), facilitation of auditory cortical evoked responses (e.g., see Figure 1 in Hars et al., 1993; Figure 7 in

Edeline et al., 1994), and associative/discriminative induction of receptive field plasticity (e.g., see Figure 1A in Dimyan & Weinberger, 1999). Therefore, the present findings strongly imply that changes in heart rate and respiration are likely to accompany the elicitation of these other effects, and indeed the present findings demonstrate that they accompany EEG activation.

The changes in heart rate and respiration elicited by NB stimulation may be behavioral components of the arousal reaction. The latter is a constellation of EEG activation and autonomic responses. In addition to cardiac and respiratory responses, the arousal reaction also includes changes in blood pressure, pupillary dilation, and the galvanic skin response (reviewed in Lynn, 1966; Sokolov, 1963). Whether or not stimulation of the NB also elicits these additional behavioral components remains to be determined.

In conclusion, the NB has been viewed as mainly involved in the modulation of cortical state. The present findings indicate that the NB is also capable of mediating behavioral activation without inducing overt body movements. Further studies of the effects of NB stimulation, both by electrical and chemical means, are needed to more fully elucidate its behavioral effects.

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Received December 21, 2001

Revision received February 28, 2002

Accepted March 28, 2002 ■