

# Corticofugal Modulation of the Tactile Response Coherence of Projecting Neurons in the Gracilis Nucleus

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**Castellanos NP, Malmierca E, Nuñez A, Makarov VA.** Corticofugal modulation of the tactile response coherence of projecting neurons in the gracilis nucleus. *J Neurophysiol* 98: 2537–2549, 2007. First published August 29, 2007; doi:10.1152/jn.00815.2007. Precise and reproducible spike timing is one of the alternatives of the sensory stimulus encoding. We test coherence (repeatability) of the response patterns elicited in projecting gracile neurons by tactile stimulation and its modulation provoked by electrical stimulation of the corticofugal feedback from the somatosensory (SI) cortex. To gain the temporal structure we adopt the wavelet-based approach for quantification of the functional stimulus–neural response coupling. We show that the spontaneous firing patterns (when they exist) are essentially random. Tactile stimulation of the neuron receptive field strongly increases the spectral power in the stimulus and 5- to 15-Hz frequency bands. However, the functional coupling (coherence) between the sensory stimulus and the neural response exhibits ultraslow oscillation (0.07 Hz). During this oscillation the stimulus coherence can temporarily fall below the statistically significant level, i.e., the functional stimulus–response coupling may be temporarily lost for a single neuron. We further demonstrate that electrical stimulation of the SI cortex increases the stimulus coherence for about 60% of cells. We find no significant correlation between the increment of the firing rate and the stimulus coherence, but we show that there is a positive correlation with the amplitude of the peristimulus time histogram. The latter argues that the observed facilitation of the neural response by the corticofugal pathway, at least in part, may be mediated through an appropriate ordering of the stimulus-evoked firing pattern, and the coherence enhancement is more relevant in gracilis nucleus than an increase of the number of spikes elicited by the tactile stimulus.

## INTRODUCTION

Sensory processing in the CNS involves dynamic adaptation of the synaptic efficiency depending on the level of alertness or behavioral conditions. In this process corticofugal projections to the subcortical relay stations may play an important modulating role adding the temporal context to the internal dynamics. The dorsal column nuclei (DCN), which include the gracilis and cuneate nuclei, are the first relay station in the lemniscal pathway that receives somatosensory information from the body through the dorsal column and projects to the somatosensory thalamus. DCN neurons receive two major excitatory synaptic inputs that control their activity: first, due to ascending somatosensory fibers by the dorsal column, which establish contact with both thalamic projection neurons and inhibitory interneurons (DeBiasi et al. 1994; Lue et al. 1996; Rustioni and Weinberg 1989); second, due to corticofugal

fibers, primarily from cells in the forelimb and hindlimb regions of the primary somatosensory (SI) cortex and, to a lesser extent, from the secondary somatosensory cortical area, running mainly through the pyramidal tract (Jabbur and Towe 1961; Kuypers and Tuerk 1964; Valverde 1966; Weisberg and Rustioni 1976). The ascending pathway has been extensively studied over the last few decades (see e.g., DeBiasi et al. 1994; Lue et al. 1996; Rustioni and Weinberg 1989), whereas little is known about the role and dynamical properties of the corticofugal pathway. Meanwhile, studying the interplay between the two pathways should shed light on the global picture of the tactile information processing in the DCN.

Recently, it has been reported that the sensorimotor cortex exerts a selective control of the somatosensory transmission at the DCN (Aguilar et al. 2003; Canedo and Aguilar 2000; Malmierca and Nuñez 1998, 2004). Indeed, the corticofugal input facilitates sensory responses of gracile neurons with overlapping receptive fields and inhibits sensory responses of cells with separate receptive fields, probably providing a synaptic mechanism for the enhancement of contrast between sensory signals. Besides, *in vitro* experiments have shown that activation of corticofugal fibers regulates both incoming sensory signals through the dorsal column and corticofugal inputs (homo- and heterosynaptic facilitation; Nuñez and Buño 1999, 2001). *N*-Methyl-D-aspartate (NMDA) receptors are activated by glutamate released from corticofugal terminals and induce Ca<sup>2+</sup> inflow through voltage-gated channels at DCN neurons, triggering these facilitating processes (Malmierca and Nuñez 2004; Nuñez and Buño 1999, 2001). Although the synaptic mechanisms of the corticofugal modulation on DCN neurons have been previously studied, the dynamic changes of this corticofugal action have not yet been well established, mainly due to the lack of adequate tools for analysis of the temporal evolution of sensory responses.

A very common method to track temporal coupling or functional association between stimulus and neural response is the peristimulus time histogram (PSTH), which characterizes the cross-correlation between two point processes, i.e., stimulus events and a neural spike train (Perkel et al. 1967). Although the PSTH examines temporal changes in the amount of generated spikes triggered by the stimulus, analyses in the frequency domain can provide a more concise description of the temporal correlation of the oscillatory patterns in spike trains. In the frequency domain spectral coherence is a well-established standard tool to analyze the linear relationship

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between two (usually continuous) signals by determining the correlation between their spectra. A high value of spectral coherence points to the presence of a functional association between, e.g., stimulus and neural response in the corresponding frequency band. Starting from this concept several different modifications of the coherence measure have been suggested (see e.g., Baccalá and Sameshima 2001; Dahlhaus et al. 1997; Korzeneiwska et al. 2003).

Although the above-mentioned measures have been shown to be very useful in different aspects of neuroscience, they suffer from the fundamental but unlikely to be fulfilled assumption on stationarity of the neural response in question and thus do not allow one to infer on the dynamical changes in associations (coupling) between stimulus and neural response. Indeed, any analysis based entirely on time averaging (PSTH) or on the Fourier transform (coherence) ignores all temporal variations in the functional coupling between tactile stimulation and neural response. An additional temporal resolution is essential and demands replacement of the classical Fourier (spectral) coherence by other methods. There have been successful attempts to adapt Fourier-based methods to short time signals, for example, by means of orthonormal sliding windows (Bayram and Baraniuk 1996; Lovett and Ropella 1997; Xu et al. 1999), which are similar to the classical Gabor transform (Mallat 1999).

Relatively recently a new method of time series analysis that can, and has been designed to, cope with complex nonstationary signals has been introduced. The new *wavelet transform* technique provides high temporal resolution with good frequency resolution and offers a reasonable compromise for these parameters. The wavelet transform has been used to analyze brain signals from the very beginning in neuroscience. Most of its applications are in electroencephalographic recordings (see e.g., Alegre et al. 2003; Castellanos and Makarov 2006; Goelz et al. 2000; Mäkinen et al. 2004; Mormann et al. 2005; Murata 2005; Quiroga and Garcia 2003; Schiff et al. 1994). However, there are few studies on synchronization between pairs of spike trains (e.g., stimulus–neural response). In this direction the wavelet cross-spectrum has been used to analyze the phase-locked oscillations in simultaneously recorded spike trains in the motor area of rhesus monkeys trained to produce a series of visually guided hand movements according to changes in the target locations (Lee 2002, 2003).

The first studies of the wavelet coherence are very recent (Grinsted et al. 2004; Klein et al. 2006; Lachaux et al. 2002; Le Van Quyen et al. 2001). The wavelet coherence, similarly to the spectral coherence, infers on the functional coupling between, e.g., stimulus and neural response, but additionally it also provides the temporal structure of the coupling. Li et al. (2007) investigated the temporal interaction in CA1 and CA3 regions in rats with induced epilepsy using wavelet coherence. In previous works (Pavlov et al. 2006, 2007) we advocated and illustrated the use of the wavelet transform for analysis of neural spike trains recorded in the trigeminal nuclei under tactile whisker stimulation.

In this paper we aim at quantification of the wavelet coherence (i.e., functional association) of the gracile neural response to tactile stimulation and show that activation of the SI cortex leads to a dynamical (i.e., varying in time) alteration of the response characteristics of the neurons mediated by the corticofugal pathway. We first describe how the wavelet coherence

can be applied to investigation of the dynamical properties of neural spike trains and then we apply the method to evaluate the dynamical changes in the neural response to tactile stimulation in the gracilis nucleus provoked by activation of the corticofugal feedback from the SI cortex. We show that the corticofugal feedback can modulate the response of gracile neurons so that spiking activity elicited by tactile stimulation can be more strongly or more weakly phase locked to the stimulus events. Existence of such modulation can be interpreted as a possibility of changing “attention” to relevant stimuli because a reliable (coherent) response of gracile neurons projecting to the thalamus will favor the transport of sensory stimuli from the periphery to the thalamus and then to the cortex.

## METHODS

### *Experimental recordings*

Data were obtained from 15 urethane-anesthetized (1.6 g/kg, administered intraperitoneally) young adult Wistar rats of either sex, weighing 180–250 g (from Iffa-Credo, Lyon, France). Animals were placed in a stereotaxic device and the body temperature was maintained at 37°C. To record the electroencephalogram (EEG), a macro-electrode (120- $\mu$ m-diameter bluntly cut insulated nichrome wire) was lowered 1.5 mm below the cortical surface into the frontal lobe. The EEG was band-pass filtered in the range 0.3–30 Hz and continuously monitored by an oscilloscope. Supplemental doses of the anesthetic were given when a decrease in the amplitude of the EEG delta waves was observed. Experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC).

**UNIT RECORDINGS.** The cisterna magna was opened to introduce the recording electrodes at a 60° angle over the surface of the nucleus. Tungsten microelectrodes (2–5 M $\Omega$ ; World Precision Instruments) were used to obtain single-unit recordings in the gracilis nucleus (A: –13.6 to –14.6 mm, L: 0.2 to 1.0 mm from the bregma; H: 0.0 to 0.5 mm from the surface of the nucleus; according to the atlas of Paxinos and Watson 1986). Position of the electrodes was visually controlled under a dissecting microscope. Unit firing was filtered (0.3–3 kHz), amplified by an AC preamplifier (DAM80; World Precision Instruments), and fed into a personal computer (sample rate: 8 kHz) with the temporal reference of the stimuli for off-line analysis using Spike2 software [Cambridge Electronic Design (CED), Cambridge, UK]. The spike amplitude and shape were continuously monitored on-line in an analog oscilloscope. Additional off-line spike amplitude and shape analyses were performed to ensure that the same cell was recorded during the entire experiment and to transform spikes into time point processes for further data analysis (see following text).

**SENSORY STIMULATION.** Tactile stimulation was performed by an electronically gated solenoid with a 1-mm-diameter probe that produced skin deflection not exceeding 0.5 mm. The receptive field (RF) of gracile neurons was carefully mapped with a small handheld brush to identify neurons responding to light mechanical stimulation of the hindlimb, as detected with an audio amplifier driven by the amplified neuronal activity. RFs were defined by the limits at which stimuli elicited changes in the unit activity. Tactile stimulation consisted of a sequence of 31 tactile pulses lasting 20 ms and delivered at the RF at a 1-Hz rate. Thus each stimulation epoch lasted 32 s.

**NEURON IDENTIFICATION.** To identify gracile neurons projecting to the thalamus, bipolar stimulating electrodes were aimed at the medial lemniscus (A: –6.5 mm, L: 0.5 to 1.5 mm, H: 8 to 9 mm). Antidromic firing was evoked by means of brief electrical pulses (0.1–0.3 ms, 50–500  $\mu$ A).

**CORTICAL STIMULATION.** To place the stimulating electrode, the bone over the contralateral SI cortex was removed. Before placing the stimulating electrode, a tungsten microelectrode for multiunit recording (0.5–1 M $\Omega$ ; World Precision Instruments) was aimed at the cortex (A: –1 to –3 mm, L: 2 to 5 mm, H: 1.2 mm) to locate a site with a vigorous multiunit response to tactile stimulation of the hindlimb area. After detecting the RF in the SI cortex, a bipolar stimulating electrode (120- $\mu$ m-diameter bluntly cut stainless steel wire) was aimed at the same site as the recording electrode (1.0-mm depth; cortical layer 5). Electrical stimulation of the selected cortical area was performed by a Grass S88 stimulator coupled to a photoelectric stimulus isolation unit. Trains of brief rectangular pulses (0.1–0.3 ms, 10–100  $\mu$ A) at 50 Hz and lasting 500 ms were applied. This type of electrical stimulation is restricted to an area <0.5 mm<sup>2</sup>.

### Data analysis

Extracellular recordings were accepted for further mathematical analysis when the fluctuation of the unit amplitude was <10% throughout the experiment. Summed PSTHs were calculated off-line with Spike2 software (CED) running on a PC. Then we evaluated the PSTH area corresponding to the poststimulus interval of 50 ms and the area corresponding to 50 ms preceding the stimulus onset. If the former area was at least threefold larger, we positively decided on the presence of the neural response elicited by the stimulus. The latency of a sensory response was measured as the time elapsed between the onset of the sensory stimulus and the largest peak in the PSTH. All data are shown as means  $\pm$  SE.

Then we analyzed the time–frequency contents of the selected spike trains and their correlation to the stimulus events. As we mentioned in the INTRODUCTION, PSTH and ordinary spectral coherence do not provide such information. Some insight, however, can be obtained by the traditional dot-raster display. Although the raster display can capture important temporal characteristics of the neural stimulus response it is merely a visual tool; i.e., no measure of stability of the neural response, for instance, can be directly derived. Moreover, a correct comparison of raster displays generated by several neurons with essentially different firing rates is difficult if not impossible. This finally leads to a problem of generalizing results over the neural population. Meanwhile the wavelet technique offers a natural way to study the temporal structure of the neural stimulus response coherence.

**WAVELET TRANSFORM OF A SPIKE TRAIN.** The continuous wavelet transform (WT) of a signal  $x(t)$  (e.g., spike train) involves its projection onto a set of soliton-like basis functions obtained by rescaling and translating along the time axis the so-called mother wavelet  $\Psi$

$$W(p, z) = \frac{1}{\sqrt{p}} \int_{-\infty}^{\infty} x(t) \psi^* \left( \frac{t - z}{p} \right) dt \quad (1)$$

where parameters  $p$  and  $z$  define the wavelet timescale and localization, respectively. The choice of the function  $\Psi$  depends on the research aim. To study rhythmic components of a signal the Morlet wavelet is well suited

$$\psi(y) = \exp(j2\pi y) \exp(-y^2/2k_0^2) \quad (2)$$

where  $k_0$  is a parameter that can be tuned according to the physical phenomena under study. In the wavelet transform (Eq. 1) the timescale  $p$  plays the role of the period of the rhythmic component. Given a characteristic timescale (i.e., the period)  $p$ , the resolution of the wavelet in the time and frequency domains is given by

$$\delta t = ck_0 p \quad \delta \omega = \frac{c}{k_0 p} \quad (3)$$

where  $c$  is a constant of the order of unity. There is a trade-off between the frequency and time resolutions: small values of  $k_0$  provide better

time resolution, whereas using large values of  $k_0$  improves frequency resolution. The commonly adopted value is  $k_0 = 1$  and the limit  $k_0 \rightarrow \infty$  corresponds to the Fourier transform. As we subsequently show, for our purpose  $k_0 = 2$  is more suitable.

Because we deal with finite-length time series (spike trains), evaluation of the wavelet spectrum (Eq. 1) will have edge artifacts at the beginning and the end of the time interval. The cone of influence (COI) is the region in the  $(p, z)$  plane where edge effects cannot be ignored. We define the size of the COI when the wavelet power is decreased by  $e^2$  (Torrence and Compo 1998), which gives  $z = \sqrt{2}k_0 p$ .

The spiking output (point process) of a neuron can be represented as a series of  $\delta$ -functions at the times when action potentials occur

$$x(t) = \sum_i \delta(t - t_i) \quad (4)$$

Equation 4 allows us to analytically estimate the wavelet coefficients

$$W(p, z) = \frac{1}{\sqrt{p}} \sum_i e^{-j2\pi(t_i - z)/p} e^{-(t_i - z)^2/2k_0^2 p^2} \quad (5)$$

Using the wavelet-transform (Eq. 5) we can perform the time–frequency analysis of rhythmic components hidden in the spike train. Wavelet coefficients can be considered as a parameterized function  $W_p(z)$ , where  $z$  plays the role of time.

**WAVELET POWER SPECTRUM AND COHERENCE.** Spectral representation of a spike train in general can be obtained by the Fourier transform. However, such transformation is known to have difficulties when dealing with point processes (Brillinger 1978). To overcome some of them in the literature use of the multitaper Fourier transform has been advocated (Jarvis and Mitra 2001). Although the multitaper transform usually provides a good estimate of the power spectrum, in the case of excessively periodic spike trains (e.g., in experimental conditions of periodic stimulation) it may fail to consistently represent the spectral density. The wavelet transform can be used as an alternative way to perform spectral analysis.

The wavelet power spectrum of a spike train can be defined by

$$E(p, z) = \frac{1}{\sqrt{\pi r k_0}} |W(p, z)|^2 \quad (6)$$

where  $r$  is the neuron mean firing rate. The normalization factor in Eq. 6 ensures unit energy of a “random” spike train [with randomly distributed spikes]. Thus for a random spike train the energy is homogeneously distributed over all interspike periods  $\langle E(p) \rangle_z = 1$ . Consequently, we quantify the power distribution in the train under study in units of the power of the random spike train with the same mean firing rate.

The global wavelet spectrum can be obtained from Eq. 6 by time averaging of the local (time-dependent) spectrum

$$E_G(p) = \frac{1}{T} \int_0^T E(p, z) dz \quad (7)$$

where  $T$  is the time length of the spike train. The global spectrum (Eq. 7) provides an unbiased and consistent estimation of the true power spectrum (Percival 1995).

By dealing with two spike trains  $N$  and  $M$  by analogy with the Fourier cross-spectrum we can introduce the wavelet cross-spectrum  $W_{NM}(p, z) = W_N W_M^* / k_0 \sqrt{\pi r_N r_M}$ . Then a normalized measure of association between two spike trains is the wavelet coherence (Grinsted et al. 2004)

$$C_{NM}(p, z) = \frac{|S[W_{NM}(p, z)/p]|^2}{S[E_N(p, z)/p] S[E_M(p, z)/p]} \quad (8)$$

where  $S$  is a smoothing operator (for details see Grinsted et al. 2004;

Torrence and Webster 1998). The coherence definition (Eq. 8) can eventually give artificially high values of coherence in the case of infinitesimally small values of the power spectrum of either signal or both signals [i.e., when  $E(p^*, z^*) \approx 0$ ]. To avoid this problem in numerical calculations we use a thresholding procedure, setting the coherence to zero when either of the power values is below a threshold.

Two linearly independent spike trains have insignificant coherence, whereas  $C(p, z) = 1$  indicates a perfect linear relationship between the spike trains at the scale  $p$  and localization  $z$ . Because we are interested in studying the coherence level (or functional coupling) between the stimulus events and neural response we focus on the frequency band corresponding to the stimulus frequency, i.e., on  $f = 1$  Hz, which corresponds to the scale  $p = 1$  s. Thus to successfully resolve the stimulus-induced frequency contents in the neural response with minimal loss in time resolution we set  $k_0 = 2$ . Then from Eq. 3  $\delta\omega \approx 1/2$  and  $\delta t \approx 2$ . Although the wavelet transform uses the timescale (period)  $p$  as a parameter, to address the frequency contents we shall further use frequency as the parameter formally defined as  $f = 1/p$ .

**STATISTICAL SIGNIFICANCE TEST.** Although a large amplitude of the coherence usually indicates the presence of a consistent phase relationship (coupling) between two spike trains in a given time interval, it is also possible that this may be a random casual variation in spike trains. Thus one should cross-check statistical significance of the observed coherence.

The statistical significance of the wavelet coherence can be assessed relative to the null hypotheses that the two spike trains generated by independent stationary processes with given distributions of interspike intervals (ISIs) are not coherent. To evaluate the significance level we use a surrogate data test (Schreiber and Schmitz 2000; Theiler et al. 1992) with Monte Carlo simulation to establish a 95% confidence interval. The surrogate spike trains are obtained from the original one by randomizing phase relations, keeping intact other first-order characteristics. We shuffle ISIs and evaluate coherence among the surrogate spike trains. To conclude positively on the connectivity between the stimulus train and neuronal response their coherence should be higher than the obtained significance level.

**STIMULUS FREQUENCY BAND AND THE POWER SPECTRUM OF ULTRASLOW OSCILLATION OF THE WAVELET COHERENCE.** The wavelet coherence allows study of the temporal structure and variation of the functional coupling among stimuli and neural response. To quantify this variation we average the neural stimulus coherence over scales in a narrow band around the stimulus frequency. An estimate of the band limits can be obtained from Eq. 3:  $f \in [(1 - c/2\pi k_0), (1 + c/2\pi k_0)]$ , which for  $c = 2$  gives 0.83–1.16 Hz. This frequency band we shall refer to as the stimulus frequency band. Obtained this way, coherence is a function of time  $C(t)$ , which then is used to evaluate the power spectrum by the conventional Fourier transform.

**EFFECT OF CORTICAL STIMULATION ON THE STIMULUS RESPONSE COHERENCE.** To examine the effect of cortical stimulation on the coherence of the neural response to the stimulus we average the local coherences over time and the stimulus frequency band

$$C_{\text{ctr}}^m = \langle C_{\text{ctr}}(t) \rangle_t, \quad C_{\text{AESC}}^m = \langle C_{\text{AESC}}(t) \rangle_t \quad (9)$$

where  $C_{\text{ctr}}(t)$  and  $C_{\text{AESC}}(t)$  are the coherences in the stimulus frequency band in control and after the SI cortex stimulation conditions, respectively. For convenience we also introduce the overall mean coherence  $C^m = (C_{\text{AESC}}^m + C_{\text{ctr}}^m)/2$ . First, we recall that  $C_{\text{ctr}}(t)$  and  $C_{\text{AESC}}(t)$  are bounded functions of time and thus the maximal increment  $\delta C^m = C_{\text{AESC}}^m - C_{\text{ctr}}^m$  depends on the overall mean coherence and cannot exceed the value  $2(1 - C^m)$ . Thus the higher the overall mean coherence is, the lower the coherence increment can be. Then we guess a linear model

$$|\delta C^m| = \alpha(1 - C^m) \quad (10)$$

where  $\alpha$  is a constant to be identified from the data.

Then for a given value of the wavelet coherence, by using Eq. 10 we can evaluate the expectation of the absolute value of the coherence increment. If the observed increment is much smaller than the expectation we can question its significance (i.e., No-effect). To decide positively on the presence of an effect on the stimulus coherence provoked by the SI cortex stimulation we require that the experimentally observed increment  $\delta C^m$  is at least  $>50\%$  of the expectation value, i.e.,  $|\delta C^m| \geq 0.5\alpha(1 - C^m)$ . Then we have a coherence increase or I-effect for positive  $\delta C^m$  and a decrease or D-effect for negative values.

## RESULTS

The analyzed data set consisted of 29 extracellular recordings (spike trains) of unitary neural activity from the gracilis nucleus measured at three different epochs: 1) spontaneous firing; and responses to periodical (1-Hz rate) RF stimulation in 2) control conditions and 3) after electrical stimulation of the SI cortex (when appropriate, the latter stimulation epoch we shall abbreviate as AESC). All neurons were identified as projecting to the thalamus because they were antidromically activated by medial lemniscus stimulation. The criteria for the antidromic identification were fixed latency with the mean  $2.0 \pm 0.08$  ms (range 1.2–2.8 ms) and the ability to follow fast ( $>100$  Hz) stimuli. The analyzed neurons showed a low spontaneous activity with the mean  $1.1 \pm 0.4$  spikes/s (range 0–10 spikes/s) whose pattern coincided with the firing characteristics of projecting neurons previously described (Nuñez et al. 2000; Panetsos et al. 1997). Also, selected neurons had a RF that overlapped ( $>50\%$ ) the stimulated cortical area (matching condition; Malmierca and Nuñez 1998, 2004).

### Example of the wavelet analysis of a neural spike train

First, let us illustrate the wavelet analysis of a representative neural spike train. Figure 1A shows the spike train during three different experimental epochs (for illustration purposes we selected a neuron with a considerable spontaneous activity). In spontaneous conditions the neuron exhibits irregular spiking pattern with a light peak at 70 ms manifested in the autocorrelation histogram (ACH, Fig. 1B, left). Mechanical stimulation in the control conditions elicited a well-pronounced neuron response with 25-ms peak latency followed by a weakly rhythmic firing with 120-ms period (Fig. 1B, middle). Electrical stimulation of the SI cortex facilitated the neural response to the tactile stimulation. The response in the PSTH became more prominent (Fig. 1B, right). However, neither the response latency nor mean firing rate (21.1 vs. 23.7 spike/s) varied much in respect to the control conditions. Furthermore, the weak oscillatory behavior observed in the tail of the PSTH in control conditions disappeared.

**WAVELET POWER SPECTRUM AND COHERENCE.** The wavelet power spectrum (Fig. 1C, left) confirms the irregularity of spontaneous firing observed in the ACH. There are many oscillatory rhythms localized both in time and frequency domains with essentially erratic distribution. Thus spiking activity has no well-defined dominant periodic activity (although there is a feeble and not-persistent-in-time power peak at 14 Hz). The distribution of the power in the control

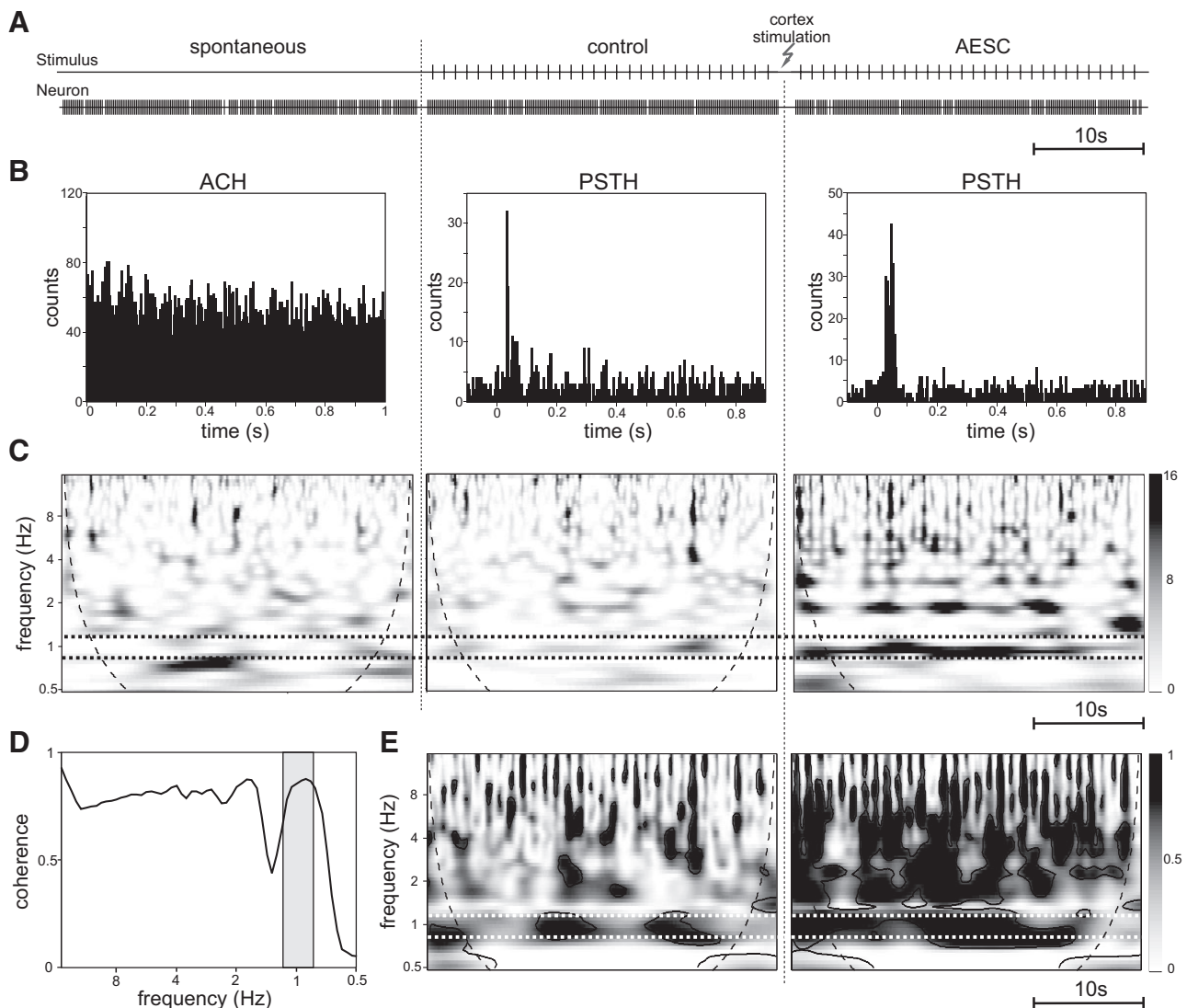


FIG. 1. Wavelet spectral and coherence analysis of experimental spike trains. *A*: stimulus events and neural spike trains during 3 experimental epochs: spontaneous activity, control 32-s-long tactile stimulation delivered to the neuron receptive field at 1-Hz rate, and the same tactile stimulation repeated after electrical stimulation of the somatosensory (SI) cortex (AESC). *B*: autocorrelation (ACH) and peristimulus time histograms (PSTHs) for the corresponding epochs. *C*: wavelet power spectra of the neural spike train for the corresponding epochs. *x*-axis corresponds to the localization  $z$  (time), whereas along the *y*-axis the oscillation frequency from 0.5 to 15 Hz in logarithmic scale is plotted. Gray intensity is equivalent to the wavelet spectral power (Eq. 6). Dashed lines define the cone of influence and horizontal dotted lines delimit the stimulus frequency band 0.83–1.16 Hz. *D*: level of statistical significance for the wavelet coherence obtained by the surrogate data test. Coherence above the curve is deemed significant. Gray area shows the frequency band of interest (around the stimulus frequency). *E*: wavelet coherence of the neural spike train to tactile stimulation events for the control epoch and after the SI cortex stimulation. Solid black lines delimit islands of statistically significant coherence (the stripe between 2 dotted lines is of interest). Gray intensity corresponds to the strength of the stimulus coherence of the neural response.

conditions (Fig. 1*C*, middle) shows a consistent peak in the stimulus frequency band (from 0.83 to 1.16 Hz, between two dotted horizontal lines). This peak indicates the presence of the stimulus-evoked rhythm in the neural firing. We also note that the peak amplitude (power) is not persistent in time but instead exhibits a low-frequency ( $<0.3$  Hz) oscillation. Such oscillation of the spectral power suggests that the neural response to the same tactile stimulation is not stable (identical) throughout time but instead has some variability, i.e., the neuron fires essentially different numbers of spikes with different ISIs to the same stimulus events along the stimulation epoch. We also observe some increase of the spectral power around 8 Hz consistent with the oscillations (120-ms period) observed in the corresponding PSTH (Fig.

1*B*, middle). In accordance with the stimulus response facilitation observed in the PSTH after the electrical cortex stimulation, the power peak at the stimulus frequency band became even more pronounced (Fig. 1*C*, right). Now we have a continuous practically black island going through the whole stimulation epoch in the stimulus frequency band. Notice, however, that the ultra-low-frequency oscillation of the power is weaker, but still exists. Besides, there is a strong increase of the power of harmonics of the 1-Hz rhythm and, on average, a higher presence of oscillations in the domain of higher frequencies.

To quantify how coherent (reliable) the neural response to the stimulus events is, we evaluated the wavelet coherence of the neural spike train and stimulus events. To decide on the

statistical significance of the found coherence level, i.e., on the presence of functional associations (coupling) between the stimulus and neural response, we performed a surrogate data test by randomizing phase relationships between two signals. Figure 1D shows a statistical significance curve ( $P$ -value 0.05) for the frequency range observed in the neural spike train. Coherence above the curve is deemed statistically significant, although if the area of the significant islands is small enough ( $\leq 5\%$ ), then the conclusion on the coherent response should be made carefully.

Figure 1E illustrates the wavelet coherence of the tactile stimulus events and evoked neural response. Because the tactile stimulation is periodic (has only one frequency), when speaking about the response coherence we shall refer to the stimulus frequency band only (delimited by dotted lines in Fig. 1E). During the control stimulation epoch we observe three islands of significant coherence in the stimulus frequency band (Fig. 1E, left). This provides evidence of the presence of a stimulus–response association previously observed in the corresponding PSTH. However, we also find that the association or stimulus–response coupling is not constant but an oscillatory function of time. Notice also that the neural power spectrum in the corresponding frequency band was not very strong (Fig. 1C, middle); however, the coherence clearly reveals the functional coupling between the neural firing dynamics and stimulus events. The stimulus coherence of the neural response becomes stronger after electrical stimulation of the somatosensory cortex (Fig. 1E, right). As we observed earlier in the wavelet power spectra (Fig. 1C, middle and right), the stimulus coherence also suffers from ultra-low-frequency oscillations.

Thus for a given neuron we observed two phenomena: 1) the strength of the functional stimulus–neural response coupling is amplified by the electrical stimulation of the SI cortex and 2) the coupling strength is a dynamical quantity slowly oscillating in time that can temporarily fall below the significant level. The latter means that stimulus–response association may be temporarily lost for a single neuron.

**GLOBAL WAVELET SPECTRUM VERSUS FOURIER POWER SPECTRUM AND ALPHA FREQUENCY BAND.** To illustrate possible pitfalls in the interpretation of the Fourier power spectrum, first we evaluated the power spectrum through the multitaper Fourier transform of the neural spike train shown in Fig. 1A. In accordance with the irregularity of firings in spontaneous conditions the Fourier spectrum (Fig. 2A) is essentially flat with a peak at 14 Hz corresponding to the earlier observed periodicity in the ACH (Fig. 1B, left). However, for the control stimulation epoch the overall spectral distribution is quite similar to that of the spontaneous spectrum, and it lacks a peak at 1 Hz corresponding to the neuron response at the stimulus frequency. Inversely, due to excessive periodicity of the neural response, after the electrical stimulation of the SI cortex we observed an unreasonably wide peak around 1 Hz followed by many strong harmonics contaminating the high-frequency range. Thus the Fourier transform of a spike train may fail to consistently represent its spectral density.

Then we used the wavelet transform as an alternative way to perform spectral analysis. Figure 2B shows the global wavelet power spectra of the neuron-firing counterpart to the Fourier spectra. The wavelet spectra are much more consistent with the oscillatory rhythms suggested by the previous analysis of spike

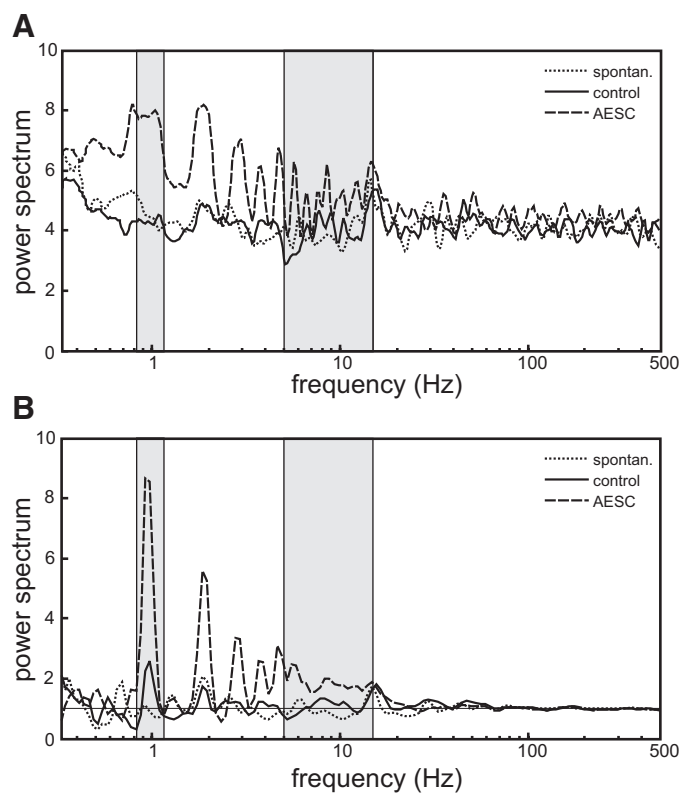


FIG. 2. Spectral analysis of spike train (corresponding to Fig. 1A) for 3 different epochs: spontaneous activity (dotted line), control tactile stimulation (solid line), and tactile stimulation preceded by electrical stimulation of the SI cortex (dashed line, AESC). Gray areas delimit alpha frequency band ranging from 5 to 15 Hz, and stimulus frequency band 0.83–1.16 Hz. A: power spectra obtained by the multitaper Fourier transform. B: global wavelet power spectra for the same epochs.

trains by the ACH and PSTHs. According to the normalization used in Eq. 6 the value of the power density equal to unity corresponds to the power spectrum of a spike train with randomly distributed ISIs, which we shortly refer to as a random spike train. Then the spectral power above (or below) unity indicates the presence (or absence) of the corresponding rhythm in the spike train with statistical power higher than just a random ratio.

During spontaneous activity the power spectrum of the neuron firing only slightly deviates from the spectrum of the random train across all frequency bands (Fig. 2B, dotted line). In agreement with the weak rhythm observed in the ACH (Fig. 1B, left), the global wavelet spectrum also has a small peak at 14 Hz. We also detected peaks at about 0.7 and 1.9 Hz. Going back to the complete wavelet spectrum (Fig. 1C, left) we find that the latter peaks are due to strong episodic events localized between 4 and 7 s and between 10 and 16 s from the epoch beginning, respectively. Thus spontaneous firing can be characterized as random, showing no strong persistent specific frequencies. Under the control tactile stimulation we observed a dramatic peak in the stimulus frequency band (Fig. 2B, solid line). Note that the peak is quite narrow and has a harmonic at 2 Hz. Stimulation of the SI cortex boosts the amplitude of the power peak in the stimulus frequency band and we also observed an important enhancement of the power in the band ranging from about 5 and 15 Hz. For the higher frequencies ( $> 15$  Hz) there is no significant deviation of the power density

from 1, whereas for the range  $<5$  Hz the harmonics of the stimulus frequency rhythm are manifested in the power spectrum. Accordingly we define the second frequency band of interest (5–15 Hz) that we shall shortly refer to as the alpha frequency band. Thus at the single-neuron level used in this study, we found that the frequency band corresponding to the evoked neural spiking activity is localized in the stimulus and alpha frequency bands.

#### *Spectral changes in the neural response provoked by electrical stimulation of the SI cortex*

To assess statistical properties of the observed changes in the spectral power of the neural firing we compared the global wavelet power spectra in spontaneous conditions and under tactile stimulation in the control and after the SI cortex stimulation conditions. Figure 3 summarizes our results.

The overall mean power in spontaneous conditions corresponds to the power of the random spike train both in the stimulus and alpha frequency bands (Fig. 3, *A* and *B*, spontan.). This confirms that the firing pattern of projecting neurons in gracilis nucleus is essentially random. Stimulation of the neuron receptive fields boosts the mean power concentrated both in the alpha and in the stimulus frequency bands (Fig. 3, *A* and *B*, control). Although the increase in the stimulus band is much stronger (7 vs. 2.5 times). Electrical stimulation of the SI cortex raises even more the power concentrated in these frequency bands (Fig. 3, *A* and *B*, AESC); however, on average, the latter enhancement is not so drastic. The effect of electrical stimulation lasted between 15 and 30 min, and then the neurons recovered their activity.

A balanced one-way ANOVA ensures that the mean spectral powers in three different epochs are significantly different with  $\alpha$ -values  $2.5 \times 10^{-5}$  for the stimulus frequency band and  $2.7 \times 10^{-5}$  for the alpha band. A multiple-comparison test shows that the values of the power during tactile stimulation in the control and after SI cortex stimulation conditions are significantly different from the power of spontaneous firing in both frequency bands, and they are statistically indistinguishable from each other.

Although the mean spectral power across both frequency bands does not significantly differ between tactile stimulations in control conditions and after electrical stimulation of the SI cortex (Fig. 3, *A* and *B*) in the majority of experiments we observed an increase of the power provoked by the cortex

stimulation. This result agrees with the previously reported facilitation of the stimulus response provoked by the SI cortex stimulation (Aguilar et al. 2003; Canedo and Aguilar 2000; Malmierca and Nuñez 1998, 2004). To quantify the percentage of the neurons exhibiting different types of the effect of stimulation of the SI cortex we evaluated the number of increases of the spectral power or I-effects, the number of No-effects (when the difference was negligible), and the number of decreases or D-effects. To decide on the type of the effect we used the relative increment of the power in the certain frequency band

$$\Delta E = \frac{E_{\text{AESC}} - E_{\text{ctr}}}{(E_{\text{AESC}} + E_{\text{ctr}})/2} \quad (11)$$

where  $E_{\text{ctr}}$  and  $E_{\text{AESC}}$  are the spectral power in the control and after the SI cortex stimulation conditions. If the absolute increment was  $<5\%$  we assigned No-effect; otherwise, according to the sign of the increment, we decided on an I- or D-effect.

Figure 3C shows that indeed after stimulation of the SI cortex in the majority of cases (66 and 69% for the stimulus and alpha frequency bands, respectively) the power of firing in both frequency bands increases, i.e., we have an I-effect of the cortex stimulation. In 17% of cases for the stimulus band and 14% for the alpha band the cortex stimulation had no effect on the spectral characteristics of the neural response. Finally, in 17% for both bands the spectral effect of the cortex stimulation was negative, i.e., the power diminished.

Thus tactile stimulation leads to a significant enhancement of the power of the neuron firing both in the alpha and in the stimulus frequency bands. Besides, electrical stimulation of the SI cortex amplifies the spectral power in these bands for about two thirds of the neurons in gracilis nucleus. We also conclude that facilitation of the neural response by the corticofugal pathway is not only in an increase of the number of spikes elicited by the stimulus but also in the ordering of the response pattern.

#### *Effect of the electrical stimulation of the SI cortex on the stimulus coherence*

Let us recall that coherence is a normalized measure of the cross-spectrum of two signals; therefore it has a sense in the frequency bands presented both in the neural spike train and in the stimulus. The latter has the fixed frequency of 1 Hz (up to

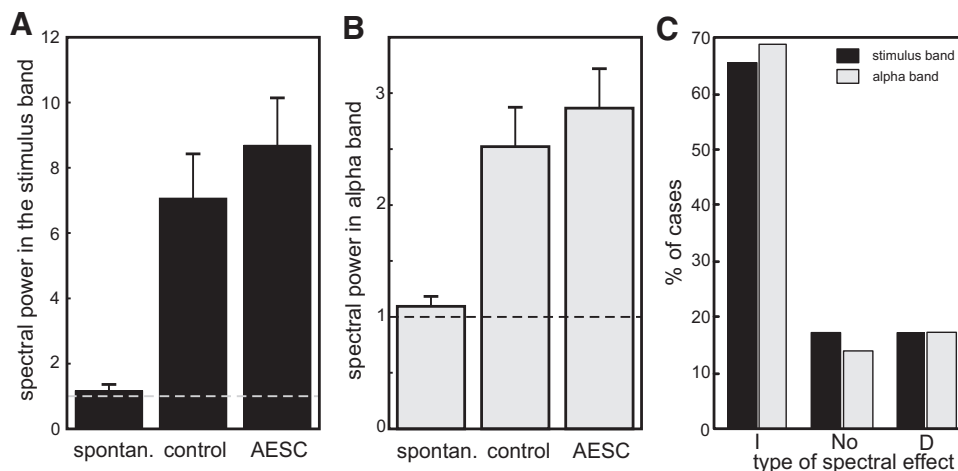


FIG. 3. Spectral characteristics of gracile projecting neurons in the stimulus and alpha frequency bands. *A*: mean power of the global wavelet spectrum and its SE in the stimulus frequency band for spontaneous conditions and during response to tactile stimulation in control conditions and after electrical stimulation of the SI cortex (AESC). *B*: same as *A* but for alpha frequency band. *C*: statistics of the types of the spectral effect of the electrical stimulation of the SI cortex for 2 frequency bands. I, No, and D stand for increase, no effect, and decrease of the spectral power, respectively. Black and gray bars correspond to the stimulus and alpha frequency bands, respectively.

small variations due to experimental setup). Accordingly, we study the wavelet coherence of the neural response to tactile stimulation in the stimulus frequency band only, whose limits were set to 0.83–1.16 Hz.

To study the effect of the cortex stimulation on the neural response coherence in the gracilis nucleus we evaluate the mean stimulus coherences in the control  $C_{\text{cntr}}^m$  and after electrical stimulation of the SI cortex  $C_{\text{AESC}}^m$  conditions. Figure 4A shows the absolute value of the coherence increment  $|\delta C^m| = |C_{\text{AESC}}^m - C_{\text{cntr}}^m|$  as a function of the mean overall coherence  $C^m = (C_{\text{AESC}}^m + C_{\text{cntr}}^m)/2$  for the experimental data set. Not surprisingly the plot shows a strong linear tendency of the coherence increment to be smaller for higher values of the overall mean coherence. By fitting the model (Eq. 10) to the data in the least-squares sense we obtain  $\alpha = 0.41$  (solid straight line in Fig. 4A). Thus for a given value of the wavelet coherence, by using Eq. 10 we can evaluate the expectation of the absolute value of the coherence increment and define the effect (No, I, or D) provoked by the cortical stimulation (Fig. 4A).

Figure 4B shows the percentage of different types of effects of electrical stimulation of the SI cortex on the tactile stimulus coherence of neuron firing in gracile projecting neurons. In the majority of cases (59%) electrical stimula-

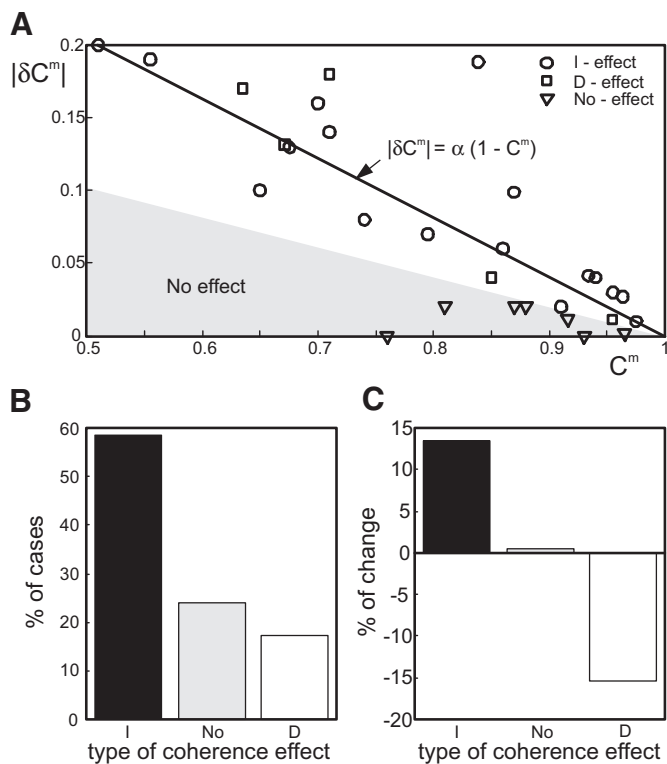


FIG. 4. Effect of the electrical activation of the SI cortex on the wavelet coherence (reliability) of the response of projecting neurons in gracilis nucleus to tactile stimulation of their receptive fields (RFs). A: absolute value of the coherence increment  $|\delta C^m|$  as a function of the mean overall coherence  $C^m$  shows a strong linear tendency. Solid straight line is the best fit of the data to the model (Eq. 10). Gray area delimits the No-effect region (data points shown by triangles) where the experimentally observed value of the coherence increment is  $<50\%$  of the expectation. Circles and squares correspond to I (or increase) and D (or decrease) types of effect of the electrical cortex stimulation on the stimulus response coherence. B: percentage of neurons exhibiting I, No, and D types of effect. C: relative changes (increase or decrease) of the coherence for I and D effects.

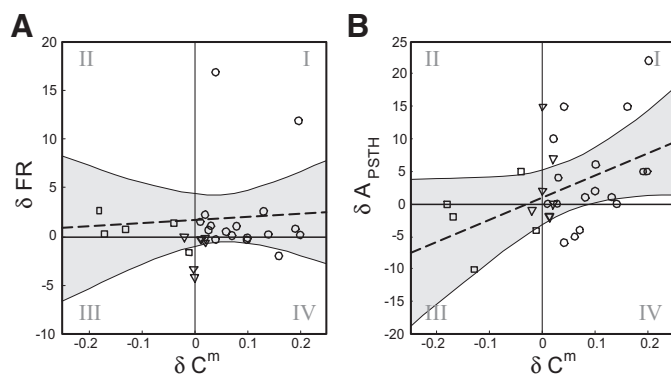


FIG. 5. Increment of the mean neural firing rate (A) and of the amplitude of the PSTH peak (B) vs. the increment of the neural stimulus response coherence. Quadrants I and III correspond to positive correlation between 2 characteristics (i.e., increase or decrease of one characteristic is accompanied by the same effect in the other), whereas quadrants II and IV correspond to negative or anticorrelation (i.e., when the effect in one characteristic is contrary to the effect in the other). Dashed straight lines and gray areas around show the best linear fits of the data and their 95% confidence limits. Direction and position of the fits imply the absence of correlation between the firing rate and coherence measures and a positive correlation of the amplitude of the PSTH peak and coherence measures. However, note the presence of cases where changes in the PSTH amplitude do not correspond to the changes in the coherence.

tion of the SI cortex facilitates more reliable (higher coherent) neural response to the tactile stimulus. Both in 24 and in 17% of cases we had no effect or decrease of the coherence, respectively. The observed relative increment of the coherence value for I- and D-effects was about the same: 13 and 15%, respectively (Fig. 4C).

We note that the positive increment of the coherence (reliability of the neuron response to tactile stimulation) was observed in a slightly lower number of cases than the increment of power in the stimulus frequency band (59% in Fig. 4B vs. 66% in Fig. 3C), which confirms the statement made earlier that an increase in the spectral power is not necessarily accompanied by an increase of the coherence. Moreover, this suggests possible subtle changes occurring in the stimulus response pattern due to the corticofugal pathway instead of a simple increase of the firing rate.

To cross-check whether the increment of the wavelet stimulus coherence correlates with conventional characteristics of the neural activity we plotted an increment of the mean firing rate  $\delta FR = FR_{\text{AESC}} - FR_{\text{cntr}}$  and an increment of the amplitude of the response peak in the PSTH  $\delta A_{\text{PSTH}} = A_{\text{AESC}} - A_{\text{cntr}}$  versus  $\delta C^m$  (Fig. 5). In these plots a data point belonging to quadrant I or quadrant III corresponds to a positive correlation between the corresponding measures, i.e., an increase or decrease in coherence is associated with an analogous effect in the other characteristic, whereas quadrants II and IV establish the contrary effect or anticorrelation. According to the above-described findings we expected that an enhancement of the reliability of the neural response to tactile stimulation (i.e.,  $\delta C^m > 0$ ) should not be necessarily reflected in the neuron firing rate, but it is reasonable to observe a better peaking of the PSTH and consequently  $\delta A_{\text{PSTH}} > 0$ .

Indeed, Fig. 5A shows that the data points in the case of the mean firing rate are distributed quite arbitrarily over the plane—the linear fit of the data confirms this. The straight line and its 95% confidence interval are essentially horizontal,



showing no significant correlation between the measures. A different picture is observed for the increment of the amplitude of the PSTH peak (Fig. 5B). The best-fit line and its 95% confidence interval have a notably positive slope. Thus as expected, we have a positive correlation of the changes provoked by the electrical stimulation of the SI cortex between the coherence and the amplitude of the PSTH peak. However, we note that an enhancement (or reduction) of the stimulus coherence is not always accompanied by the increase (or decrease) of the PSTH amplitude. This means that for a considerable number of experiments the PSTH measure fails to predict the effect of changes in the coherence of the neural response to the tactile stimulus.

#### Ultra-low-frequency oscillation of the stimulus response coherence

In Fig. 1E we qualitatively observed that the tactile stimulus coherence slowly oscillates in time both for the control experimental conditions and after electrical stimulation of the SI cortex. Let us now quantify these oscillations and study their possible functional role.

Figure 6A shows two stripes cut out of the corresponding coherence functions in the stimulus frequency band shown in Fig. 1E between two horizontal dotted lines. To examine mean coherence and its modulation in time we average the local coherence over the stimulus frequency band. The obtained time series for the control  $C_{\text{ctr}}(t)$  and after the SI cortex stimulation  $C_{\text{AESC}}(t)$  conditions give a measure of the reliability of the neuron response to stimulation events along the corresponding stimulation epoch (Fig. 6A, bottom). At the beginning of the stimulation epochs (up to  $\sim 20$  s) the stimulus response coherence is higher after the electrical cortex stimulation than in the control conditions. Then both characteristics exhibit some decay (i.e., the neuron firing becomes less stimulus coherent) and no substantial difference between the coherence values is observed. Over all the stimulation epochs we observed slow oscillation of relatively high amplitude. We note that the period of slow oscillation is much lower than the wavelet temporal resolution (about 10 to 15 vs. 2 s), which ensures the correct identification of the coherence oscillatory behavior.

The observed oscillation may have a functional role. Indeed, for the control stimulation epoch the coherence temporarily

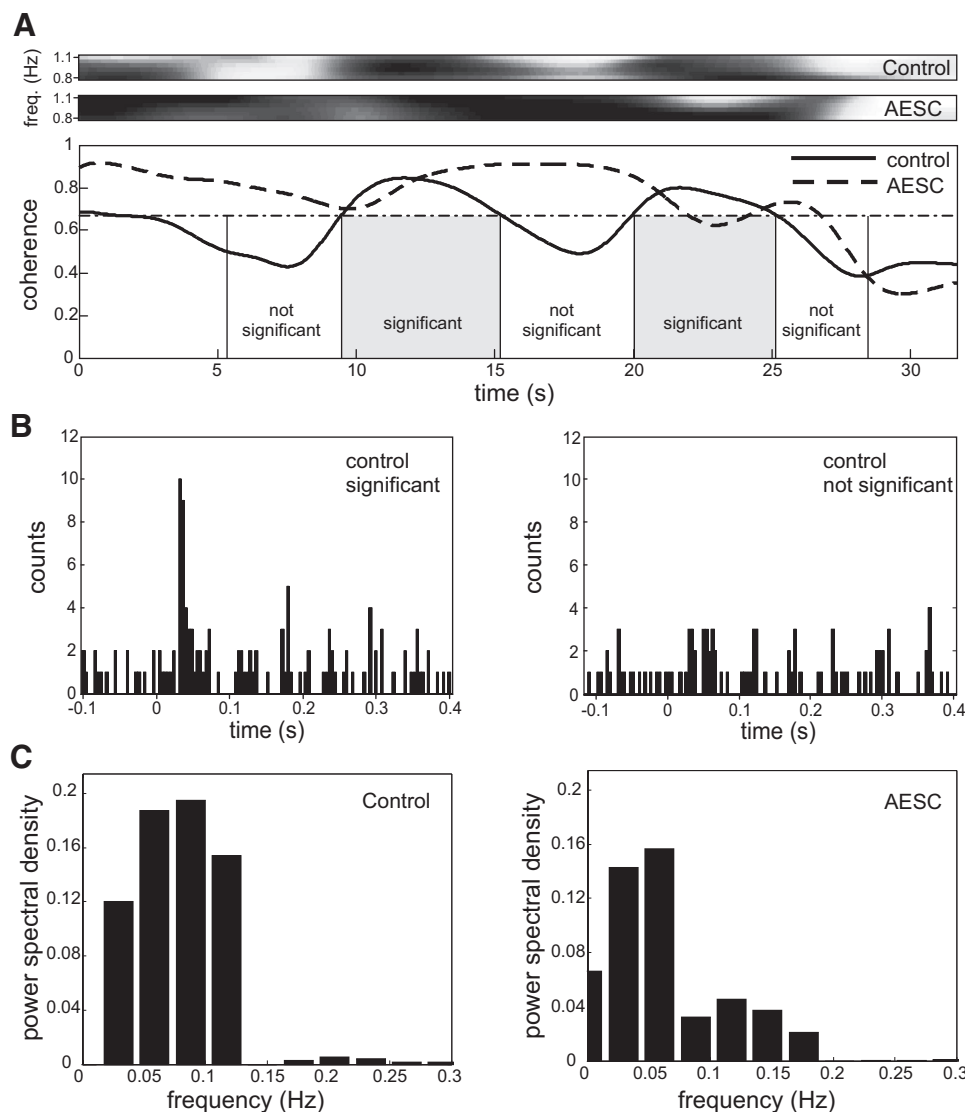


FIG. 6. Oscillatory behavior of the wavelet coherence of the neural response to tactile stimulation events in the stimulus frequency band. *A*: top strips show coherences evaluated in the stimulus frequency band 0.83–1.16 Hz (correspond to those shown in Fig. 1E between horizontal dotted line) for the control (“control”) and after electrical stimulation of the SI cortex (“AESC”) for the representative neuron. Gray intensity corresponds to the local coherence value. Zero on the time axis corresponds to the beginning of each epoch. *Bottom*: thick curves show the integral (averaged over the stimulus frequency band) wavelet stimulus coherence of the neuron response along the stimulation epochs. Thin dash-dotted horizontal line defines the level of statistical significance for the coherence in the control stimulation conditions. According to the statistical significance we define time windows of significant (gray boxes) and nonsignificant (white boxes) coherence. *B*: PSTHs of the neural response in control conditions evaluated over time windows with coherence above (*left*) and below (*right*) significance level. In the windows of the coherent response the neuron shows a pronounced peak, whereas it loses the stimulus correlation outside of the coherent windows. *C*: Fourier power spectra of the oscillation of the wavelet coherences in control (control) and after the SI cortex stimulation conditions (AESC).

falls below the significance level (Fig. 1E, left and Fig. 6A, bottom). Thus we can define time windows (segments) with coherence above or below the level of statistical significance. In Fig. 6A these windows are shown by white and gray boxes, so that the total length of the significant and nonsignificant segments is the same. Obviously, in windows with high coherence the neuron should exhibit a strong functional stimulus–response relationship. However, when the stimulus coherence is not significant this functional association may be lost. The “raw” PSTH (Fig. 1B, middle) does not provide evidence of this phenomenon. However, by splitting the spike train into two parts according to the significance of the observed coherence we indeed observe an essential difference in the PSTHs (Fig. 6B). In regions with significant coherence, the neuron exhibits a well-pronounced stimulus response (Fig. 6B, left), whereas its firing becomes practically stimulus uncorrelated in the time windows of nonsignificant coherence (Fig. 6B, right). We can interpret this behavior as a temporal loss of the functional connectivity between the tactile stimulus and the neuron. We also note that electrical stimulation of the SI cortex increases the stimulus–response coherence and it stays above the level of significance during practically the whole stimulation epoch and only after about 27 s the coherence becomes nonsignificant. In such an “alerted” state the neuron maintains functional coupling to the sensory stimulus sending coherent spikes to the thalamus.

Figure 6C shows Fourier power spectral densities of the ultra-low-frequency oscillation of the stimulus coherence in the control and after cortex stimulation conditions. In the first case the spectrum has a peak at 0.09 Hz, whereas after the SI cortex stimulation the peak shifts to lower frequency (0.06 Hz) and becomes smaller.

Figure 7 shows the mean frequency and power of the coherence oscillations averaged over the neuron population during tactile stimulation in the control conditions and after the electrical cortex stimulation. The mean frequency in control conditions was 0.065 Hz, which is slightly lower than the oscillation frequency after the cortex stimulation, 0.068 Hz. However, there is no statistically confirmed significant difference between the two means. Similarly, the mean oscillation power is slightly (but not significantly) higher in the case of tactile stimulation preceded by electrical stimulation of the SI cortex. Thus the mean frequency and amplitude of the

ultra-low-frequency oscillations averaged over the neural population are not affected by the electrical stimulation of the SI cortex.

## DISCUSSION

Although neurons can communicate using the time-averaged firing rate (Shadlen and Newsome 1998), precise and reproducible spike timing is also frequently observed in the CNS, increasing the likelihood that stimulus-elicited firing patterns encode sensory information (Abeles et al. 1993; Bair and Koch 1996; Mainen and Sejnowski 1995). The latter possibility, if applicable, should manifest itself in the somatosensory system as a repeated response pattern of projecting gracile neurons coherent with the stimulus events. Then their synchronized stimulus-driven discharges will induce excitatory postsynaptic potentials (EPSPs) within a narrow temporal window in thalamic cells, increasing the chances of generating spikes to be further transmitted to the somatosensory (SI) cortex (Nicoletis et al. 1995; Steinmetz et al. 2000). For this reason we studied the stimulus–response coherence of the firing patterns in gracilis nucleus and its temporal evolution over stimulation epochs. This analysis revealed that the coherence enhancement may be more relevant in sensory processing than an increase in the number of spikes elicited by the tactile stimulus.

On the other hand the corticofugal feedback projecting from the SI cortex to the gracilis nucleus closes the sensory information processing loop. It has been hypothesized that oscillations in the SI cortex could facilitate an association between functionally related cells (Murthy and Fetz 1992, 1996; Roy and Alloway 1999). This “association hypothesis” may also be applied to the gracilis nucleus. Indeed, sensory inputs may be integrated by oscillatory neuronal networks composed of gracile neurons that are spatially distributed, but share common receptive fields. Their activity may be modulated and enhanced through the corticofugal feedback by the SI cortex. Thus the rhythmic synchronization may increase the contrast between the evoked EPSPs from rhythmically entrained neurons and the synaptic outputs from noncoherent neurons. A selective facilitating effect of the corticofugal feedback has been previously described in the somatosensory system (Canedo and Aguilar 2000; Malmierca and Nuñez 1998, 2004) and in other sensory pathways (see e.g., Jen et al. 2002; Sillito et al. 1994; Yan and Suga 1996). The facilitating effect is due to the activation of NMDA receptors in gracile neurons (Malmierca and Nuñez 2004; Nuñez and Buño 2001). This cortical selective feedback, called “egocentric selection” by Jen et al. (2002), may play a pivotal role in gating the sensory information that reaches the thalamus and then the cortex. To validate and develop the association hypothesis we have studied the modulation of the tactile stimulus coherence in gracile neurons by electrical activation of the SI cortex. Our results show that activation of the corticofugal pathway in a majority (~60%) of cases increases rhythmic activities synchronized with the sensory stimulus.

The achieved results have been made possible by using wavelet coherence for spike train analysis. Although some rough description of the somatosensory loop could be obtained on the basis of analysis of PSTHs, methods from the rapidly growing fields of nonlinear dynamics and complex systems

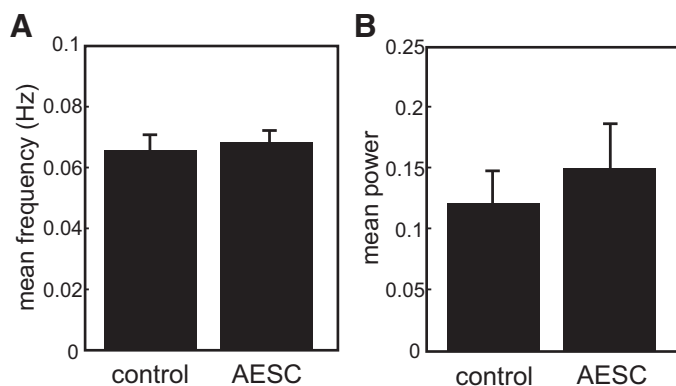


FIG. 7. Statistical properties of the ultraslow oscillations of the stimulus response coherence of projecting neurons in the gracilis nucleus in control conditions and after electrical stimulation of the SI cortex (AESC). A: mean oscillation frequency. B: mean oscillation power.

theory can provide new insights into the underlying complex biological processes (Pavlov et al. 2006). In this line we have shown how the wavelet approach for analysis of nonstationary signals can be adapted for the investigation of spike trains and can be used for quantification of the functional stimulus–neural response coupling. The coupling between two signals (i.e., stimulus and neural response) can be detected by means of the spectral coherence. However, its Fourier transform origin limits the practical application to the neural spike trains. Here the wavelet coherence is better suited and can be directly evaluated from the spike trains. Besides providing valuable temporal structure of the functional relationships it deals better with point processes (spike trains). For the optimal use of wavelet coherence it is desirable: 1) to tune the Morlet parameter according to the problem and 2) to test coherence significance. For the constant frequency stimulus (1 Hz) we have found that  $k_0 = 2$  allows better resolve stimulus-induced firing rhythm. The coherence significance affects our (statistical) belief to which extent the observed functional associations are not due to chance. The latter can be tested by Monte Carlo simulation with surrogate spike trains obtained by shuffling ISIs.

By analysis of the wavelet power spectra we have shown that the spontaneous firing pattern (when it exists) of projecting neurons in the gracilis nucleus is essentially random and it is not affected by electrical stimulation of the SI cortex. The latter means that the corticofugal stimulation does not increase the overall neural excitability, but specifically facilitates synaptic sensory responses. Tactile stimulation of the neuron receptive field, as expected, strongly increases the spectral power in the stimulus frequency band. Our results also show an enhancement of the power in the alpha frequency band (5–15 Hz), in agreement with the previously reported data (Nuñez et al. 2000; Panetsos et al. 1998). Although at the single-neuron level we have found changes in the alpha and stimulus frequency bands only, other frequency bands (e.g., gamma) may be present at the neural population (small networks) level. We have further demonstrated that electrical stimulation of the SI cortex increases the power for about 66 and 69% of the projecting neurons in the stimulus and alpha frequency bands, respectively. However, the mean increase is not significant. This argues that the observed facilitation of the neural response by the corticofugal pathway is not extensive but, at least in part, may be mediated through an appropriate ordering of the stimulus-evoked firing pattern in the gracilis nucleus.

To verify this hypothesis we addressed the question of how coherent the neural response to the tactile stimulus is. Although the spectral power of the neural spike train in the stimulus frequency band can be sufficiently high, this does not ensure a high coherence of the neural response to the tactile stimulation. The level of coherence strongly depends on the repeatability of the stimulus-elicited firing pattern, whereas due to the normalization, the signal power in the given frequency band is less important. We also found no significant correlation between the increment of the firing rate and coherence, but we have shown that there is a positive correlation of the changes provoked by the electrical cortex stimulation in the coherence and the amplitude of the stimulus response peak in the PSTH. However, we note that an enhancement (or reduction) of the stimulus coherence is not always accompanied by an in-

crease (or decrease) of the PSTH amplitude. This means that the peak amplitude is not a reliable measure for evaluating the coherence of the neural response to the tactile stimulus. We have shown that an increment of the stimulus coherence provoked by electrical stimulation of the SI cortex is observed in about 59% of gracile projecting neurons with overlapping receptive fields (which is 7% lower than the power increase), whereas in 17% we observed a decrease of the stimulus–response coherence. The latter effect may be due to simultaneous activation of cortical fibers from overlapped and nonoverlapped receptive fields. This suggests that selective synchronization of stimulus-driven discharges may enhance the contrast between synaptic inputs from the RF and from other synaptic inputs. Therefore the SI cortex may contribute to the fine focusing of sensory responses in the gracile neurons, enhancing the activity of functionally related neurons and filtering out the irrelevant sensory inputs from the periphery.

The possibility of studying the temporal structure of the stimulus–response coherence allowed us to describe ultraslow fluctuations in tactile responses of single projecting neurons. We note that such oscillations are not directly observable either in the Fourier spectrum or in the PSTH of the neural response. Instead, they represent slow modulation of the coherence (or reliability) of the neural response to the tactile stimulation over a long timescale; i.e., the neuron fires essentially a different number of spikes with different ISIs to the same stimulus events along the stimulation epoch. Thus besides the observation of a facilitating of the tactile stimulus–neural response functional coupling by the electrical stimulation of the SI cortex, we have provided evidence that the functional coupling between the sensory stimulus input and neural response oscillates slowly in time. During this oscillation, the stimulus coherence can temporarily fall below the significant level. The latter means that the stimulus–response association may be temporarily lost for a single neuron. This phenomenon argues that the information processing in gracilis nucleus occurs on the network level, which may be “energetically” beneficial for the system. The mean frequency of the observed coherence oscillation was about 0.07 Hz. Oscillations in the same frequency band (0.02 to 0.2 Hz) have been reported in studies of human EEG (Vanhatalo et al. 2004). The authors showed that large-scale ultraslow oscillations in widespread cortical regions may represent a cyclic modulation of cortical gross excitability. This ultraslow oscillation of cortical activity might be transferred to the gracilis nucleus through the corticofugal projections, thus modulating tactile responses.

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