

Absence of Rapid Sensory Adaptation in Neocortex during Information Processing States

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Summary

One prominent feature of sensory responses in neocortex is that they rapidly adapt to increases in frequency, a process called “sensory adaptation.” Here we show that sensory adaptation mainly occurs during quiescent states such as anesthesia, slow-wave sleep, and awake immobility. In contrast, during behaviorally activated states, sensory responses are already adapted. For instance, during learning of a behavioral task, when an animal is very alert and expectant, sensory adaptation is mostly absent. After learning occurs, and the task becomes routine, the level of alertness lessens and sensory adaptation becomes robust. The primary sensory thalamocortical pathway of alert and expectant animals is in the adapted state, which may be required for adequate sensory information processing.

Introduction

Cortical responses to sensory stimuli depress with repeated stimulation above certain frequencies, which means that sensory inputs reaching the neocortex are low-pass filtered. This phenomenon, called sensory adaptation, has been described in virtually all sensory modalities (Hellweg et al., 1977; Nelson, 1991; Ohzawa et al., 1982; Wilson, 1998). The functional role of sensory adaptation is unclear, but it has been suggested to serve as a means to enhance sensory coding and as a mechanism to affect perception of subsequent stimuli (Adorjan et al., 1999; Fairhall et al., 2001; Kohn and Whitsel, 2002).

Sensory adaptation is particularly strong in the neocortex (Chung et al., 2002) but is also present in the thalamus. Studies have reported different levels of adaptation in the thalamus. For instance, some studies report that thalamocortical neurons respond to whisker stimulation at up to 12 Hz (Hartings and Simons, 1985, 1998; Simons and Carvell, 1989), while other studies report strong adaptation at frequencies above 5 Hz (Diamond et al., 1992; Lee et al., 1994) or 2 Hz (Ahissar et al., 2000). These discrepancies in the degree of sensory adaptation in the thalamus can be explained by differences in the level of thalamic arousal (Castro-Alamancos, 2002a). During aroused states typical of information processing, electroencephalographic activity is characterized by low-amplitude fast activity, called activation, which contrasts with the large-amplitude regular and slow activity typical of quiescent states (Moruzzi and Magoun, 1949) (the terms “activated versus nonactivated state” are used instead of “desynchronized versus synchronized state” because cortical activity may be more synchro-

nized during activated states [Munk et al., 1996]). During activated states, the relay of high-frequency sensory inputs is allowed through the thalamus (Castro-Alamancos, 2002a, 2002b). Consequently, sensory adaptation is mostly absent in the thalamus during activated states.

Sensory adaptation in the neocortex may also be affected by behavioral state. This hypothesis is supported by the dramatic effects that behavioral state has on thalamocortical pathways (Castro-Alamancos and Connors, 1996; Castro-Alamancos and Oldford, 2002; Fanselow and Nicolelis, 1999; Steriade et al., 1969). For instance, during activated states, low-frequency sensory inputs reaching the cortex through a primary sensory pathway are suppressed at the thalamocortical connection, a process called here sensory suppression (Castro-Alamancos and Oldford, 2002). This sensory response suppression results from the activity-dependent depression of thalamocortical synapses, caused by increased firing of thalamocortical neurons during arousal (Castro-Alamancos and Oldford, 2002; Swadlow and Gusev, 2001). In addition, enhanced tonic inhibition in neocortex may also contribute to sensory suppression (Castro-Alamancos, 2002c) because thalamocortical cells are exceptionally well coupled to inhibitory interneurons (Bruno and Simons, 2002; Swadlow, 1995), and thus increased thalamocortical firing may well result in enhanced cortical inhibition. During aroused states, when sensory suppression is present, cortical receptive fields are focused at a spatial level and thus become more selective to the principal input (Castro-Alamancos, 2002c; Simons and Carvell, 1989; Worgotter et al., 1998). In addition to these spatial changes, it is likely that during arousal there are also changes in the temporal characteristics of cortical responses, such as sensory adaptation.

Recent evidence shows that cortical sensory adaptation (i.e., the reduction of cortical sensory responses with increased input frequency) is produced by the activity-dependent depression of thalamocortical synapses (Chung et al., 2002). Similarly, sensory suppression during arousal (i.e., the reduction of cortical sensory responses during arousal) is also due to the activity-dependent depression of thalamocortical synapses (Castro-Alamancos and Oldford, 2002). Since both processes (sensory adaptation and sensory suppression during arousal) share a common mechanism, it is logical that they should mutually exclude each other; in other words, if one of them is expressed, the other one would not. In the present study, we investigated this possibility by measuring cortical sensory adaptation during different behavioral states in the rat whisker barrel cortex using anesthetized and freely behaving rats.

Results

Sensory Adaptation in Neocortex Is Reduced in Anesthetized Animals during Activated States

Local field potentials were recorded from layers IV–III of the barrel cortex in urethane-anesthetized rats. Single-

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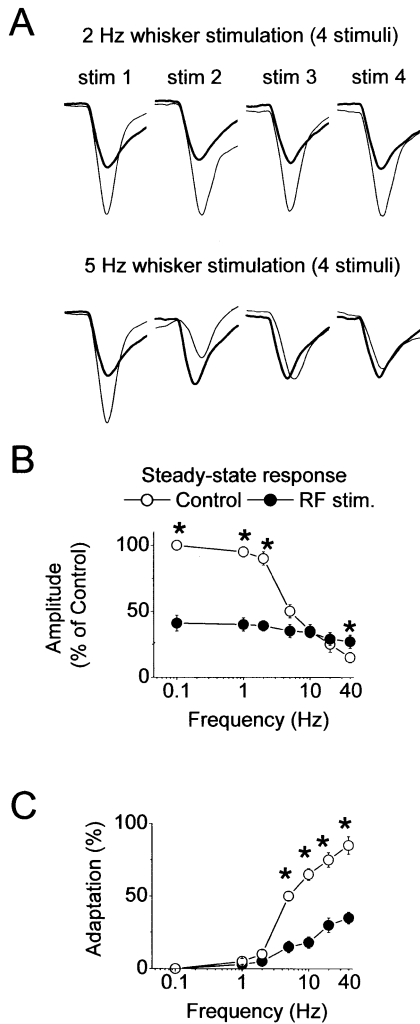


Figure 1. Reduction of Sensory Adaptation in Anesthetized Rats during Activation

(A) Local field potential responses evoked by whisker deflections and recorded from layers IV-III of urethane-anesthetized rats. Shown are the first four responses in a whisker stimulus train evoked at 2 Hz (above) and at 5 Hz (below) during control (quiescent) states (thin traces) and during activated states produced by stimulating the brainstem reticular formation (thick traces).

(B) Spectrum analysis of whisker evoked responses during control (open circles) and activated states (closed circles; RF stim.) in urethane-anesthetized rats. The average response amplitude of the tenth response in a stimulus train (steady-state response) is displayed as a percentage of the control response delivered at 0.1 Hz ($n = 6$ rats). The response was defined as the maximum amplitude of the whisker-evoked negative field potential response measured during a 10 ms time window starting 6 ms after the whisker deflection (same for [C]). * $p < 0.001$.

(C) Spectrum analysis of the percent adaptation of whisker evoked responses measured by comparing the amplitude of the first and tenth responses in a stimulus train (%) during control states (open circles) and during activated states (closed circles; RF stim) in urethane anesthetized rats ($n = 6$). * $p < 0.001$.

or multiwhisker deflections on the contralateral face produce a negative local field potential response with an onset latency of about 5.5 ms (Figure 1). The local field potential is a population response reflecting the linear sum of the fields generated by current sinks and sources

from multiple cells surrounding the electrode. Local field potentials recorded with relatively low-impedance electrodes ($< 1 \text{ M}\Omega$) are generated mostly by slow subthreshold postsynaptic activity. The fast action potentials (i.e., spikes) from single cells are low-pass filtered by the extracellular space (or filter settings) and contribute little to the field potential. Only when large numbers of cells fire synchronously, then population spikes may also contribute to the field potential response (Mitzdorf, 1985; Nicholson, 1979; Purpura, 1959). Previous work using current source density analysis (CSD) has shown that the amplitude of the negative local field potential response evoked in layers IV-III by whisker stimulation reflects the size of a current sink in those layers that is triggered by thalamocortical afferents (Castro-Alamancos and Oldford, 2002; Oldford and Castro-Alamancos, 2003; Swadlow et al., 2002). Thus, the negative local field potential response is well correlated with simultaneously recorded spike activity from local cells (Castro-Alamancos and Oldford, 2002).

Repetitive whisker deflections above 2 Hz in urethane-anesthetized rats produce strong adaptation of sensory responses (Ahissar et al., 2000; Chung et al., 2002; Sheth et al., 1998). Sensory adaptation in the neocortex is observed using a variety of electrophysiological methods including local field potentials (Figure 1), CSD (Figure 2), multiunit recordings (Figure 3A), and single-unit recordings (Figures 3B and 3C). Thus, the response amplitude and slope of evoked responses sharply decrease with frequency (Figures 1–3). In contrast, during activated states, produced by stimulating the brainstem reticular formation (Castro-Alamancos, 2002a, 2002c; Castro-Alamancos and Calcagnotto, 2001; Castro-Alamancos and Oldford, 2002), cortical sensory responses display much less adaptation (Figures 1–3). Figure 1B displays population data from field potential recordings ($n = 6$ rats). Each data point was derived from 30 to 60 trials per whisker stimulation frequency (0.1, 1, 2, 5, 10, and 40 Hz; trains of ten stimuli) and per condition (control versus activated). The results show that whisker-evoked responses below 5 Hz (i.e., 0.1–2 Hz) during activated states were significantly reduced ($p < 0.001$) as compared to control states. Whisker responses at 40 Hz, which are already robustly reduced by frequency, were significantly larger ($p < 0.001$) during activated states than during control states. These changes resulted in the strong reduction of sensory adaptation during activated states. Figure 1C displays the amount of adaptation ($n = 6$ rats) measured by comparing the first and tenth responses for each frequency train. Sensory responses above 2 Hz adapted significantly more during quiescent states than during activated states ($p < 0.001$ for 5–40 Hz; $n = 6$; Figure 1C). For example, responses at 10 Hz were reduced (adapted) by $65\% \pm 4\%$ during quiescent states, while during activated states they were reduced by only $18\% \pm 6\%$.

Figure 2 shows examples of CSDs corresponding to sensory responses evoked in the barrel cortex by whisker deflections during control states and during activated states produced by stimulating the brainstem reticular formation in a urethane-anesthetized rat. The current flow distribution reveals that a whisker deflection produces two short-latency sinks (red) centered around layer IV ($\sim 800 \mu\text{m}$) and upper layer VI ($\sim 1500 \mu\text{m}$). Both

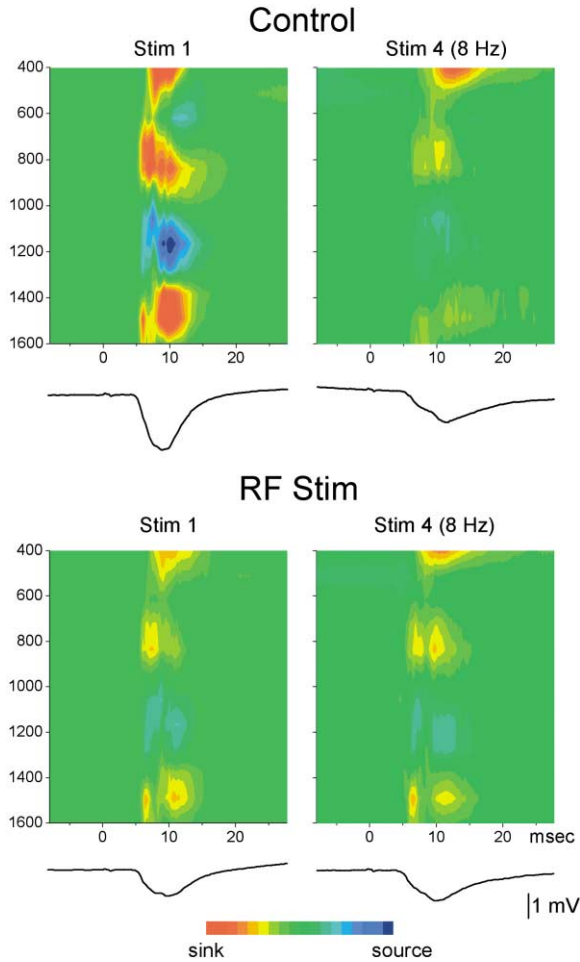


Figure 2. Laminar Profile of the Reduction of Sensory Adaptation during Activation
CSD of sensory responses evoked in the barrel cortex by whisker deflections before (control; upper panels) and after stimulating the brainstem reticular formation (RF Stim; lower panels). The left panels represent responses to the first stimulus at low frequency (0.1 Hz), while the right panels represent responses evoked at high frequency (8 Hz in the case shown). The current flow distribution (sinks in red, sources in blue) reveal that a whisker deflection produces two short-latency sinks centered around layer IV (~800 μm) and upper layer VI (~1500 μm). Both of these sinks are reduced by repetitive stimulation at high frequency (upper right panel) or by activation produced by stimulating the brainstem reticular formation (lower panels). Note that during activation, the current flow in response to the 0.1 Hz stimulus (lower left panel) is basically indistinguishable from the current flow evoked by the 8 Hz stimulus (lower right panel). The field potential traces recorded in layer IV (800 μm) are also shown for each CSD. Each CSD is the average of ten evoked responses.

of these sinks are reduced by repetitive stimulation at high frequency or by activation produced by stimulating the brainstem reticular formation. Thus, during activation, the current flow in response to low-frequency whisker deflections (e.g., 0.1 Hz) is basically indistinguishable from the current flow evoked by higher frequency whisker deflections (e.g., 8 Hz). During quiescent states (control), the amplitude of the layer IV and the layer VI current sinks depressed significantly in response to 8 Hz whisker stimulation ($n = 3$ experiments;

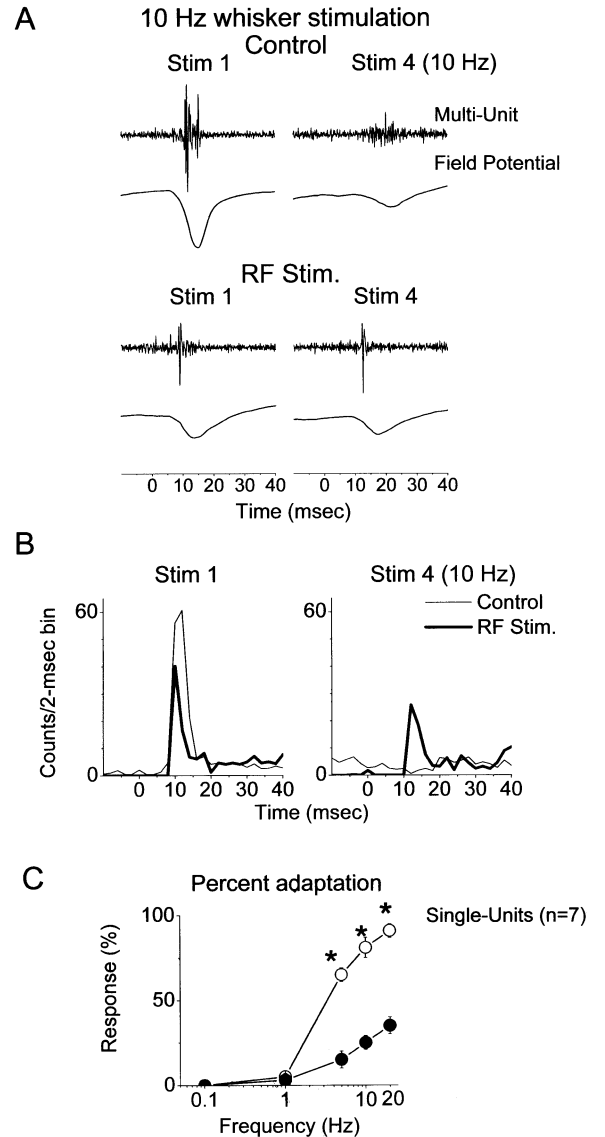


Figure 3. Unit Recordings Show Reduced Sensory Adaptation during Activation

(A) Multiunit recordings in correspondence with field potential recordings evoked by whisker deflections during control (quiescent) states and during activated states produced by stimulating the brainstem reticular formation (RF Stim.). Shown are the responses evoked by the first whisker stimulus delivered at 0.1 Hz and the responses evoked by the fourth stimulus in a train delivered at 10 Hz. Traces correspond to single trials.
(B) Time histograms of single-unit activity from a cell in layer IV-III (850 μm in depth), displayed as the number of counts per 2 ms bins in response to whisker deflections during control (quiescent) states and during activation (RF Stim.). Shown are the responses to the first stimulus in a train delivered at 0.1 Hz and the fourth delivered at 10 Hz. The whisker deflection is evoked at time 0.
(C) Spectrum analysis of the percent adaptation of whisker-evoked responses evoked in single-unit recordings measured by comparing the number of counts produced by the first and fourth responses in a stimulus train (%) during control states (open circles) and during activated states (closed circles; RF stim) in urethane-anesthetized rats ($n = 7$ cells). The response was defined as the counts occurring during a 10 ms time window starting 6 ms after the whisker deflection. * $p < 0.001$.

$p < 0.0001$), but the depression was not different between each layer, so that layer IV and layer VI depressed similarly (~55%). In contrast, during activation, the amplitude of the layer IV and layer VI current sinks was not affected by the 8 Hz whisker stimulation, so that there was no significant sensory adaptation.

Figure 3 shows similar results obtained with multiunit recordings (Figure 3A) and single-unit recordings (Figures 3B and 3C) from cells in layers IV-III of urethane-anesthetized rats. During quiescent states, robust unit activity is evoked at low frequencies in correspondence with the large local field potential negativity that reflects a layer IV-III current sink, and these responses strongly adapt with frequency. However, during activated states, induced by stimulating the brainstem reticular formation, unit responses to low-frequency stimuli are suppressed while responses to high-frequency stimuli are enhanced (Figures 3A and 3B). Consequently, cortical unit responses show much less adaptation during activated states. Figure 3C consists of population data derived from single-unit recordings ($n = 7$). Single-unit responses were measured during a 10 ms time window starting 6 ms after a whisker deflection. As with the field potential responses, single-unit recordings show that sensory responses adapted significantly more during quiescent states than during activated states ($p < 0.001$; for 5–40 Hz; $n = 7$; Figure 3C).

The reason for the reduction of sensory adaptation during activated states is 2-fold. First, during activated states, the responses to low-frequency stimuli are suppressed. This is reflected in a reduction of the response amplitude of field potential recordings, a reduction of the number of cells that respond during multiunit recordings and a reduction in the probability of discharge for most cells during single-unit recordings. Second, during activated states, the responses to high-frequency stimuli are larger than during control states (quiescent). This was expected among other reasons because thalamic neurons respond with higher efficacy to high-frequency sensory inputs during activated states (Castro-Alamancos, 2002a). Thus, during activation, the slope and amplitude of high-frequency field potential cortical responses increase, while the latency of multiunit and single-unit responses decreases. Although fewer cells respond in neocortex during activated states, these responses appear to be more synchronous (see Figure 3A). Notice the dispersed unit activity evoked at 10 Hz during quiescent states, which contrasts with the sharp population spike evoked during activated states. Such a change is compatible with an increase in spike synchrony during activated states (Munk et al., 1996). Therefore, during activated states, fewer cells appear to respond more synchronously, and show little sensory adaptation.

Sensory Suppression Occurs during Active Behavioral States

To test if similar effects occur during behavior, cortical sensory responses were monitored from chronically implanted electrodes in the neocortex of freely behaving animals during different behavioral states. A bipolar stimulating electrode was implanted subcutaneously in the whisker pad in order to allow reliable and repetitive stimulation of the whisker pad during all behavioral con-

ditions. In addition, a recording electrode was implanted in layers IV-III of the barrel cortex. During surgical implantation, the stimulating and recording electrodes were carefully aligned to produce a response that mirrored the response evoked by whisker deflections in anesthetized animals. Thus, stimulation of the whisker pad produced a field potential response in the neocortex that was virtually identical to the response observed in anesthetized animals using whisker deflections. The main significant difference was that the onset latency was shorter for the whisker pad electrical stimulation (4.4 ± 0.3 ms for electrical stimulation of the whisker pad versus 5.5 ± 0.2 ms for whisker stimulation), reflecting the fact that sensory nerve fibers are directly activated by the electrical stimulation. Otherwise, the amplitudes and shapes of both cortical responses were similar.

In a first set of experiments, animals were placed in an open field and recordings were obtained during spontaneous behavior. The behavior of the rat was also recorded using a video camera and a VCR. In these experiments, a single stimulus was applied to the whisker pad every 2 s. Figure 4 shows an example from such an experiment. Figure 4A displays samples of continuous local field potential recordings during three different behavioral states (i.e., sleep, awake immobility, and active exploration); the whisker pad-evoked response can also be observed every 2 s. Figure 4B plots the amplitude of the evoked responses. In this case, the rat was initially in slow-wave sleep (i.e., cortical field potentials displayed large-amplitude slow oscillations and the animal is laying in the cage with eyes closed) and the cortical-evoked response was largest, as the animal woke up the evoked response was suppressed becoming smallest during very active periods of exploration. Thus, during sleep, awake quiescent states, and activated states, the size of the evoked response changes dramatically, so that during sleep, the response is largest, and during active behavioral states, the response is smallest. These changes in response amplitude occur rapidly (in the order of seconds) and dynamically in relation to the behavior of the animal. Population data was obtained from a total of 12 recording sessions (1–3 hr per session) of spontaneous behavior from five animals (30 responses were measured per session for each behavioral state condition). The results show that the amplitude of the cortical response evoked by whisker pad stimulation was suppressed on average by $23\% \pm 4\%$ ($n = 12$; $p < 0.001$) during awake immobility and $65\% \pm 6\%$ ($n = 12$; $p < 0.001$) during active exploration as compared to slow-wave sleep. Thus, sensory responses evoked at low frequencies are rapidly and dynamically affected by behavioral state so that during active behavioral states sensory suppression is prevalent.

Reduction of Sensory Adaptation by Sensory Suppression

In order to test if sensory suppression that occurs during behaviorally activated states reduces sensory adaptation, we monitored the responses evoked by trains of whisker pad stimuli delivered at different frequencies in behaving animals. Figure 5A shows sample traces of

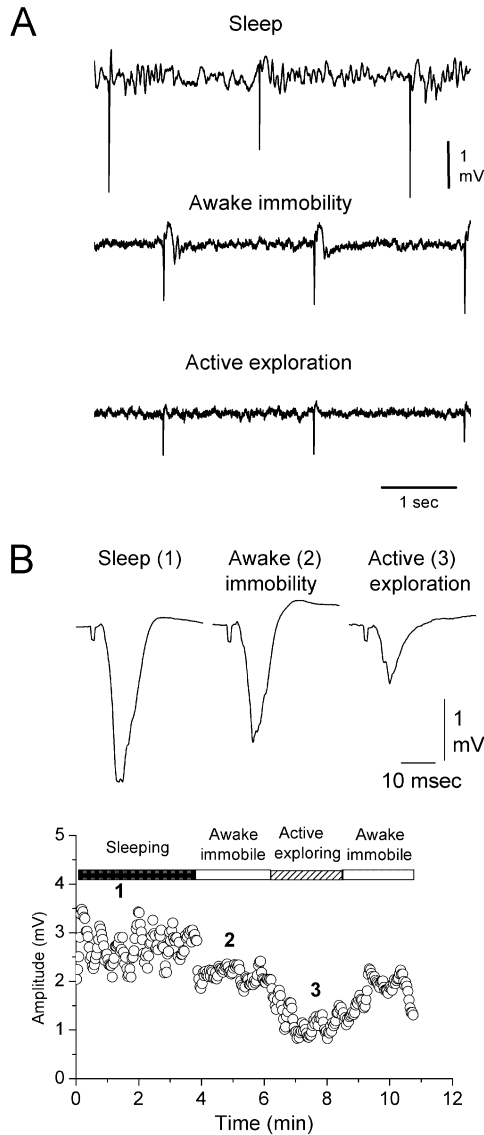


Figure 4. Sensory Suppression during Active Behavioral States
(A) Sample local field potential activity recorded in the barrel cortex of a freely behaving rat during sleep, awake immobility, and active exploration. A single whisker pad stimulus was delivered every 2 s. Each trace is 5 s.
(B) Example of an experiment during which the amplitude of the field potential response evoked in barrel cortex by whisker pad stimulation was measured during different behavioral states that occurred during spontaneous behavior. Whisker pad stimulation was delivered every 2 s. Each point is the average of three responses.

whisker pad stimulation delivered at different frequencies in freely behaving animals during quiescent and active behavioral states. During quiescent states, whisker pad-evoked responses showed strong sensory adaptation, like in urethane-anesthetized rats. However, during active behavioral states, whisker pad-evoked responses were suppressed and adaptation was reduced. These changes occurred rapidly in relation to the behavioral state. For example, Figure 5B shows an experiment during which trains of 10 Hz (20 stimuli) whisker pad stimula-

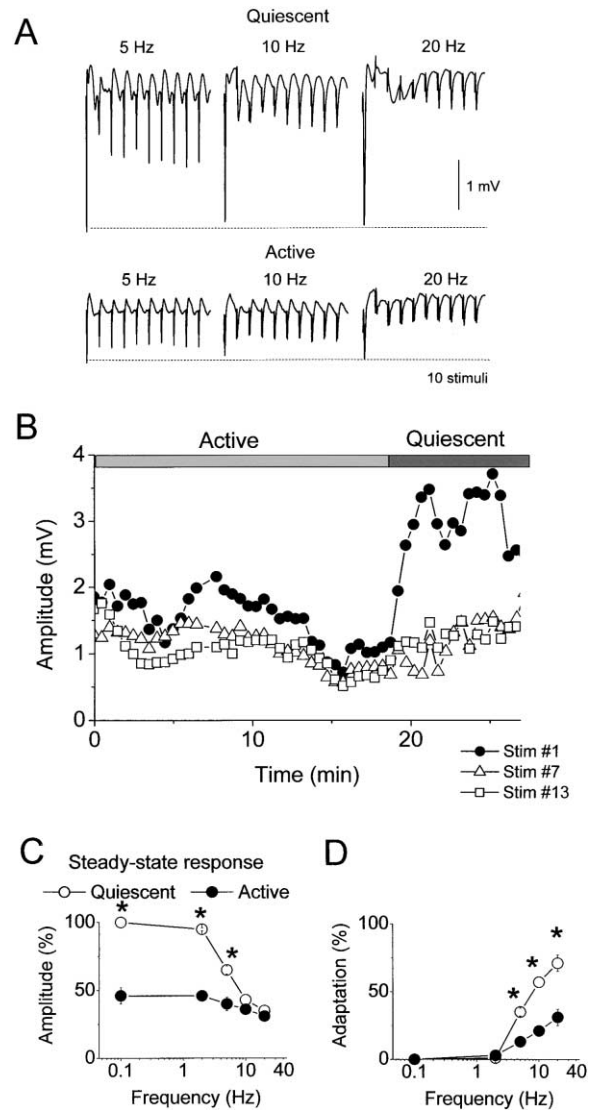


Figure 5. Reduction of Adaptation during Activated Behavioral States

(A) Sample traces of field potential responses evoked in barrel cortex by whisker pad stimulation delivered at 5, 10, and 20 Hz in freely behaving rats during awake immobility and active behavioral states.
(B) Example of an experiment during which whisker pad stimulation at 10 Hz was evoked every 15 s in a freely behaving rat. Plotted are the amplitude of the response to the 1st, 7th, and 13th stimulus in the train. The rat was initially active in the cage at around minute 18 became quiescent.
(C) Population data showing the amplitude of the field potential responses evoked by whisker pad stimulation at different frequencies during quiescent and behaviorally activated states. The steady-state responses for each frequency are displayed (i.e., response to stimulus #10 in a train) as a percent of the quiescent response at 0.1 Hz ($n = 20$ recording sessions from a total of four rats; 30 response trains for each frequency are measured per session and state). * $p < 0.001$ quiescent versus active.
(D) Population data showing the amount of adaptation during quiescent states and behaviorally activated states. Adaptation is plotted as a percentage and was calculated by comparing the first and tenth responses in a train delivered at different frequencies ($n = 20$). * $p < 0.001$ quiescent versus active.

tion were delivered every 15 s. Plotted is the amplitude of three of the evoked responses in each train (stimulus 1, 7, and 13) and each point is the average of three trains. During active behavioral states the response to the 1st stimulus in the train was strongly suppressed much more so than the responses to the 7th and 13th stimuli. Hence, sensory adaptation is small during active states. In contrast, during quiescent states (slow-wave sleep and awake immobility were included in the same group) the response to the first stimulus selectively increases and adaptation becomes quite large. Population data derived from 20 recording sessions ($n = 4$ rats) shows that during quiescent states, sensory adaptation was quite strong for frequencies above 2 Hz, similar to what is observed in urethane-anesthetized animals. However, during active exploratory states, sensory adaptation was strongly reduced, so that there was significantly less effect of frequency on cortical responses during those states. Similar to the effect of brainstem reticular formation stimulation in urethane-anesthetized animals, the reduction of adaptation during behaviorally activated states resulted mostly from suppression of the response to the first stimulus (i.e., the low-frequency responses; Figure 5C). Hence, the reduction of adaptation during activated states reflects the fact that stimulus-evoked responses, even to the first stimulus, are already small. Figure 5D displays the amount of adaptation measured by comparing the first and tenth responses for each frequency train. Sensory responses above 2 Hz adapted significantly more during quiescent states than during activated states ($p < 0.001$ for 5–20 Hz; $n = 20$; Figure 5C; 40 Hz was only tested in a few trials and is not included in the analysis). Similar results were also obtained when multiunit activity was recorded from the cortical recording electrodes in freely behaving animals (see Supplemental Figure S1 at <http://www.neuron.org/cgi/content/full/41/3/455/DC1>). Therefore, during behaviorally activated states, sensory adaptation is mostly absent, and this occurs in association with a suppression of the responses to low-frequency sensory stimuli (i.e., sensory suppression).

Is Adaptation Reduced during Performance in a Behavioral Task?

The reduced sensory adaptation during behaviorally activated states could reflect a neural mechanism by which the thalamocortical system sets itself into the information processing mode. These dynamic changes may serve to switch how the thalamocortical system handles incoming sensory inputs. In order to test this hypothesis, we trained animals in a behavioral task that used the whisker pad stimulation as a conditioned stimulus (CS).

Animals were trained in an active avoidance task in which a 10 Hz whisker pad stimulus delivered for 5 s signaled the subsequent delivery of an aversive stimulus (mild foot shock). During the 5 s presentation of the CS, the animals could avoid the aversive stimulus by performing an avoidance response that consisted of moving to the adjacent compartment in the shuttle box. An avoidance response would also suspend the presentation of the CS until the next trial (presented randomly; mean intertrial interval = 30 s). Animals learn quite readily to avoid the aversive stimulus by moving to the adjacent compartment during the 5 s presentation of

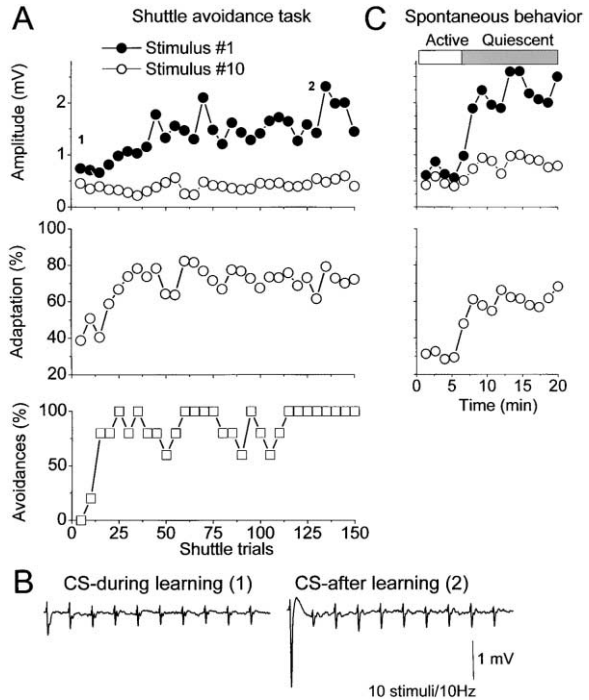


Figure 6. Adaptation Is Reduced during Learning of an Active Avoidance Task

(A) Example of an experiment in which a rat was trained in an active avoidance task using 10 Hz whisker pad stimulation as a CS. Upper panel plots the amplitude of the whisker pad-evoked response to the first and tenth stimulus of the CS train in blocks of five trials. Middle panel plots the percent adaptation between the first and tenth stimulus of the CS train in blocks of five trials. Lower panel plots the percent of trials that the animal responded to the CS with an avoidance response in blocks of five trials.

(B) Sample traces of the CS-evoked field potential responses in neocortex. The CS consisted of 10 Hz whisker pad stimulation. Displayed are the first ten stimuli of the CS train during learning (initial 50 trials) and after learning.

(C) Example of a recording session from the same animal shown in (A) that was conducted the day before the avoidance training. The animal was allowed to behave freely in this session. During the initial 5 min, the animal was quite active exploring the environment but thereafter became quite quiescent. The measurements plotted are the same that are displayed in (A) for the corresponding plots.

the CS (Figure 6A, lower panel). The mean response latency for a trained animal that has performed more than 50 trials is 2.4 s (the latency range is 1.9–3.5 s). During the execution of the task, the amplitude of the field potential response evoked in the barrel cortex during the presentation of the CS was measured. The analysis was confined to the first ten responses in the 10 Hz train used as a CS. Figure 6 shows data corresponding to the first 200 trials in the active avoidance task from a representative animal. During the initial trials (i.e., 50 first trials) when the animals are learning the task, the response to the first whisker pad stimulus in the CS train is small (i.e., sensory suppression is robust) and sensory adaptation (measured by comparing the first and tenth responses in the CS train) is mostly absent (Figures 6A and 6B). However, as animals learn the task and their performance improves to 100% avoidances, the response to the first stimulus in the CS increases (i.e., sensory suppression is reduced) and sensory adaptation enhances.

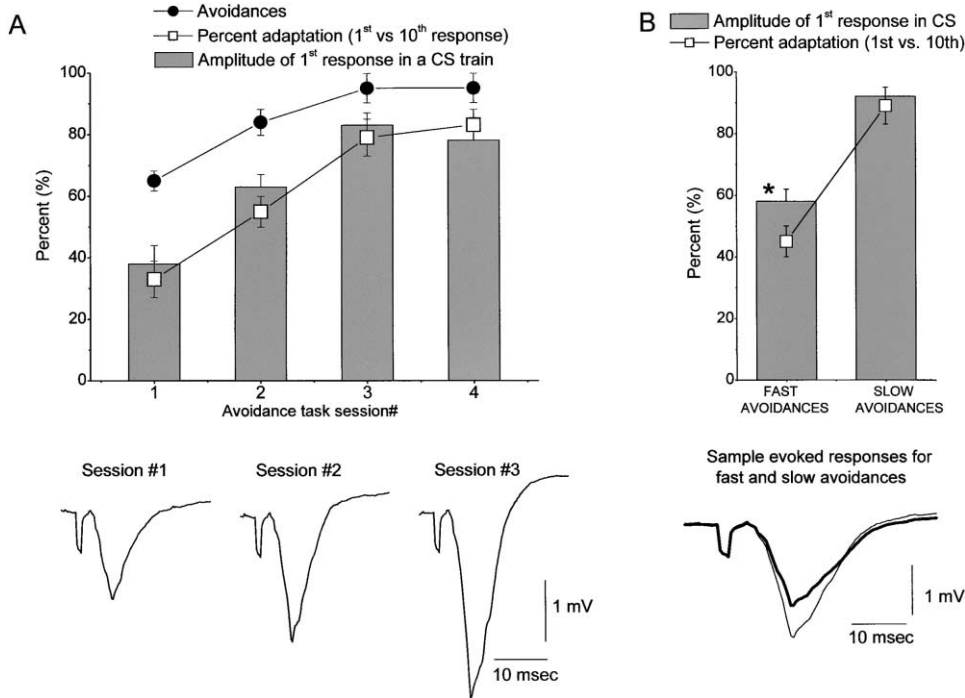


Figure 7. Adaptation is Reduced during Alertness

(A) Population data of the percent avoidances (closed circles), percent adaptation (open squares), and the amplitude of the response to the first whisker pad stimulus plotted as a percent of the quiescent response during spontaneous behavior (bars) for blocks of 50 trials from five rats. For each measure, session 1 was significantly smaller than session 4 ($p < 0.001$). Shown are sample traces of the response to the first whisker pad stimulus in the CS train for the different sessions.

(B) Comparison of response amplitudes and percent adaptation to the first stimulus in the CS train for trials in which the animal avoided rapidly (< 2.5 s latency) or slowly (> 2.5 s latency) in the task after learning had occurred (> 50 trials). A fast avoidance indicates that the animal was more alert. The responses to the first stimulus in a CS train are displayed as a percent of the responses during quiescent states recorded in previous spontaneous behavior sessions. Percent adaptation is calculated by comparing the first and tenth responses in a CS train. Shown are sample traces of the first response in a CS train corresponding to slow and fast (thick trace) avoidance trials. * $p < 0.001$, fast versus slow avoidances for response amplitudes and percent adaptation.

These changes resembled those observed during spontaneous behavior in the same rats during previous recording sessions, so that during quiescent states sensory suppression is mostly absent and adaptation is present while during active states sensory suppression is prevalent and adaptation is reduced. These changes were observed in every animal tested in the active avoidance task ($n = 5$) and were found to be related to the level of alertness in the task (see Supplemental video MOVIE1.AVI at <http://www.neuron.org/cgi/content/full/41/3/455/DC1>). Thus, during learning of the task animals are quite alert and expectant to the CS. During this state, sensory suppression is prevalent and adaptation is reduced. In contrast, after learning has occurred and behavioral demands are easily met by the animals, these become noticeably less alert and expectant in the task, and like during spontaneous quiescent states, sensory adaptation is again prevalent and sensory suppression is not present. This is supported by the observation that the same pattern of activity is found in the same animals during spontaneous behavior. Figure 6C shows a recording session that occurred the day before the shuttle box avoidance task. During this session, the same animal behaved freely while the cortical response to a train of whisker pad stimulation at 10 Hz was monitored. During behaviorally activated states, the response to the first stimulus is suppressed and adaptation is re-

duced, but as the animal changes to a quiescent state, the response to the first stimulus enhances and adaptation is large.

Population data from animals trained in the shuttle avoidance task (Figure 7) revealed that the response to the first stimulus in the CS train and sensory adaptation are significantly smaller ($n = 5$ rats; $p < 0.001$) during learning of the task (initial 50 trials) than after learning has occurred (150–200 trials). In addition, for trained animals (i.e., after more than 50 trials), sensory suppression was significantly stronger, and adaptation was smaller in those trials that the animal avoided with a short latency (< 2.5 s) as compared to trials that were avoided more slowly ($n = 60$ trials per group taken from three animals; $p > 0.001$ slow versus fast). This indicates that when the animal is alert in the task, and thus responds faster to the CS, sensory suppression is strong and adaptation is reduced.

Discussion

The results described here indicate that during activated states in which animals are alert (i.e., actively exploring the environment or actively expecting stimuli), sensory-evoked responses in the neocortex are suppressed and rapid sensory adaptation is reduced. In contrast, during quiescent states such as slow-wave sleep or awake

immobility, sensory-evoked responses are strong in neocortex and adaptation is present. Thus, during the processing of sensory inputs, adaptation is mostly absent. These properties change rapidly and dynamically to meet information processing demands imposed by behavioral contingencies. Sensory suppression during arousal has been shown to be caused by the activity-dependent depression of thalamocortical synapses produced by increased thalamic firing during arousal (Castro-Alamancos and Oldford, 2002). Interestingly, rapid sensory adaptation in the neocortex has also been shown to be caused by the activity-dependent depression of thalamocortical synapses (Chung et al., 2002). It is thus reasonable to find that both processes reduce each other since they share a common mechanism. Indeed, during the behavioral states in which sensory suppression is present, rapid sensory adaptation is mostly absent, while when sensory suppression is absent sensory adaptation is robust.

Sensory responses have been shown to be affected by a variety of behaviors at different levels of processing including sensory brainstem, sensory thalamus, and sensory cortex (e.g., [Chapin and Woodward, 1981; Fanselow and Nicolelis, 1999; Nelson, 1984]), and additional changes are likely to occur at even higher levels of processing (Kleinfeld et al., 2002). Defining the properties of these neural networks during information processing states is essential to understand how the brain actually processes sensory information. Interestingly, both in the visual cortex of cats and in the barrel cortex of rodents, receptive fields of cortical neurons are focused during activated states or light anesthesia as compared to nonactivated states or deeper anesthesia (Castro-Alamancos, 2002c; Simons and Carvell, 1989; Worgotter et al., 1998). Such changes may be required to set the thalamocortical system in the appropriate mode for information processing. The resulting enhanced selectivity may be advantageous for sensory processing, such as for example two-point discrimination in the somatosensory system. Sensory adaptation caused by repetitive sensory stimulation has also been proposed as a way to focus sensory representations in neocortex (Kohn and Whitsel, 2002; Moore et al., 1999; Sheth et al., 1998). Thus, it is logical that during alert and expectant states, typical of active information processing and learning, sensory suppression is prevalent and adaptation is mostly absent. In contrast, the functional role of the large unadapted (nonsuppressed) responses that occur at low frequencies during quiescent states is not obvious. They have been proposed to serve as a mechanism of heightened sensitivity for detecting transient stimuli (Chung et al., 2002; Fanselow and Nicolelis, 1999; Moore et al., 1999; Sherman, 2001). Thus, these large evoked responses could serve to alert quiescent animals of the presence of a stimulus. Although this topic is beyond the aim of the present study, the results presented here suggest that this hypothesis is plausible. For instance, after learning had occurred, the animals became less alert in the task and sensory suppression to the CS was absent (i.e., evoked responses to the first stimulus in the CS train were large). Seemingly the animals may be using these unadapted responses as a wake-up call of the presence of the CS. It is also noteworthy that the effects observed during learning of the

behavioral task in the present study cannot be related to fear produced by the aversively motivated task (LeDoux, 2000). This is supported by the fact that the changes observed during learning of the task occur also during normal active exploration where fear is presumably not a factor. Thus, the results do not suggest an involvement of fear in the effects described.

The present study indicates that when a stimulus reaches the neocortex during an alert state it encounters a depressed thalamocortical synapse, and probably also enhanced inhibition, both leading to sensory suppression and the reduction of sensory adaptation. Although, fewer cells in neocortex respond to the sensory stimulus during activated states, the results are also consistent with the idea that the fewer responding cells are better synchronized. These effects may well serve to focus sensory inputs to their appropriate cortical representations, as a means of enhancing selectivity while also allowing for enhanced synchronization between responding neurons, which seems to be a hallmark of attention (Fries et al., 2001; Steinmetz et al., 2000) and of activation (Munk et al., 1996). These two effects, enhanced selectivity and synchronization, may serve to produce salient responses in higher order cortical areas leading to a behavioral outcome. In conclusion, during alertness and attentive states, rapid sensory adaptation is mostly absent, which may enhance selectivity by focusing sensory inputs. This occurs dynamically to meet information processing demands dictated by behavioral contingencies. Thus, sensory responses at even the earliest stage of cortical processing are strongly regulated by behavioral state and attention.

Experimental Procedures

Acute Procedures

Adult Sprague-Dawley rats (300 g) were anesthetized with urethane (1.5 g/kg intraperitoneally) and placed in a stereotaxic frame. All skin incisions and frame contacts with the skin were injected with lidocaine (2%). A unilateral craniotomy extended over a large area of the parietal cortex. Small incisions were made in the dura as necessary and the cortical surface was covered with ACSF containing 126 mM NaCl, 3 mM KCl, 1.25 mM NaH₂PO₄, 26 mM NaHCO₃, MgSO₄·7H₂O (1.3), 10 mM dextrose, CaCl₂·2H₂O (2.5). Body temperature was automatically maintained constant with a heating pad. The level of anesthesia was monitored with field recordings and limb-withdrawal reflexes and kept constant at about stage III/3 using supplemental doses of urethane (Friedberg et al., 1999).

Electrophysiological Procedures

Extracellular field potential and multiunit recordings were performed using 0.5–1 M Ω electrodes filled with ACSF. Single-unit recordings were performed using \sim 10 M Ω electrodes filled with ACSF. These electrodes generally record only a well-discriminable single-unit of very large amplitude (greater than ten times the noise). Filter settings for field potentials were generally 1–50 or 1–3000 Hz, and for multi-unit single-unit they were 300–3000 Hz. Field potentials and unit activity were recorded in the primary somatosensory neocortex (barrel cortex). The recording electrode was placed at 800–1000 μ m from the surface. Field potential polarity is displayed as negative down. A stimulating electrode was placed in the area of the laterodorsal tegmentum to evoke arousal in anesthetized animals. Coordinates (from bregma and the dura [Paxinos and Watson, 1982]) for the stimulating electrode in the laterodorsal tegmentum (brainstem reticular formation; 100 Hz, 1 s) were posterior = 9 mm, lateral = 0.7 mm, and depth = 5–6 mm. Electrical stimuli consisted of 200 μ s pulses of <200 μ A and were evoked using a concentric stimulating electrode. To obtain CSDs, a 16 channel linear silicon probe with 100 μ m intersite spacing (CNCT, University of Michigan) was in-

serted into the barrel cortex perpendicular to the pial surface. Field potential recordings were obtained simultaneously from the 16 sites on the probe, and CSD was derived as previously described (Castro-Alamancos and Oldford, 2002). Each CSD is the average of ten evoked responses.

Sensory Stimulation

The sensory stimulation in anesthetized animals consisted of deflecting large caudal whiskers (one to four). The selected whiskers were inserted into a glass micropipette (1 mm diameter) that was glued to the membrane of a miniature speaker. Application of a 1 ms square current pulse to the speaker deflected the micropipette and the whiskers inside $\sim 400 \mu\text{m}$. Whisker stimulation was applied between 0.5 and 10 s after the RF stimulation. Sensory responses were measured during a 10 ms time window starting 6 ms after the whisker stimulus. For field potential responses, the maximum amplitude of the negative field potential was measured during the time window. For unit responses, the number of counts during the time window was measured. During multiunit recordings, a threshold detector was used to detect spikes at twice the noise level. Sensory responses were measured similarly during chronic procedures.

Chronic Procedures

Adult Spague-Dawley rats (300 g) were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally) and placed in a stereotaxic frame. All skin incisions and frame contacts with the skin were injected with lidocaine (2%). A recording electrode was placed in the barrel cortex. An insulated stainless-steel bipolar electrode was placed in the whisker pad subcutaneously to stimulate the whisker pad. The separation between both poles was 0.5–1 mm. The wires were normally placed around whiskers C2–C4. All electrodes and connectors were held in place using miniscrews and dental cement. During recovery from surgery, the animals received buprenorphine (Sc. 0.02 mg/kg). Animals were allowed 5–7 days before testing. Electrophysiological recordings were performed as in anesthetized animals, but JFET-operational amplifiers were attached to the recording electrodes at the animal's head connector. Filter settings were as for the acute procedures (see above). During the recording sessions, the cortical field potential activity was recorded in synchrony with video tape recording of the behavior. This allowed differentiating between active and quiescent behavioral states. Active states consisted of active exploration. Quiescent states consisted of awake immobility and slow-wave sleep. During active exploration, animals are actively engaged in exploring the cage (e.g., sniffing, whisking), although not necessarily moving around the cage. The animal can be observed either actively engaging the environment or expecting a stimulus. During awake immobility, the animal is not moving, has its eyes open, and has not engaged in active exploration for some time. During slow-wave sleep, the animal is lying in the cage with eyes closed and field potential activity displays large amplitude low-frequency activity. Active exploration and awake immobility are easily definable by watching the animal's behavior. Slow-wave sleep requires in addition confirmation that the pattern of field potential activity is consistent with that state.

Whisker Pad Stimulation

Since it is difficult to deliver controlled whisker deflections reliably to freely behaving rodents, we used electrical stimulation of the whisker pad to produce reliable stimuli. A low-intensity (0.2–0.8 mA) 1 ms current pulse is delivered through two wires that are implanted under the skin in the whisker pad. The stimulus is set at an intensity that produces a reproducible and consistent cortical response but no muscle twitches. The stimulation can be delivered at even high-frequency rates (20–40 Hz) producing no observable behavioral interferences. In fact, animals sleep during repeated presentations of trains of stimuli at high frequencies (e.g., 20 Hz trains of 50 stimuli every 30 s) or low frequencies (e.g., single stimuli every 2 s). Although the whisker pad stimulus is completely neutral, it can be used as a very effective conditioned stimulus in a conditioning task (see below active avoidance task). For population analysis during spontaneous behavior, peak amplitudes of whisker pad-evoked responses ($n = 30$) classified as active or quiescent by monitoring the video recordings were measured per animal.

Active Avoidance Task

Animals were placed in a standard rat shuttle box (Med Associates) that consists of two compartments separated by a 3 cm partition

from the grid floor that the animals have to transverse to shuttle between compartments. A trial in the task consists of a 5 s avoidance interval followed by a 5 s escape interval followed by a random (average 30 s) intertrial interval. During the avoidance interval, a conditioned stimulus (CS) consisting of a 10 Hz whisker pad stimulus train is presented for the duration of the interval or until the animal produces an avoidance response by moving to the adjacent compartment, whichever occurs first. If the animal produces an avoidance response the escape interval is not presented. However, if the animal does not avoid, then during the escape interval, a mild scrambled electric foot shock (0.1 mA) is delivered through the grid floor of the shuttle box, which motivates the animal to move readily to the adjacent compartment. During the intertrial interval, the animal awaits the presentation of the next CS. The task is computer controlled using MedPC software (Med Associates) and is also video taped in synchrony with the electrophysiological recording. In the study, data are expressed as mean \pm SD. Comparisons between groups were performed using *t* tests.

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