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Acetylcholine-dependent potentiation of temporal frequency representation in the barrel cortex does not depend on response magnitude during conditioning

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Abstract

The response properties of neurons of the postero-medial barrel sub-field of the somatosensory cortex (the cortical structure receiving information from the mystacial vibrissae can be modified as a consequence of peripheral manipulations of the afferent activity. This plasticity depends on the integrity of the cortical cholinergic innervation, which originates at the nucleus basalis magnocellularis (NBM). The activity of the NBM is related to the behavioral state of the animal and the putative cholinergic neurons are activated by specific events, such as reward-related signals, during behavioral learning. Experimental studies on acetylcholine (ACh)-dependent cortical plasticity have shown that ACh is needed for both the induction and the expression of plastic modifications induced by sensory–cholinergic pairings. Here we review and discuss ACh-dependent plasticity and activity-dependent plasticity and ask whether these two mechanisms are linked. To address this question, we analyzed our data and tested whether changes mediated by ACh were activity-dependent. We show that ACh-dependent potentiation of response in the barrel cortex of rats observed *after* sensory–cholinergic pairing was not correlated to the changes in activity induced *during* pairing. Since these results suggest that the effect of ACh during pairing is not exerted through a direct control of the post-synaptic activity, we propose that ACh might induce its effect either pre- or post-synaptically through activation of second messenger cascades.
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1. The barrel field of rodents is plastic

During active exploration of their environment, rats move their vibrissae on both sides of the face in coordinated waves mainly at frequencies between 4 and 12 Hz [21,41]. The cortical structure receiving the sensory information from the facial vibrissae is the postero-medial barrel sub-field (PMBSF) of the primary somatosensory cortex. The sensory whiskers from the mystacial pad are mapped onto layer IV of the PMBSF as discrete units named "barrels". The detailed description of the organization of the barrel cortex into discrete architectonic modules [104] has triggered a large number of functional studies in the last 30 years, taking advantage of its unique punctuate characteristic. In particular, the vibrissal system of the rodent has become one of the dominant models for investigating the mechanisms of sensory information processing (reviewed in [5,62,77,79,81,85]), as well as the mechanisms of sensory plasticity (reviewed in [28,34,63,64]) within the associated cortical column.

Previous studies have shown that temporal characteristics of tactile responses of neurons in the barrel subfield, as well as its anatomical structure are not fixed and can be significantly modified in an experience-dependent manner following behavioral training (see review in [63]), and modified sensory experiences (e.g. two-whisker pairing, [26]). In the protocol developed by Diamond et al. sensory experience was manipulated by a pairing procedure where all whiskers but two adjacent ones were trimmed off. During a period preceding the

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electrophysiological recording, the animal explored the environment with two vibrissae. The analysis of receptive fields after this restrained sensory experience showed a substantial reorganization of the cortical integration of peripheral information, such that responses to the adjacent paired whisker as well as responses to the principal whisker were significantly enhanced in supra- and infra-granular layers. Long-term potentiation and depression of intercolumnar connections (avoiding the thalamo-recipient layer IV) could directly contribute to the observed functional changes in neuronal responses to adjacent vibrissae [26,84]. This indicates that this functional plasticity is based on modifications of local circuits linking neighboring cortical columns.

2. The functional plasticity in the barrel field depends on ACh

The study of the conditions required for the induction of neuronal plasticity in the adult primary sensory cortices has led to the implication of neuromodulators ([69], review in [90]). ACh released in the cortex from fibers originating in the NBM [71] is a major candidate [27,76,87,95]. Indeed, cortical map reorganization and neuronal receptive field changes in sensory cortices have been shown to depend on the integrity of the cholinergic system arising from the NBM [9,10,56, 57,67,88].

For example, an excitotoxic lesion of the NBM by the local injection of NMDA blocks the reorganization of the primary somato-sensory cortex of the cat following the amputation of a digit and the stimulation of an adjacent digit. The surface activated by the stimulated finger revealed by the 2-DG method is reduced in lesioned animals whereas it is increased in normal animals ([57], see also [55] for an ibotenic acid-induced NBM lesion in the rat). Along the same line, the plasticity of responses to the adjacent paired whisker after the two-whisker pairing protocol described above [25] is blocked by a lesion of the NBM by the specific compound 192 IgG-saporine [9,88]. However, when the lesioned animals are trained in a task involving the use of the paired whiskers, there is an apparent restoration of plasticity [89], indicating that non-cholinergic mechanisms can compensate the lesion of the NBM.

Thus, reduced levels of ACh in the cortex do not provide an adequate neurochemical environment for the induction of functional plasticity [27,95]. It can be suggested thus that a certain local concentration of ACh has to be reached for inducing plasticity. If this were the case, pairing specific sensory stimuli with increased levels of ACh should induce changes in cortical response properties.

3. Sensory–cholinergic pairings induce functional plasticity

Sensory–cholinergic pairings indeed facilitate the neuronal responses to the paired stimulus [7,16,29,32,65, 72–74,86,93,98,101], in a way similar to the shifting of neuronal representations towards a behaviorally relevant stimuli [102].

In the awake rat, a pairing between NBM stimulation and a sound induces a facilitation of the response to the paired stimulus after only 20 associations [48]. A similar result is obtained in the anesthetized rat when the NBM stimulation is strong enough to desynchronize the EEG [30]. The increased response to the paired stimulus is concomitant with a reduction of response to non-paired stimuli including the initially preferred stimulus [7]. Similar results have been obtained using more intense pairing schedules (300–500 associations per day during 4 weeks) between the auditory stimulus and the stimulation of the NBM [58–60]. Very recently, Kilgard and colleagues have reported a facilitation of response to a fixed sequence of three sounds previously paired to the stimulation of the NBM [61]. The results of Merzenich's laboratory suggest that the changes in neuronal selectivity observed after sensory–cholinergic pairings are sufficiently extensive to affect the whole primary auditory cortex. The determination of the cortical tonotopic representational map shows indeed an important reorganization of the cortical network. The cortical surface dedicated to the paired frequency doubles in size while no increase in cortical representation was found in ACh-depleted animals by lesioning NBM with 192 IgG-saporine [59]. In conclusion, neuronal responses can be modified by sensory–cholinergic pairings. The precise change of the receptive fields depends on the spatio-temporal characteristics of the paired stimulus [60].

Many of the facilitation effects described above have been blocked by an application of the muscarinic receptor antagonist, atropine, during the induction phase of plasticity, i.e. during pairing [30,48,74].

4. Dependence of the expression of response potentiation on ACh

Delacour et al. [23] observed that the facilitation of response induced by the contiguous stimulation of two vibrissae or groups of vibrissae in the awake rat could also be blocked by atropine [24]. Thus, in this case, ACh receptor activation seems necessary for the expression of plasticity.

The requirements for ACh during the expression phase of plasticity have not been extensively studied. Increasing experimental and theoretical evidence is

accumulating however for a differential involvement of ACh during the acquisition and retrieval phases of memory [43,50,78,80]. For example, in the olfactory cortex, ACh exerts a differential effect on thalamocortical versus intracortical pathways [50]. Based on these observations, Hasselmo and Bower proposed that increased levels of ACh promote learning of new information by enhancing afferent inputs and enabling plasticity, whereas decreased cholinergic levels facilitate retrieval [50].

Nevertheless, behavioral studies have shown instances in which retrieval of a newly acquired memory depends on the similarity between the endogenous neurochemical state that develops during training and the one that develops during testing (endogenous state-dependent learning, discussed in [53]). A variety of substances have been shown to produce state-dependent learning: alcohol [66], amphetamines [68], benzodiazepines [54]. Particularly relevant for our results is the phenomenon of nicotine-induced state-dependent learning [42,83,100]. These findings suggest that at the cellular level, retrieval of an ACh-induced plasticity could be improved by the presence of ACh during testing. We have reported that in the barrel cortex of anesthetized rats, ACh plays a dual role in neuronal plasticity: it is essential both during the induction and the expression phases [32,93].

The study was done on single neurons of the barrel field of the rat primary somatosensory cortex [1] using a combined electrode [2] for multiple single-unit recording and microiontophoretic applications [47]. Cortical neurons were conditioned by associating a specific sensory input (vibrating a whisker at a given frequency) and local iontophoresis of ACh. We then asked whether the expression ('retrieval') of the conditioned ('learned') neuronal response is affected by increased levels of ACh during testing. This was achieved by testing the cells in two situations, one in which the response to the stimulation of the whisker at different temporal frequencies was studied in the absence of ACh, and another in which ACh was present during testing, thereby restoring the physiological conditions under which the pairing was performed.

Pairing whisker stimulation with iontophoretically applied ACh yielded selective lasting modifications of responses in one third of the recorded cells, the expression of which depended on the presence of exogenous ACh. Administration of ACh during retrieval revealed frequency-specific changes in response (mostly increments) that were not expressed when tested without ACh or when the muscarinic antagonist, atropine, was applied concomitantly. Several examples of frequency-specific increments in response, induced by the pairing and expressed exclusively under the application of ACh, are shown in Fig. 1. The principal or in few cases an adjacent whisker for each recorded cell was stimulated at 5 (first row), 8 (second to fourth rows) or 11 Hz (last two rows in Fig. 1) during the pairing period (24 trains over a period of 120 s). The potentiation of the response was maximal for the conditioned frequency (two-tailed KS, $P < 0.01$) in all the examples. This effect was not expressed if the cell's temporal-frequency tuning curve was determined in the absence of ACh (left column in Fig. 1, without ACh; two-tailed KS, $P > 0.1$ for all the examples).

Thus, the main result of this study is that the expression of ACh-induced neuronal plasticity depends critically on the similarity between pairing and testing conditions. The requisite for a similarity between the acquisition and the recall conditions is thus analogous to the well known behavioral phenomenon of "state-dependent learning", in which the retrieval of memorized information is possible only when the animal or the human subject is in the same behavioral context as during the learning phase. The possible involvement of ACh in state-dependent learning was first explicitly proposed by Zornetzer [105]: "*In normal memory formation the specific pattern of arousal present in the brain at the time of training may become an integral component of the stored information. The neural representation of this specific pattern of arousal might depend on the pattern of activity generated by brainstem acetylcholine, catecholamine and serotonin systems. It is this idiosyncratic and unique patterned brain state, present at the time of memory formation, that might need to be reproduced, or at least approximated, at the time of retrieval in order for the stored information to be elaborated.*" This hypothesis, extended later on by Izquierdo [52], was substantiated by a large number of behavioral experiments [53]. In our experimental model, the increased levels of ACh provided an internal state to the cortical network activated by a patterned sensory input (at a specific frequency). The frequency at which the whiskers were oscillated could correspond, in a natural situation, to the encoding of

[1] Experiments were performed on adult rats (300 ± 25 g) obtained from the Animal Breeding Unit of The Weizmann Institute of Science. Maintenance, manipulations, and surgery followed institutional animal welfare guidelines, which meet the NIH (USA) standards. Briefly, anesthetized rats (urethane, 1.5 g/kg) were mounted in a modified stereotaxic device [107] which allows free access to the somatosensory cortex and to vibrissae. The right PMBSF was exposed, the dura removed and neural activity recorded with a multi-electrode array of tungsten-in-glass electrodes. Whiskers were stimulated mechanically by a linear electromagnetic vibrator (pulses of 10, 5 ms rise time and 5 ms fall time, 160 μm at ∼5 mm from the snout) at different temporal frequencies.

[2] The combined electrode was composed of a tungsten core surrounded by six micropipettes. The pipettes were filled with ACh chloride (1 M, pH 4.5), Atropine sulphate (0.1 M, pH 4.5) and NaCl (3 M) for current balance.

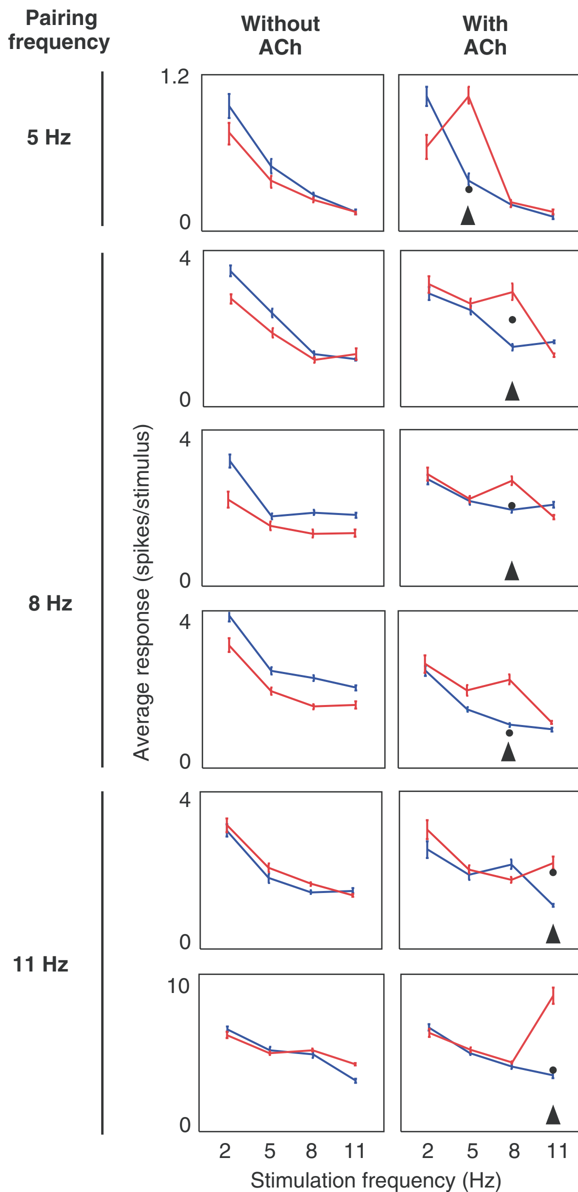

Fig. 1. Examples of temporal frequency tuning curves (average response in action potentials per stimulus as a function of temporal frequency of stimulation of a whisker), of six neurons before (in blue) and after (in red) a sensory-cholinergic pairing at three different frequencies: 5 Hz (first row), 8 Hz (rows two to four) and 11 Hz (two last rows). Arrowheads indicate the paired frequency. For the same cell, tests were done in two conditions: without application of ACh during recall (left column), and with iontophoresis of ACh (right column). Black dots correspond to the observed activity of the recorded neuron during pairing. Note that while the effects are very specific, the control of activity during pairing was not dictating the amplitude and sign of the change.

particular stimulus features or to a carrier whisking frequency on which fine temporal modulations would signal, for example, the location [6,17,97,106] or identity [46,94] of an object. Our results suggest that both acquisition and recall are controlled by the cortical release of ACh.

5. Does ACh-dependent plasticity follow rules of activity-dependent plasticity?

Most of the work on cortical plasticity cited above were interpreted within the framework of Hebb's rule [51]. Hebbian synapses were originally proposed as a way of reinforcing functional coupling between coactive cells in a cellular assembly. This neurophysiological postulate predicts that a period of maintained temporal correlation between pre- and post-synaptic activity will lead to an increase in the efficacy of excitatory synaptic transmission. [3] The problem of the divergence of synaptic weights caused by a straightforward application of Hebb's principle can be solved by using various rules of normalization which require, in addition to Hebb's rule, depression of the gain of other competing synapses [96]. Thus, most algorithms currently used to model synaptic plasticity in the developing or adult cortex include both synaptic potentiation and depression rules. They may be summarized by the same general equation where the change of synaptic efficacy as a function of time equals the product of a pre- and a post-synaptic terms (review in [40]). The "covariance hypothesis" [15,91] replaces the absolute levels of pre- and post-synaptic activity by the difference of instantaneous pre- and post-synaptic activities from their respective average values over a certain time window. The covariance rule enables stability at the network level, but not at the single synapse level. Two related rules enable also stability at the level of the single synapse by conditioning modifications on deviations from an activity-dependent set point. The first (BCM rule, [15] is based on a covariance rule, where modifications at a given synapse depend on a deviation from a set-point or threshold, which is determined be the level of post-synaptic activity. The second rule [1,2,36] postulates that a change in synaptic efficacy depends on deviations from a set point determined by the average covariance, computed over some short-term history window.

The temporal contiguity requirement of Hebbian potentiation in cortex was first estimated in the 20–100 ms range, both in vivo [4,8,103], and in vitro [38,49]. Recent work suggests an even tighter temporal contingency rule (10–20 ms range) and a temporal order between the test PSP and the back propagating spike with potentiation occurring when the pre-synaptic signal arrives before the post-synaptic action potential and depression occurring when the post-synaptic cell fires before the pre-synaptic volley [14,33,70], review in [13], see also [12] for an anti-Hebbian example of STDP).

[3] A symmetric version of Hebb's postulate was later proposed for the case of inhibitory synapses, where functional coupling can be increased by reducing the strength of inhibitory synapses activated at the same time as the post-synaptic cell [96].

In the case of cortical plasticity, striking uniformity can be found in the application of Hebbian-like principles to visual (review in [11]), auditory (review in [31]) and somatosensory (review in [18]) networks. Similar covariance rules hold in the awake animal, whether supervision is imposed externally by the experimenter [19], or mediated via self-generated attention related modulatory signals as shown in auditory [1] and somatosensory [99] cortex. In particular, Ahissar and collaborators applied cross-correlation techniques for studying the plasticity of "functional connectivity" between pairs of neurons in the auditory cortex in awake monkeys performing a sensory discrimination. The correlation of activity between two neurons was artificially controlled by activating the target cell of the pair (the post-synaptic cell), by the presentation of its preferred auditory stimulus, every time (and immediately after) the other cell fired spontaneously. Under these Hebbian conditions, reversible changes in functional coupling could be induced only when the animal was attentive to the tone used to control the activity of the post-synaptic cell. These changes lasted for a few minutes and followed the covariance hypothesis predictions but with the deviation already presented above, namely, modifications depended on *changes* of covariance and not on the absolute level of covariance. Potentiation of the functional link was induced when the covariance was increased during the pairing protocol; conversely, depression was observed when the covariance was reduced during the Hebbian association period (periods of reduced coupling were observed when the auditory stimulus inhibited the ongoing activity of the cell, instead of inducing a response). Thus, these experiments indicate that this Hebb-like requirement is necessary, but not sufficient, for cortical plasticity in the adult cortex to occur: internal signals indicating the behavioral relevance, and which probably implicate noradrenergic and cholinergic neuromodulation [3] are also required.

Thus, within the framework of Hebbian plasticity, induction of synaptic plasticity requires an increase in covariance of pre- and post-synaptic activities. In our experiments on ACh-dependent plasticity, the pre- and post-synaptic activities during the conditioning are controlled by the sensory stimulus, but they could be modulated as well by ACh. Our protocol did not allow us to test Hebbian rules directly because we monitored the activity of the post-synaptic cell alone. Yet, the assumption that plastic modifications depend on post-synaptic activity, made by most activity-dependent models [20], could be tested in our paradigm. Thus, we examined the dependency between the modifications expressed after pairing by each cell and the changes of activity during the induction phase, i.e. during pairing.

Fig. 2 shows, for the stimulation at the paired frequency, the relationship between the neuronal activity

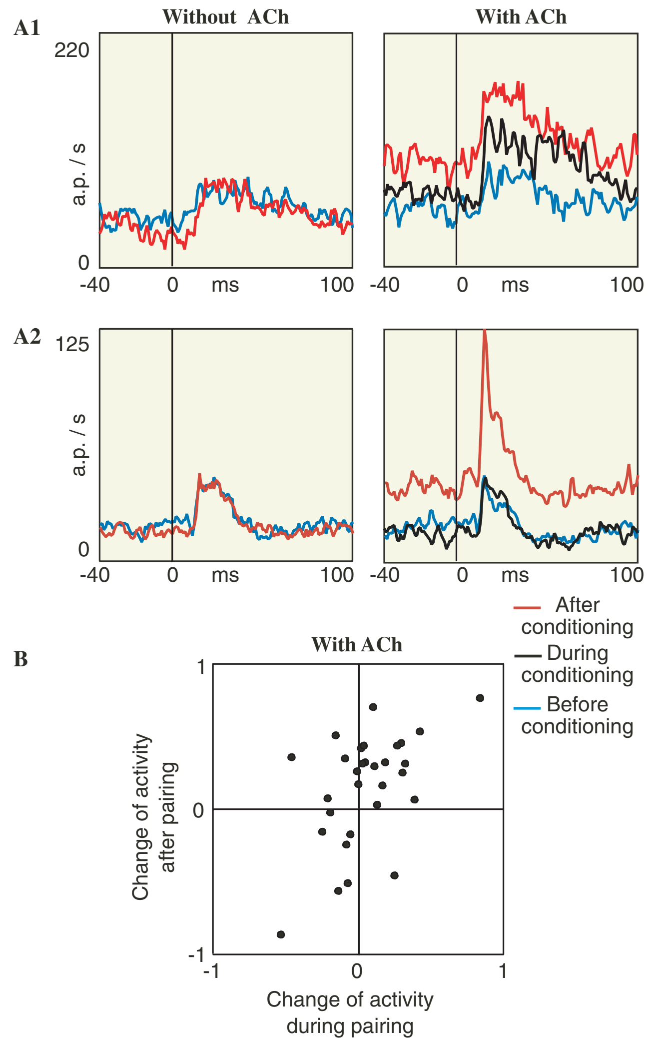

Fig. 2. Correlation between changes in response observed during and after pairing. (A) PSTHs of response for two cells (A1 and A2) before (blue), during (black) and after (red) pairing, without (at the left) and with ACh (at the right) application. Stimulus is applied at 0 ms. Note that whereas a potentiation of the response is observed during ACh application in A1, no change of activity was imposed during pairing in cell A2. (B) Population analysis showing for each cell with a significant change in response to the paired frequency (see [93] for calculation of significant plasticity), the change in response during and after pairing while tested with ACh application. The correlation coefficient calculated on these data points is not statistically significant ($r^2 = 0.12$, $p = 0.1$).

during and after pairing. Fig. 2(A1) presents the PSTHs of response of a neuron during the deflection of the principal vibrissa at 8 Hz, before (in blue), during (in black) and after (in red) pairing in the two test conditions, namely without and with ACh. In this particular case, the potentiation of response observed after pairing follows the same sign than that imposed during pairing. Conversely, in the case presented in Fig. 2(A2), no change in response is observed during pairing whereas a significant potentiation of response is expressed afterwards. Thus, we have not observed a systematic

correlation between the imposed activity and the sign and amplitude of the change in response expressed after pairing under ACh (examples of a lack of systematic changes during pairing are also presented in Fig. 1 where the level of activity during pairing is given for each case). Notice that the increase in overall activity during testing with ACh in the two examples of Fig. 2 does not correspond to an increase in general excitability of the cells for two reasons: First, the activity preceding the stimulus in the PSTH is not spontaneous activity. Due to the cyclic nature of the stimulation, it does correspond to the overall response of the cell to the stimulation train. Second, the increase in overall activity was observed exclusively while stimulating at the paired frequency and not at other unpaired frequencies [32,93]. This selectivity in the effect precludes the interpretation that the potentiation of response might simply result from the increase in cell's excitability.

A population analysis of neurons that show a significant change in response to the paired frequency is presented in Fig. 2(B). The change of activity after conditioning is plotted as a function of the change in activity observed during pairing for each cell; these two variables were not correlated ($r^2 = 0.12$, $p = 0.1$).

The lack of systematic correlation that we observed between imposed and retrieved activity has been reported previously by other groups. It has been described during cellular conditionings in the visual cortex [45] and in the auditory cortex during sensory–cholinergic pairings [29,75]. Whether this lack of correlation implies that Hebbian-like rules are not involved in ACh-dependent plasticity, or that changes in activity levels during pairing did not reflect covariance changes in these experiments, need to be further investigated.

The result presented here has important theoretical implications. Plasticity algorithms have focused on Hebbian mechanisms, in which the modification of a synapse depends on the simultaneous activation of its pre- and post-synaptic elements. Modulation of plasticity was modeled by a third factor, often under the assumption that neuromodulators would enable or gate plasticity [82]. Other interpretations have hypothesized that ACh would mainly act by promoting post-synaptic activity in the cortex, thereby facilitating the conditions for Hebbian covariance [27]. This scheme is not supported by a recent article that examined specifically the relation between Hebbian plasticity and cholinergic system [22]. Based on the pairing protocol initially used by Frégnac and collaborators in the visual cortex [35,37,92], Weinberger and colleagues have studied the efficacy of a cellular conditioning, associating an auditory stimulus with a juxtacellular current injection, applied after a stimulation of the NBM. They have found that cholinergic activation did not facilitate activity-dependent plasticity, and if any it had a detrimental effect. This finding is in line with the two phenomena being mediated via different mechanisms, which might compete on the same resources.

Our results indicate that after the induction of the synaptic modification, a differential expression takes place in the presence and absence of ACh. In the context of synaptic plasticity algorithms, it calls for a direct influence of ACh on the synaptic weight or on the input–output relationship of the neuron for a given input (i.e. the integrative power of the neuron, see [39]), independently of the role of ACh in enabling synaptic weight change. ACh might induce this effect either pre-synaptically or bypassing the post-synaptic activity of the cell by acting directly on second messenger cascades [44].

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