Stimulus-specific adaptation in the inferior colliculus: The role of excitatory, inhibitory and modulatory inputs

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Abstract

Patients suffering from pathologies such as schizophrenia, depression or dementia exhibit cognitive impairments, some of which can be reflected in event-related potential (ERP) measurements as the mismatch negativity (MMN). The MMN is one of the most commonly used ERPs and provides an electrophysiological index of auditory change or deviance detection. Moreover, MMN has been positioned as a potentially promising biomarker candidate for the diagnosis and prediction of the outcome of schizophrenia. Dysfunction of neural receptors has been linked to the etiopathology of schizophrenia or the induction of psychophysiological anomalies similar to those observed in schizophrenia.Stimulus-specific adaptation (SSA) is a neural mechanism that contributes to the upstream processing of auditory change detection. Auditory neurons that exhibit SSA specifically adapt their response to repetitive sounds but maintain their excitability to respond to rare ones. Thus, by studying the role of neuronal receptors on SSA, we can contribute to detangle the cellular bases of the impairments in deviance processing occurring in mental pathologies. Here, we review the current knowledge on the effect of $GABA_A$-mediated inhibition and the modulation of acetylcholine on SSA in the inferior colliculus, and we add unpublished original data obtained blocking glutamate receptors. We found that the blockade of $GABA_A$ and glutamate receptors mediates an overall increase or decrease of the neural response, respectively, while acetylcholine affects only the response to the repetitive sounds. These results demonstrate that GABAergic, glutamatergic and cholinergic receptors play different and complementary roles on shaping SSA.

Overview

Event-related potentials such as the mismatch negativity response (MMN) have been extensively used as a neurophysiological index of preattentive auditory sensory memory as it occurs in response to a sensory stimulus that violates previously established patterns of regularity (1). The MMN is measured as the difference between the auditory-evoked potential elicited by a repetitive sound compared with the potential elicited by a rare, unexpected sound (larger amplitude) in electroencephalographic studies. MMN has been positioned as a potentially promising biomarker candidate for the diagnosis of pathologies such as schizophrenia (2, 3) among others. Patients with schizophrenia exhibited a reduced ability to detect acoustic changes reflected in reduced MMN (4-6). Schizophrenia has been associated with alterations in neurotransmission as the one mediated by the NMDA receptor (7). Moreover, diverse studies have showed that acoustic MMN is sensitive to cholinergic modulation (8-11) or to nitrous oxide e.g. (N_2O) (12). Thus, a starting point for elucidating how alterations in neurotransmission contribute to deficits in deviance detection is to employ animal models to pharmacologically isolate the role of specific modulatory substances on event-related potentials or on correlated neuronal activity. Recent studies have demonstrated that MMN-like responses occur in animal models like the rat (3, 13). Likewise, neurons that exhibit a specific decrement in their response to repetitive but not to rare sounds have been characterized in animals. This specialized neural response is referred as 'stimulus-specific adaptation' (SSA). SSA is a particular type of neuronal adaptation (14) that occurs in the non-lemniscal subdivisions of the inferior colliculus (IC) (15), auditory thalamus (16) and primary auditory cortex (17). SSA is thought to contribute to the upstream processing of deviant and repetitive signals reflected in event-related potentials (18, 19). Cellular mechanisms underlying SSA are likely to act at the sites of

synaptic input on IC neurons and those might include synaptic depression and/or facilitation or inhibition. Moreover, several studies have demonstrated that different neuromodulators disinhibit neural circuits representing a mechanism for gating excitatory and inhibitory synaptic plasticity (revised in (20)). For example, acetylcholine transiently disrupts excitatory-inhibitory balance underlying neural receptive fields (21, 22). Thus, recent work in our laboratory has focused on the effect of blocking or activating putative excitatory, inhibitory and neuromodulatory inputs on IC neurons exhibiting SSA. In the following, we will first describe hitherto unpublished original data obtained blocking glutamate receptors and then we review our previous work on the effect of $GABA_A$ mediated inhibition (23, 24) and the modulation of acetylcholine (ACh) on SSA (25).

Excitatory, inhibitory, and cholinergic inputs to the IC

The IC is the main auditory midbrain center (26) and is characterized by the convergence of ascending and descending auditory projections. Hence, multiple excitatory, inhibitory and modulatory inputs converge onto single IC neurons (26-30) that also receive neuromodulatory inputs from multiple sources (for a review see (31)).

Excitatory inputs to the IC are made of glutamatergic projections and arise from the ventral and dorsal cochlear nuclei, lateral and medial superior olive and ventral nucleus of the lateral lemniscus (26, 32, 33) (Fig. 1). The excitatory neurotransmission in the auditory midbrain is mostly mediated through glutamatergic receptors. Ionotropic glutamate receptors mediate excitatory input at most nuclei in the ascending auditory pathway including the IC. For example, recordings in brain slices of the IC after electrical stimulation of the lateral lemniscus fibers demonstrated that there were two distinct components of the excitatory responses (34): a rapid, short latency component

that was mediated by AMPA receptors, and a component with longer latency and duration that was mediated by NMDA receptors. NMDA receptors have been associated with the generation of MMN (35-39). Interestingly, Umbricht *et al.* (40) applied NMDA antagonists to human volunteers and found a reduced MMN, similar to that previously found in schizophrenia (41-44). In a recent study, Kompus *et al.* (45) found that healthy individuals with increased indicators of glutamatergic neurotransmission presented shorter latencies to MMN for changes in sound duration. But animal studies are controversial. While Farley *et al.* (46) found that SSA in auditory cortical neurons of rats was insensitive to the systemic application of NMDA antagonists, Featherstone *et al.* (47), using a probably more sensitive murine model with a heterozygous alteration of the NMDA receptor NR1 subunit gene, reported a significant reduction in the expression of NMDA receptors that caused a distinct decrement of MMN. Thus NMDA receptors may be linked to the generation, shaping and/or modulation of SSA.

Inhibitory inputs to the IC are mediated by GABA and glycine (48-51). Glycinergic inhibition arises from the ipsilateral lateral superior olive and the ventral nucleus of the lateral lemniscus (50, 52) while GABAergic inputs arise from several extrinsic and intrinsic sources (Fig. 1). Extrinsic GABAergic sources includes the lateral superior olive and the superior paraolivary nucleus (53), ventral nucleus of the lateral lemniscus ipsilaterally, and the dorsal nucleus of the lateral lemniscus bilaterally (54-57). In addition local IC GABAergic neurons (51, 58, 59) affect neural responsiveness through intrinsic or commissural projections (60, 61). The GABAergic-mediated inhibition acts on $GABA_A$ and $GABA_B$ receptors expressed across IC neurons. The pharmacological manipulation of the $GABA_A$ receptors significantly affects sound-evoked responses (62, 63), modifying different response properties including frequency tuning (62, 64-66),

response to sound intensity (67), coding of interaural time and level differences (68-70) as well as IC responsiveness to binaural motion cues (71).

Neuromodulatory influences to the IC include those mediated by noradrenergic (72, 73), serotoninergic (29, 74-76), dopaminergic (77, 78) and cholinergic projections (30). The cholinergic inputs originate in the pontomesencephalic tegmentum that includes the pedunculopontine and laterodorsal tegmental nucleus. Those cholinergic neurons are innervated by auditory cortical neurons from layer V (30, 79) (Fig. 1). Very little is known about the type and distribution of the cholinergic receptors on IC neurons and their functional impact on neural firing. Overall, both cholinergic receptors (muscarinic and nicotinic) are expressed in the IC (80, 81) and they are likely to be pre- as well as postsynaptic receptors (reviewed in (82)). Earlier studies revealed diverse effects of ACh on IC neural responses (potentiated and suppressed sound-evoked activity) suggesting ACh exerts a complex and dynamic modulation (83-85).

Experimental Approach

In vivo iontophoresis is a powerful technique that allows the pharmacological manipulation of neuronal responses at the synaptic level. Therefore, it is an excellent choice to determine the role of synaptic inputs on sensory processing, since it allows maintaining intact the whole neural circuitry. This technique consists in the minute release of different and selective compounds (agonists, antagonists, e.g.) very close (usually around 20-40 µm) to the recorded neuron to reversibly block or activate specific receptors. Recordings are performed using so-called piggy-back electrodes, which are made of a recording electrode (usually a glass or tungsten electrode) attached to a multibarrel glass micropipette (Fig. 2A). The glass barrels contain the neuroactive substances that are retained and ejected by the application of current injections (in the

range of nA) (86, 87). Then, different neuroactive compounds can be co-released to simulate the natural heather of neurotransmitters and neuromodulators that occurs in natural conditions.

To study auditory SSA, one pair of frequencies usually surrounding the characteristic frequency of each neuron (frequency of a sound capable of evoking a response at the lowest sound intensity) is chosen from its frequency response area (FRA; spectrum of frequencies and intensities that evoke a suprathreshold response, Fig. 2B). Those frequencies are presented under the 'oddball paradigm' widely used in human studies (88) and more recently in animal studies (17). The oddball paradigm consists in the presentation of one frequency at high probability of occurrence (standard tone) while the second frequency is presented rarely (deviant tone). Afterwards, the relative probabilities of the pair of frequencies are switched to validate that the neuron adapts to the repetitive stimulus and the decrease in response is due the frequency response (Fig. 2C). The amount of SSA to both frequencies is estimated by the Common-SSA index (CSI) which reflects the normalized difference in the evoked response between deviant and standard tones with values between −1 and 1. Positive CSI values indicate a stronger response to deviant tones while negative CSIs indicate a stronger response to standard tones. A CSI value of zero reflects an equal response to deviant and standard tones (Fig. 2D). By repeating this paradigm before, during and after the iontophoretic application of specific drugs we can dissect the contribution and specificity of different receptors on the neural response to deviant and to standard tones and its effect on CSI, i.e., we can determine what role, if any, they play on SSA.

Effect of glutamatergic excitation on SSA

In order to study the effect glutamate on SSA, we recorded from 37 neurons in the IC using an oddball stimulation paradigm, as described above, before, during and after the microiontophoresis application of either CPP or NBQX. These drugs are selective antagonists of the NMDA or AMPA/kainate glutamate receptors, respectively. Here we report for the first time a total of 53 applications of drugs, consisting of 28 applications of CPP and 25 applications of NBQX. In 15 cases both drugs were tested sequentially on the same neuron, so the second drug was applied after the effects of the first one had disappeared. At the beginning of each experiment we isolated a single unit, and then we played trains of stimuli in an oddball paradigm, in order to obtain the baseline response of the neuron. We continued recording the responses to this stimulation protocol during the local application and afterwards until the neuronal responses returned to their baseline levels.

Effect on spike counts

The application of both CPP and NBQX produced a significant decrement on the neuronal response, measured as spike counts. Since we measured two sound frequencies for each drug application, we took 56 measurements of the effect of CPP (Fig. 3A), and most of those (47 for standards, 43 for deviants) showed a significant decrease in the number of spikes evoked per trial (Bootstrapping, 95% confidence interval). The application of CPP caused an average decrement of ~60% on the responses to both standard and deviant stimuli (Fig. 3A). The measurements for the application of glutamate antagonists are summarized in Table 1.

The application of NBQX also resulted in a decrement of the spike counts (Fig. 3B). In this case, we obtained 50 measurements during the application of NBQX, where 40 standard cases and 33 deviant cases showed a significant decrease in the number of spikes evoked per trial. The application of NBQX caused an average decrement of ~70% on the responses to the standard stimuli (Fig. 3B). In contrast, (Fig. 3B), the application of NBQX caused an average decrement of ~54% on the responses to deviant stimuli.

As previously reported (15), the responses before the application of drugs were stronger for deviant stimuli than for standard stimuli (Fig. 3C,D). The reduction of the spike rates due to the effect of both drugs was significant (2-way ANOVA) for the standard stimuli as well as for the deviant stimuli, as shown in Figure 3C,D.

Effect on first spike latency

We found that the first spike latency (FLS) of the responses to standard stimuli was larger than in response to deviant stimuli, which is consistent with previous studies (15). The application of CPP produced a significant increment of the FSL (Bootstrapping, 95% confidence interval) in 20/56 cases in response to the standard stimuli (Fig. 4A) and 26/56 cases in response to the deviant stimuli (Fig. 4A). The effect of the FSL was larger during the application of NBQX, which caused a significant increment in 24/50 standard cases (Fig. 4B) and 30/50 deviant cases (Fig. 4B). Moreover, NBQX not only increased the latency of more neurons, but also the increment was larger. While some neurons experienced a significant increment of latency during the application of CPP, it did not cause a significant change at the population level (2-way ANOVA) in response to standard nor deviant stimuli (Fig. 4C). In contrast, the effect of NBQX (Fig. 4D) was

large enough to be significant at the population level, for both standard and deviant stimuli.

Effect on SSA index

The effect of the drugs on the common SSA index (CSI) was very variable. We recorded from units with a very large range of baseline CSI, from -0.06 up to 0.93 (Fig. 5A,B). Out of the 28 units tested with CPP, 20 showed an increment of the CSI during the application, while 8 showed a decrement. In the case of NBQX, in 13 out of 25 units the CSI increased during the application of the drug, while in 12 units it decreased. For both drugs the average effect was an overall increment of the CSI, ~0.1 in the case of CPP (Fig. 5A) and ~0.05 in the case of NBQX (Fig. 5B). Nevertheless, due to the high individual variability, the effects of the drugs on the CSI at the population level were not significant (2-way ANOVA, Fig. 5C), probably because the effects on individual neurons were averaged out. The values found for the frequency-specific SSA index (SI_f) were very similar to those obtained for the CSI (Table 1).

Effect on the time course of adaptation

We analyzed separately the temporal dynamics of adaptation to the standard and deviant stimuli across the population, during the oddball paradigm (Fig. 6). As in previous studies (24), the time course of adaptation for the standard stimuli was fitted by a double exponential function $f(t) = A_{ss} + A_r \times e^{-t/\tau(r)} + A_s \times e^{-t/\tau(s)}$. This function contains rapid and slow decay components, before reaching a steady-state.

The goodness of fit of the double exponential function to the responses to standard stimuli was good, with $r^2 > 0.65$ in all cases. As expected from the spike count results, the overall response was smaller during the application of the drugs (Fig. 6A,B), due

mainly to a smaller steady-state component (A_{ss}) (Fig. 6A,B). The application of both drugs made the fast time constant (τ_r) faster, especially in the case of NBQX. The application of the drugs made the slow time constant (τ_s) slower in the case of the CPP application, but not for NBQX.

The adaptation to the deviant stimuli was very low under the control (Fig. 6C,D; red dots) and effect (Fig. 6C,D; yellow dots) conditions, for both drugs. The time course of adaptation for deviant stimuli was best fitted to a linear function f(t) = a + bt, and in none of the cases the slope coefficient (b) was significantly different to zero. The main effect of the drugs was to reduce the constant component (a), from to roughly the half.

Effect of GABAergic-mediated inhibition on SSA

The first attempt to disentangle how the synaptic inhibitory inputs shape SSA was carried out by (24). This study manipulated the GABAergic inhibition that adapting neurons in the IC receive to address whether the adaptation to the standard tone was generated by the activation of the $GABA_A$ receptors. The blockade of the $GABA_A$ receptors using the specific antagonist (gabazine) exerted a profound effect on the magnitude and dynamics of SSA by increasing the neural firing rate and by altering the temporal response pattern. An example of the typical effect exerted by gabazine on the firing of adapting IC neurons is illustrated in Figure 7. This neuron exhibited significant SSA during the control condition, i.e. previous to the gabazine application (Fig. 7A), and responded to the deviant sound presentations but quickly adapted its response to the standard tone after a few presentations. Neurons like this one exhibit shorter response latency to the deviant than to the standard tone. The overall effect of blocking $GABA_A$ receptors is an augmentation in the response strength to both, deviant and standard stimulus (Fig. 7B). As clearly shown for this neuron, the number of spikes per trial

increased but the response strength remained larger for the deviant tone (Fig. 7C). Gabazine also decreases the response latency to deviant and standard stimuli but does not abolish the difference between them. These results demonstrate that the firing pattern and response latency of these neurons depends mainly on the probability of the stimulus even during gabazine application. Another interesting finding of the study by Pérez-González and colleagues was that the effect of gabazine was faster on the response to the standard tone than to the deviant in some neurons (34%) but the contrary did not occur in any IC neuron. This variability of the gabazine effect was reflected in the time course of the difference signal (difference in the neural PSTH) between the response to deviant and to standard tone (23). Consistent with the effect of GABA in other sensory systems (89, 90), the blockade of GABAergic-mediated inhibition elicits a generalized augmentation in the neural excitability of IC neurons by increasing their evoked response to both tones regardless of their probability of occurrence (Fig. 7C,D). This enhanced responsiveness decreases the ratio between the deviant/standard responses. This is known as iceberg-effect (89) and in the particular case of the application of gabazine, the simultaneous increment of the firing rate to both stimuli results in a drop of the CSI (Fig. 8), reflecting the decrease in the deviant to standard response ratio. Hence, synaptic inhibition acting on $GABA_A$ receptors regulates the strength of the response to deviant and standard tones but does not generate the SSA. These results point to the possibility that other neurotransmitters may be also participating in the generation or modulation of SSA in the IC.

Effect of cholinergic modulation on SSA

The control of attention engages different modulatory substances such as ACh (91, 92). In humans, cholinergic manipulation affects auditory novelty detection (9, 10, 93).

Likewise, diverse studies in animals support the notion that ACh release is necessary for the induction of auditory plasticity (94-97). Moreover, it is likely that the mechanism of attentional modulation on sensory processing operates at multiple stages, including cortical and subcortical nuclei. To understand the relation between large scale signals as the MMN and neuronal processing at different stages along the auditory pathway, a first approach was to study the influences of ACh on single-neuron SSA responses (25).

The local application of ACh and antagonists of the muscarinic and nicotinic receptors elicited a heterogeneous and baseline-dependent effect on SSA. An example of single neuron response is displayed in Figure 9. This neuron showed an intermediate SSA index (CSI = 0.73, Fig. 9A) that significantly decreased during the ACh application (CSI = 0.41, Fig. 9B). The firing pattern of the response became more robust to the deviant and standard stimuli as shown by the temporal course of the neural firing (Fig. 9C). Interestingly, the strength of the cholinergic effect was stronger on the driving response to the standard tone than to the deviant one (Fig. 9D). In general, ACh exerts a drop in the SSA index (Fig. 10) mainly due to an augmentation of the response to the standard tone, i.e, ACh decreases response adaptation. The diminished adaptation agrees with the role of ACh in exerting a neural circuit disinhibition by transiently altering the excitatory-inhibitory balance (revised in (20)). Our original study (Ayala and Malmierca, 2015) also revealed that not all IC neurons undergo cholinergic modulation. A subset of IC neurons (partially adapting) were significantly affected by ACh and a second group of neurons (extremely and not adapting) exhibited responses insensitive to ACh (Fig. 10B). Interestingly, the non-affected neurons are the ones that lack of or exhibit extreme levels of SSA. This baseline-dependent effect contrasts with the generalized drop of SSA exerted by the $GABA_A$-receptor blockade across neuron with different SSA levels (Fig. 8B). The same selective effect on partially adapting neurons

was elicited when the muscarinic and nicotinic receptors were blocked. The blockade of the muscarinic receptors elicited a stronger effect indicating these receptors are mainly mediating the cholinergic modulation on SSA. In conclusion, the study by Ayala and Malmierca (25) showed that ACh decreases the CSI of IC neurons with intermediate SSA levels by selectively decreasing the adaptation to the standard tone.

The functional significance of the cholinergic modulation on subcortical SSA can be though under the framework that indicates ACh affects the balance between feedback and feedforward neural processing (82, 92). ACh increases the efficacy of feedforward/thalamocortical input connections onto excitatory neurons in layer IV (98-102). Increased ACh levels switch sensory processing from a predominant influence of internal, corticocortical inputs to a predominant influence of external, thalamocortical inputs (92, 103). Thus, the cholinergic modulation occurring on SSA responses in IC neurons might contribute to enhance the ascending processing converging in the auditory thalamus *en route* to the auditory cortex. Finally, it is worth to mention the similarity in the baseline-dependent effects of cholinergic modulation exerted on population coding of more complex acoustic regularities. In this regard, a MMN study performed in non-smoker individuals found that nicotine enhances and diminishes change detection according to their baseline change detection processing (9). Also, nicotine has been shown to alleviate the MMN amplitude attenuation induced by NMDA blockade (104). Complementary studies at different neural stages of processing recording single-neuron and population activity under pharmacological manipulation or under behavioral tasks known to modify the animal's attentional demands will contribute to bridge the gap between cellular and large-scale effects of neuromodulators on change detection.

General discussion and final remarks

The iontophoretic manipulation of GABAergic, glutamatergic and cholinergic receptors on SSA suggests those receptors play different roles on shaping SSA in the IC. At the population level, the blockade of $GABA_A$-mediated inhibition increases the overall spike count and decreases the response latency to deviant and standard stimuli (Fig. 11A), while the blockade of glutamatergic excitation has an opposite effect (Fig. 11B). On the other hand, the activation of cholinergic receptors exerts a delicate modulation only on the response to the standard stimuli without affecting the timing of the response (Fig. 11C). Moreover, the different effect produced by Ach, excitation and inhibition is reflected on the time course of the response to the standard tone. The adaptation in the response to the standard tone fits a double exponential function which includes rapid and slow decays as well as a steady-state component in the response (24). While the magnitude and timing of all these three components are drastically affected by gabazine, only the magnitude of the sustained component is augmented by ACh application (Fig. 11D). The delicate modulation of ACh that selectively increases the evoked response to the standard sound without affecting the timing of the neural response contrasts with the gain control exerted by $GABA_A$-mediated inhibition in IC (24) and MGB neurons (105), as well as by glutamatergic excitation. From these results, we can conclude that glutamatergic excitation, ACh and $GABA_A$-mediated inhibition produce different effects on the adaptation dynamics. While GABA and glutamate may work together to preserve an exquisite excitatory/inhibitory balance to act together as a balanced gain control system, maintaining the responses within a range that optimizes the deviant to standard ratio, ACh contributes to maintain the encoding of repetitive sounds more selectively.

Taken together, these studies highlight the differential and complementary role of putative receptors on the modulation of SSA. Moreover, these experiments contribute to reveal how glutamatergic- or other neurotransmitter-related dysfunctions linked to the etiopathology of mental illness might be affecting the upstream neural processing supporting MMN-like responses observed along the auditory pathway. Likewise, our data might indicate how such a basic auditory response as the SSA will be affected by pharmacological interventions using agonist or antagonist compounds for the clinical treatment of mental disorders like schizophrenia.

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YAA, DPG and MSM wrote the manuscript. DPG performed the experiments of glutamate iontophoresis, analyzed the data and wrote the results.

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Legends

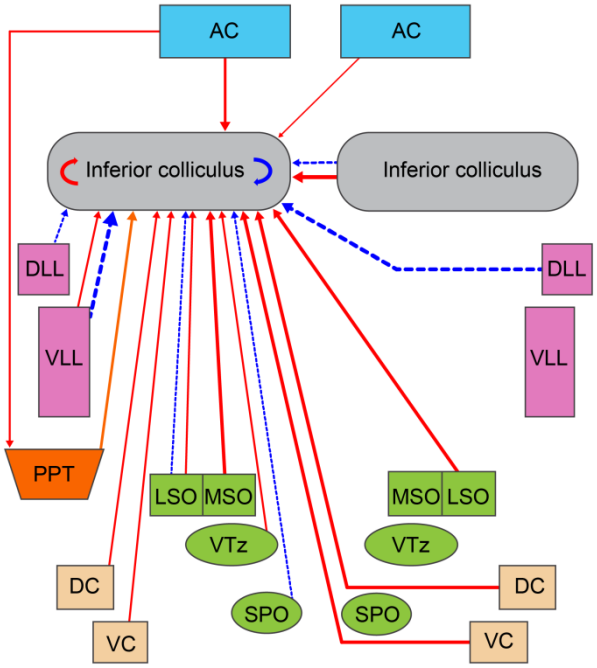

Figure 1. Schematic diagram of the excitatory (red), inhibitory (blue) and cholinergic (orange) projections to the inferior colliculus. The strength of the inhibitory and excitatory projections are depicted by the thickness of the lines. AC: auditory cortex, DLL, VLL: dorsal and ventral nucleus of the lateral lemniscus, respectively, PPT: pedunculopontine tegmental nucleus, LSO, MSO: lateral and medial superior olive, respectively, VTz, ventral nucleus of the trapezoid body, SPO: superior periolivary complex, DC, VC: dorsal and ventral subdivisions of the cochlear nucleus. Modified from (26).

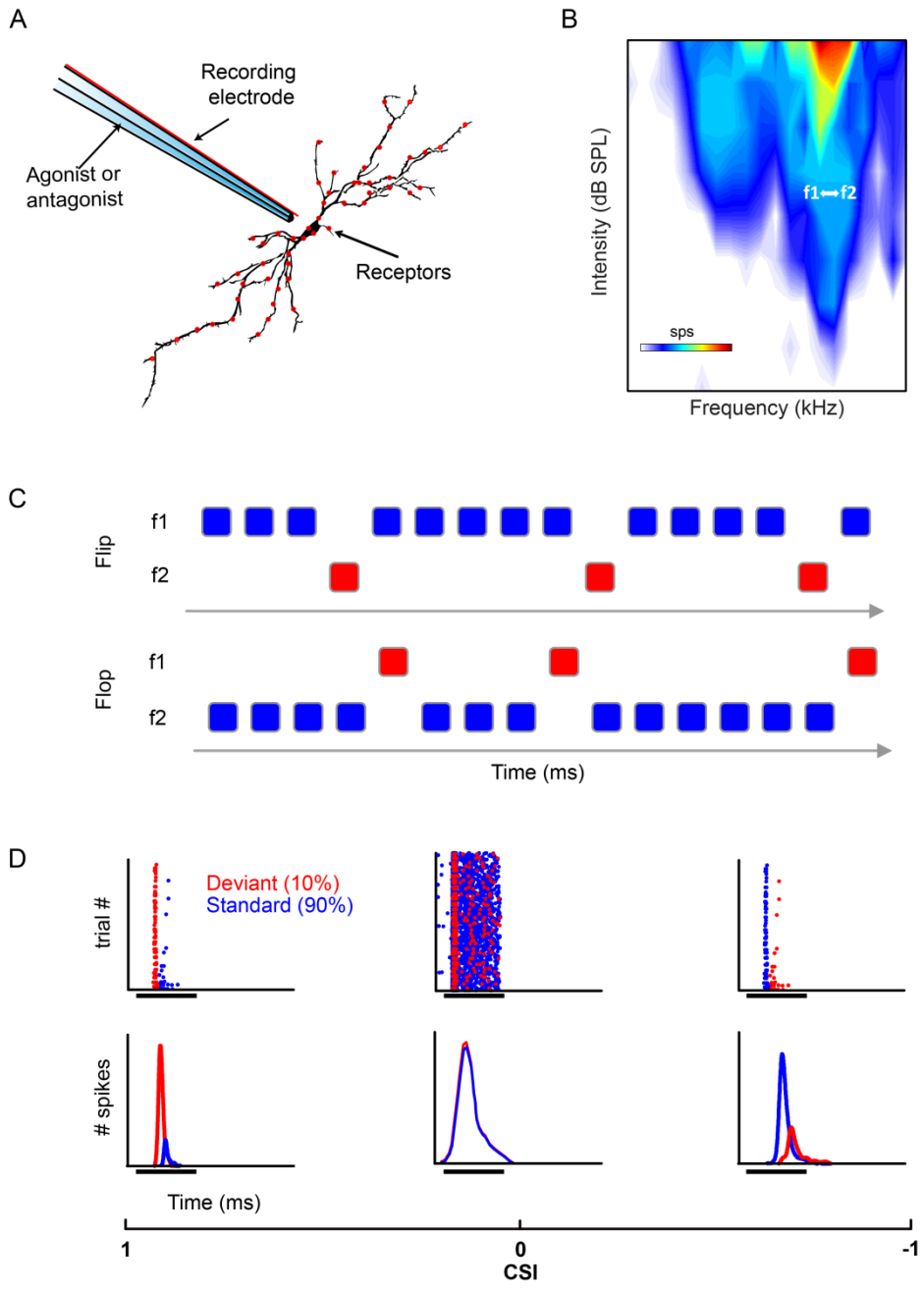

Figure2. Iontophoresis and oddball paradigm. A. A 'piggy-back' electrode is used to record single-neuron activity and to release neuroactive substance in the vicinity of the recorded neuron in order to block or activate specific receptors. The piggy-back electrode consists in a tungsten recording electrode attached to a glass multibarrel pipette which contains the neuroactive substances. B. Representation of a frequency response area, i.e., frequencies and intensities that evoke a suprathreshold respond, of an

IC neuron. Two frequencies (f1, f2) at the same intensity and evoking similar firing response are selected by the experimenter to be presented under the oddball paradigm. C. The oddball paradigm consists in the presentation of one frequency (f1) as a common or repetitive sound (blue: standard, high probability of occurrence) while the second frequency (f2) is presented as a rare sound (red: deviant, high probability of occurrence). This first sequence is often referred as flip, while a second flop sequence consists in the inversion of the relative probabilities of f1 and f2. D. Examples of dot rasters and peri-stimulus time histograms of the response to the deviant (red) or standard (blue) tone of IC neurons with different levels of SSA. The amount of SSA is quantified by the Common SSA index (CSI) whose positive values indicate adaptation in the response to the standard tone, zero value represents an equal and not adapted response to both tones, and negative index values indicate an adapted and smaller response to the deviant sound.

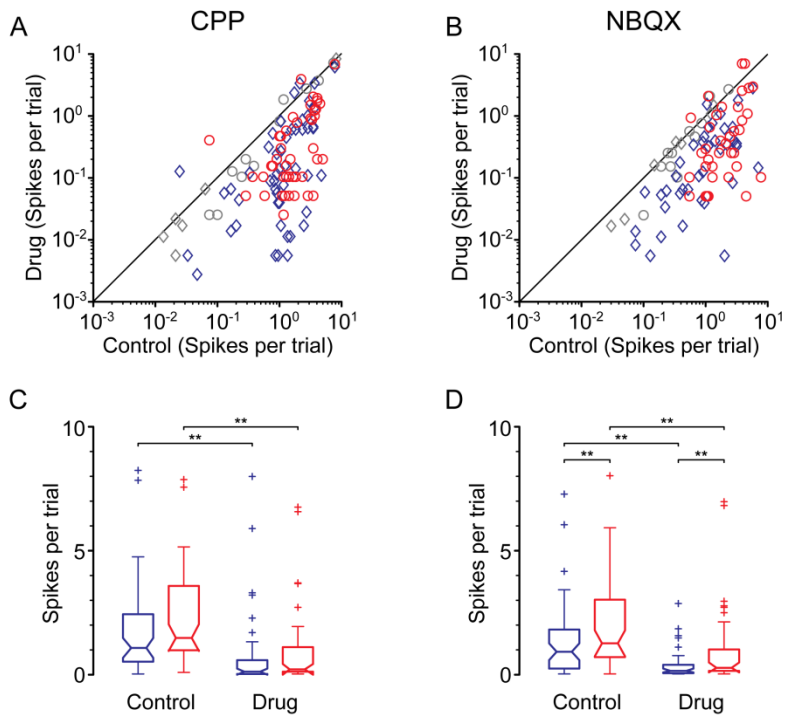

Figure 3: Effect of glutamate receptor antagonists on the responses of neurons during an oddball paradigm. The majority of neurons showed a decreased response (expressed as spikes per trial) during the application of either CPP (A) or NBQX (B), independently of whether the tone was presented as a standard (diamonds) or a deviant (circles). The colored markers indicate a significant change in the response relative to the control condition. At the population level, both drugs (C, CPP; D, NBQX) caused a significant decrement on the neuronal responses, for the standard (blue) and the deviant (red) stimuli alike.

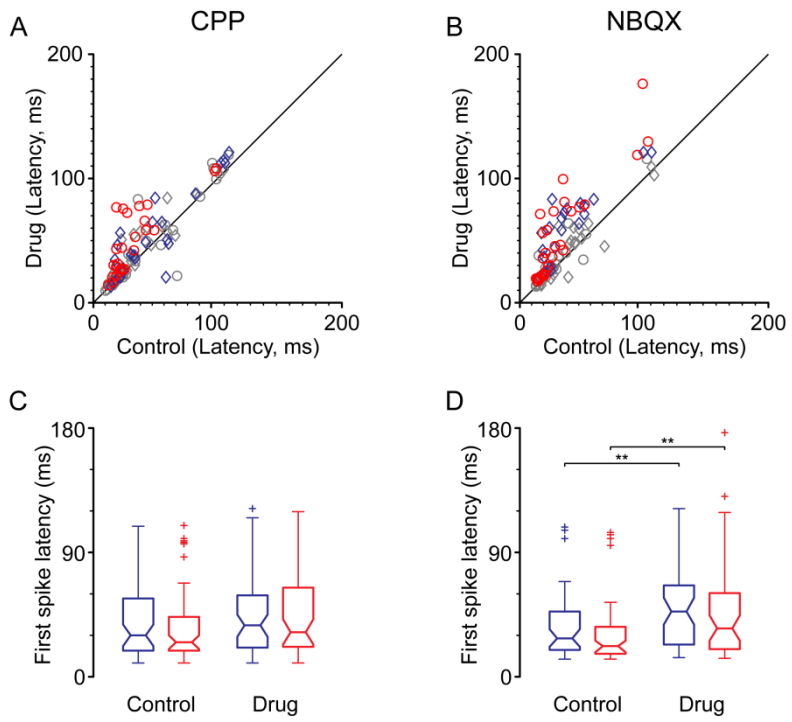

Figure 4: Effect of glutamate receptor antagonists on the first spike latency of during an oddball paradigm. The application of CPP (A) and NBQX (B) caused a significant increment of the first spike latency in most of the neurons recorded, regardless of whether the stimuli were presented as standard (diamonds) or deviants (circles). The colored markers indicate a significant change in the response relative to the control condition. At the population level, while the change due to the drug application was not significant in the case of CPP (C), the application of NBQX caused a significant increment of the first spike latency for both the standard (blue) and the deviant (red) stimuli.

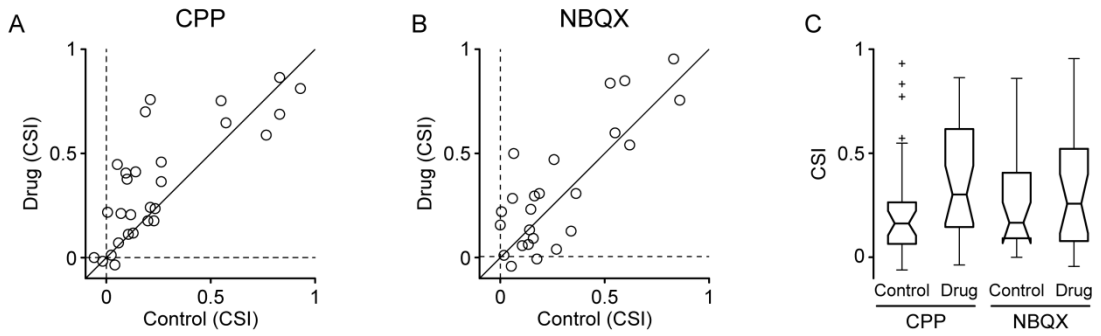

Figure 5: Effect of glutamate receptor antagonists on the common SSA index (CSI). While the overall effect was an increment of the CSI during the application of both drugs (A, CPP; B, NBQX), at the population level (C) the amount of increment was not statistically significant.

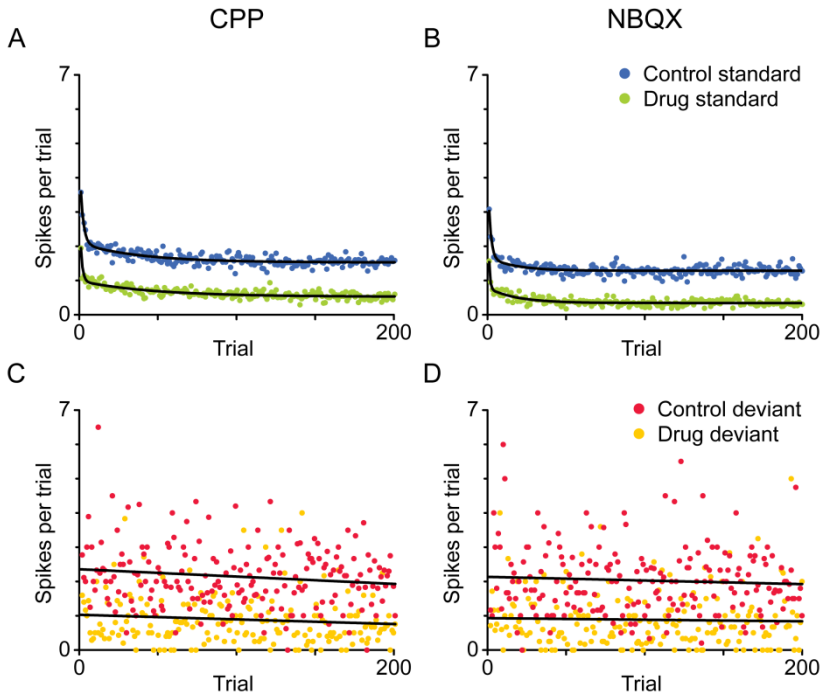

Figure 6: Time course of adaptation during the oddball paradigm and glutamatergic receptor antagonists. The application of CPP and NBQX (green dots in A and B, respectively) reduced the responses to the standard stimuli, compared to the control condition (blue dots), and also made the adaptation faster. In contrast, there was very little adaptation for the deviant stimuli (C, D) where the effect of both drugs (yellow dots) was essentially a linear decrement of the responses compared to the control condition (red dots). One trial equals 250 ms.

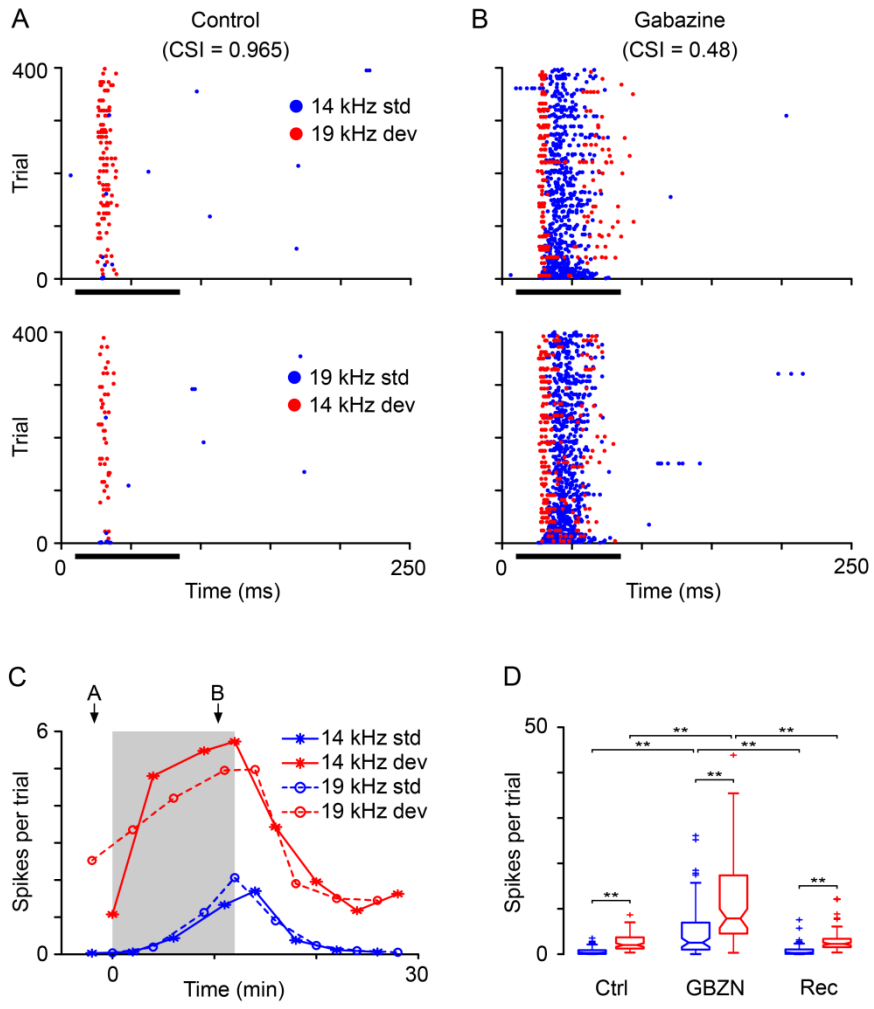

Figure 7. Typical effect of the blockade of the $GABA_A$-mediated inhibition on neural firing. A. Dot raster of the response of an adapting IC neuron to deviant and standard tones previous to the gabazine application. Black bars: tone duration. B. Dot raster of the neural response to the oddball paradigm during the blockade of the $GABA_A$ receptors with gabazine. C. Time course of the spike count in response to f1 and f2 presented as deviant and standard tones before, during and after the application of gabazine. Gray shaded area: duration of the gabazine injection which starts at T = 0. The A and B arrows correspond to the times of the response displayed in panels A and B. D. Population box plot of the spike count to the deviant and standard tone in the control (Ctrl), gabazine application (GBZN) and recovery condition (Rec). The asterisks

indicate significant differences (Friedman test, $p < 0.01$). Deviant, red; standard, blue in all panels. Modified from (24).

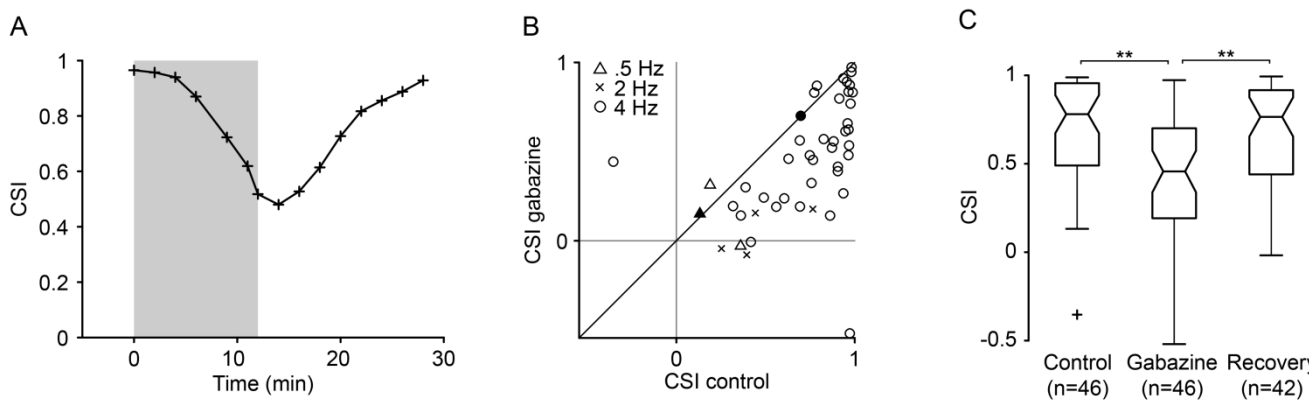

Figure 8. Effect of the blockade of the $GABA_A$-mediated inhibition on SSA index.

A. Time course of the CSI of the example neuron displayed in Fig. Gaba1A-C before, during and after the injection of gabazine. Gray shaded area: duration of the gabazine injection which starts at T = 0. B. Change in the CSI of a population of IC neurons (n = 46). Gabazine significantly decreased most of the CSI (open symbols) obtained at different repetition rates of stimulation (symbols). C. Population box plot of the CSI values during the control, gabazine injection and recovery condition. The asterisks indicate significant differences (Friedman test, $p < 0.01$). Modified from (24).

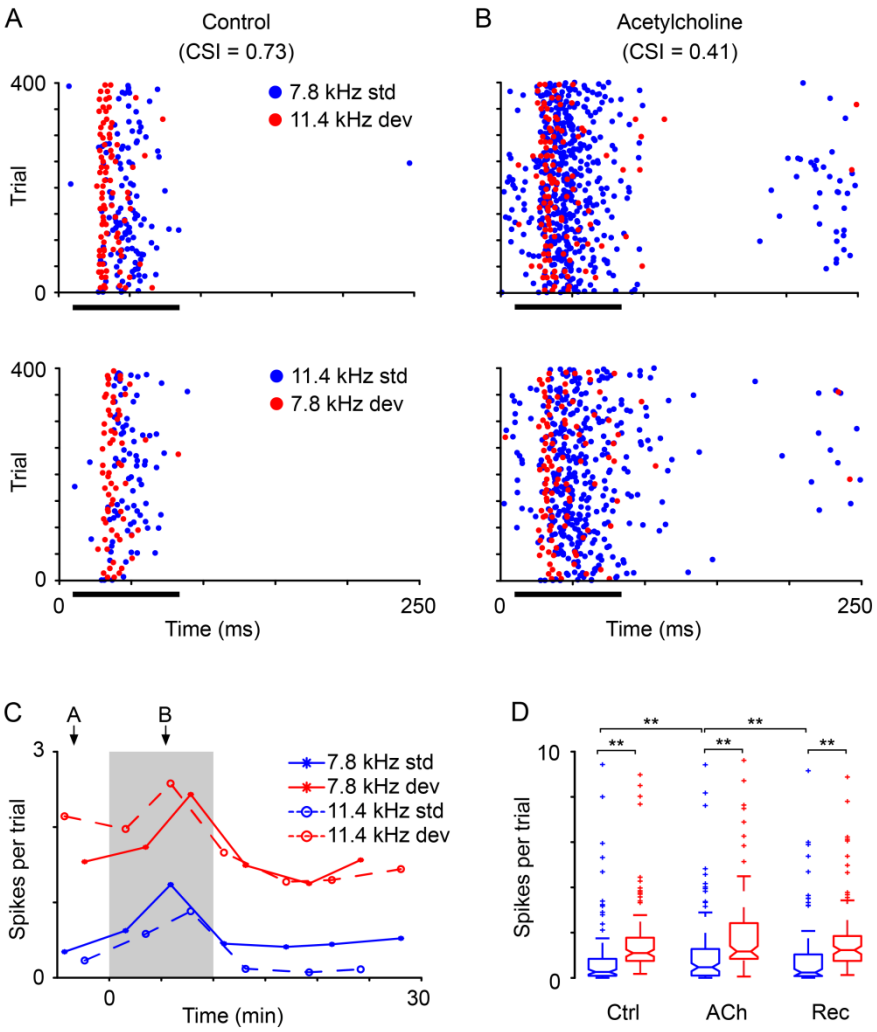

Figure 9. Typical effect of the activation of the cholinergic receptors on neural firing. A. Dot raster of the response of a partially adapting IC neuron to deviant and standard tones previous to the acetylcholine application. Black bars: tone duration. B. Change in the spiking response to deviant and standard tones during the acetylcholine injection. C. Time course of the spike count in response to f1 and f2 presented as deviant and standard tones before, during and after the application of acetylcholine. Gray shaded area: duration of the acetylcholine injection which starts at T = 0. The A and B arrows correspond to the times of the response displayed in panels A and B. D. Population box plot of the spike count to the deviant and standard tone in the control

(Ctrl), acetylcholine application (ACh) and recovery condition (Rec). The asterisks indicate significant differences (Friedman test, $p < 0.01$). Deviant, red; standard, blue in all panels.

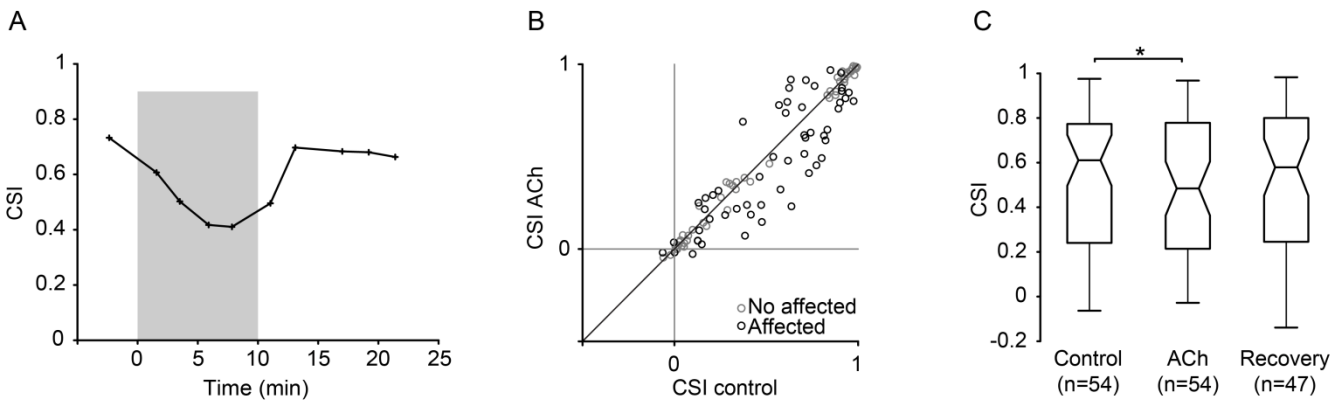

Figure 10. Effect of the activation of the cholinergic receptors on SSA index. A. Time course of the CSI of the example neuron displayed in Fig. 9A-C before, during and after the injection of acetylcholine. Gray shaded area: duration of the acetylcholine injection which starts at T = 0. B. Change in the CSI of a population of IC neurons (n = 105) elicited by acetylcholine. An augmentation of acetylcholine significantly modified the CSI of the majority of IC neurons with intermediate levels of SSA (open symbols) while those neurons that lack or exhibit extreme SSA remain unaffected by acetylcholine application. C. Population box plot of the CSI values during the control, acetylcholine injection and recovery condition. The asterisks indicate significant differences (Friedman test, $p < 0.05$).

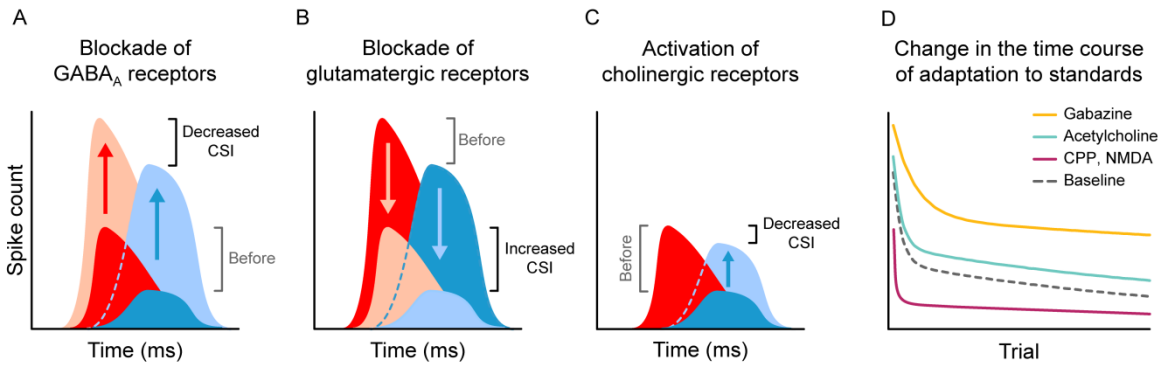

Figure 11. Schema of the effect of inhibition and acetylcholine on SSA. A. The blockade of the $GABA_A$ receptor by the iontophoretic injection of gabazine increased the overall response (shown here as PSTH) of IC neurons to both deviant (red) and standard (blue) stimuli, decreasing the CSI. B. On the other hand, the application of glutamatergic receptor antagonists reduced the responses to deviants and standards and increased the CSI. C. The activation of the cholinergic receptors by acetylcholine increases only the response to the standard tone of IC neurons with partial levels of SSA. D. Gabazine exerts a drastic change in the time course of adaptation in the response to the standard tone by increasing the fast and slow components of adaptation as well as the steady-state of adaptation. Acetylcholine affects only the sustained component of the time course of adaptation. CPP and NMDA make the time constants faster and reduce the steady-state. Modified from (24).

Table 1: Effect of glutamate receptor antagonists on neuronal responses. Mean and SD for the different measurements taken. The units are trials (equivalent to 250 ms) for τ_r and τ_s, and spikes per trial for A_{ss}, A_r and A_r. CSI: common SSA index, SI(f): frequency-specific SSA index, *: significant effect of the drug ($p < 0.05$, ANOVA; 95% confidence interval for the fittings).

	CPP (n = 28)		**NBQX (n = 25)**	
	Control	**Effect**	**Control**	**Effect**
Spikes per trial				
Standard	1.628 ± 1.707	0.634 ± 1.426 *	1.321 ± 1.529	0.384 ± 0.564 *
Deviant	2.187 ± 1.791	0.866 ± 1.416 *	2.002 ± 1.747	0.917 ± 1.487 *
First spike latency (ms)				
Standard	40.257 ± 28.656	45.478 ± 30.933	36.926 ± 24.200	49.429 ± 28.787 *
Deviant	36.279 ± 26.990	44.628 ± 30.700	31.166 ± 23.261	45.733 ± 37.461 *
CSI	0.254 ± 0.284	0.359 ± 0.277	0.271 ± 0.253	0.324 ± 0.299
SIf	0.235 ± 0.292	0.339 ± 0.426	0.268 ± 0.308	0.338 ± 0.408
Time course fitting (standards)				
τ_r	1.883	1.199 *	1.563	0.678 *
τ_s	38.65	47.55	17.47	18.410
A_{ss}	1.526	0.525 *	1.283	0.342 *
A_r	2.574	2.234	2.665	3.533
A_s	0.560	0.460	0.394	0.442
Time course fitting (deviants)				
a	2.358	1.029 *	2.134	0.930 *
b	-0.002	-0.001	-0.001	0.000