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VAGUS NERVE STIMULATION MODULATES CORTICAL SYNCHRONY AND EXCITABILITY THROUGH THE ACTIVATION OF MUSCARINIC RECEPTORS

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Abstract—Vagus nerve stimulation (VNS) is an FDA approved treatment for drug-resistant epilepsy and depression. Recently, we demonstrated the capacity for repeatedly pairing sensory input with brief pulses of VNS to induce input specific reorganization in rat auditory cortex. This was subsequently used to reverse the pathological neural and perceptual correlates of hearing loss induced tinnitus. Despite its therapeutic potential, VNS mechanisms of action remain speculative. In this study, we report the acute effects of VNS on intra-cortical synchrony, excitability, and sensory processing in anesthetized rat auditory cortex. VNS significantly increased and decorrelated spontaneous multi-unit activity, and suppressed entrainment to repetitive noise burst stimulation at 6–8 Hz but not after application of the muscarinic antagonist scopolamine. Collectively, these experiments demonstrate the capacity for VNS to acutely influence cortical synchrony and excitability and strengthen the hypothesis that acetylcholine and muscarinic receptors are involved in VNS mechanisms of action. These results are discussed with respect to their possible implications for sensory processing, neural plasticity, and epilepsy.

Key words: vagus nerve stimulation, epilepsy, acetylcholine, auditory cortex, scopolamine, synchrony.

Electrical stimulation of the vagus nerve (VNS) has been used to treat more than 60,000 patients with drug-resistant epilepsy and is under investigation as a treatment for several other neurological disorders and conditions. Among these, VNS increases alertness (Malow et al., 2001; Rizzo et al., 2003), and enhances recovery of motor and cognitive function in animal models of traumatic brain injury (Smith et al., 2005). Recently, we developed a novel and potentially therapeutic method for inducing targeted neural plasticity by repeatedly pairing brief pulses of VNS with acoustic sensory input. This technique was subsequently used to successfully reverse the neurological as well as the perceptual correlates of hearing loss induced tinnitus in adult animals. VNS-tone pairing closely replicated prior studies which induced robust cortical reorganization by pairing tones with electrical stimulation of the cholinergic nucleus basalis (NB) (Kilgard and Merzenich, 1998a).

Since VNS-tone pairing induced cortical plasticity to a degree strikingly similar to NB-tone pairing, similar mechanisms may underlie both effects. NB stimulation has been shown to acutely enhance sensory processing (Goard and Dan, 2009), as well as learning and memory (Miasnikov et al., 2008) in several animal models and is currently under investigation for the treatment of cognitive deficits in human subjects with mild to moderate Alzheimer's disease. The possibility of replicating these effects with VNS (a less invasive technique, as opposed to the highly invasive nature of NB stimulation) substantiates further investigation into VNS mechanisms of action which are not yet established. Consequently, the purpose of the present study was first to test whether or not, and to what extent, brief activation of VNS acutely modulates cortical synchrony, excitability, and sensory processing in control conditions as well as in the presence of the muscarinic antagonist scopolamine.

EXPERIMENTAL PROCEDURES

Subjects

Adult male Sprague–Dawley rats weighing 350–400 g were used in this study. All experimental procedures comply with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University committee on Animal Research at the University of Texas at Dallas. The number of animals was kept to the minimum necessary to ensure statistical validity. All animals were maintained on a normal 12 h/12 h light/dark schedule, with food and water available *ad libitum*.

Surgical protocol

Animals were anesthetized with sodium pentobarbital (50 mg/kg; Sigma-Aldrich Corp., St. Louis, MO, USA). Supplemental pentobarbital (8 mg/ml) was periodically administered i.p. to maintain a state of areflexia (evaluated by a lack of hind leg withdrawal upon toe-pinch) throughout the surgical procedures and during the recording session. Body temperature was maintained at 37 °C with a heating pad (ATC-1000 WPI). After a surgical level of anesthesia was obtained, the skull was fixed in a palato-orbital restraint and exposed through a rostrocaudal incision. The temporalis muscle was resected and the dura over the right auditory cortex was exposed through a craniotomy of approximately 6 mm by 4 mm. The dura was resected and the cortex was maintained in a bath of sterile physiological saline to prevent desiccation.

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Abbreviations: LC, locus coeruleus; PSTH, peri-stimulus time histogram; RRTFs, repetition rate transfer functions; VNS, vagus nerve stimulation.

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Primary auditory cortex was initially localized based on auditory evoked latencies (10–20 ms) and frequency tuning characteristics using bipolar tungsten electrodes (FHC) (Kilgard and Merzenich, 1998a). Next, 16-channel tungsten/polyimide Omnetics based micro-wire arrays (2 by 8, Tucker-Davis-Technologies, 500 μm electrode separation) were inserted to a depth of 600 μm, corresponding approximately to layer IV/V and the entire exposed cortex was covered with Kwik-Cast silicone elastomer (WPI).

For vagal nerve exposure, a rostro–caudal incision was made in the ventral aspect of the neck on the left side. Using glass probes, muscles were separated and the left cervical-vagus nerve was separated from the carotid artery (see Fig. 1A, B). The vagus nerve was gently guided into a cuff constructed from Micro-Renathane® (0.080" O.D.×0.040" I.D.) tubing and braided platinum iridium (.006" diameter) wire with Teflon insulation. The platinum-iridium wires lined the inside of the cuff, with the insulation removed to provide conductivity, allowing bipolar stimulation only around the nerve. The platinum-iridium wires from the cuff to the head attachment were threaded subcutaneously along the neck to the top of the skull as described previously (Engineer et al., 2011).

Vagus nerve stimulation parameters

Each 500 μs charge-balanced biphasic pulse was delivered at an intensity of 0.8 mA. The stimulation was delivered as a train of 15 pulses presented at 30 Hz (500 ms train duration). Preliminary studies confirmed these stimulation parameters sufficient to attenuate EEG amplitude without otherwise influencing behavior (Engineer et al., 2011).

The effect of VNS on spontaneous multi-unit activity was determined by creating a spontaneous firing rate modulation index (post-VNS−pre-VNS)/(post-VNS+pre-VNS) (Otazu et al., 2009). This index compared firing rate during a 100 ms window before each VNS train to activity in a 100 ms window beginning at the end of the stimulation train (repeated every 10 s for 100 repetitions).

Acoustic stimulation and recording

Tucker Davis Technologies (Alachua, FL, USA) neurophysiology hardware (RX6, RX5, RA16PA) and software (OpenEx Suite) were used for signal filtering (0.3–8 kHz), amplification (10,000×)

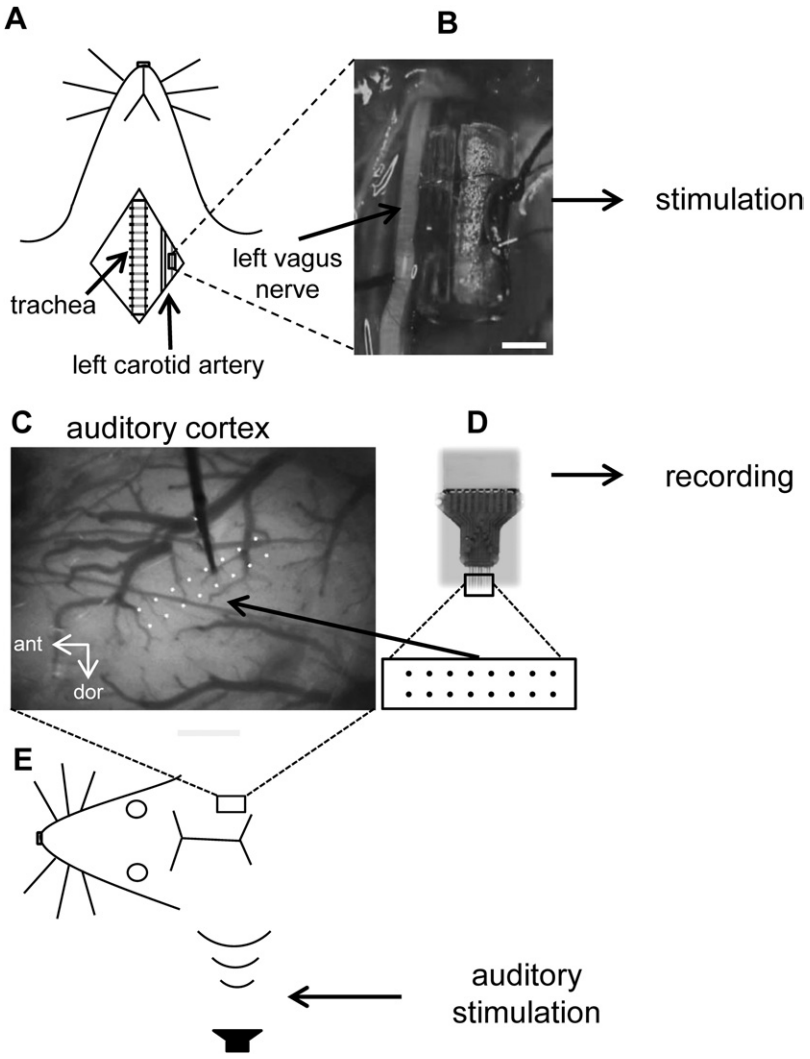

Fig. 1. Experimental setup. (A) Animals were anesthetized and the left vagus nerve was separated from the carotid artery and guided into a bipolar stimulation cuff shown in (B). The auditory cortex was then exposed and initially mapped using bipolar tungsten electrodes (dark region shown in the upper central portion in (C) before 16 channel arrays were inserted to a depth of 600 μm. Typical location of insertion and electrode arrangement are shown in (C, D) respectively. (E) Animals were then placed in a custom holder leaving the ears unobstructed and auditory stimuli were presented in free field. The scale bar shown in (B) = 1 mm.

and data acquisition. Auditory stimulation consisted of six (25 ms/4 ms rise/fall 65 dB SPL) noise bursts presented at randomly interleaved rates of 4–30 pulses/s 15 times each and were repeated every 4 s. Repetition rate transfer functions (RRTFs) were quantified by measuring multi-unit response firing rate following noise burst trains presented at each repetition rate. RRTFs were normalized by dividing the response to each noise burst by the response to the first noise burst in the train. Values greater than 1 represent facilitation and values less than 1 represent depression (Kilgard and Merzenich, 1998b). Recordings were made in an electrically shielded sound-attenuating chamber and sounds were presented in free field via a calibrated speaker (sigcal software and FF1 speaker, Tucker-Davis Technologies). Cross-correlation functions were computed for each recording pair (grouped by cortical separation) by counting the number of spike coincidences of the two clusters for various time shifts (−50 to 50 ms) between the two spike trains (1 ms bin size) and normalized by dividing each of its bins by the square root of the product of the number of discharges in both spike trains (Kilgard et al., 2007). Because multi-unit data were used, no assumptions are made on neural connectivity. For experiments evaluating the effects of VNS under muscarinic blockade, we administered 30 minutes prior to recording the anti-cholinergic muscarinic receptor antagonist scopolamine hydrobromide (1 mg/kg, i.p.) (Sigma-Aldrich Corp., St. Louis, MO, USA). This dose has been shown to prevent cortical desynchronization induced by cholinergic activation (Dringenberg et al., 2002; Dringenberg, 2003; Miasnikov et al., 2008) and confirmed effective in attenuating VNS-induced EEG desynchronization in preliminary experiments. Data analysis was performed on multi-unit cortical responses obtained from the recording sessions with NeuroExplorer and Matlab software packages. Statistical significance on spontaneous activity was determined by paired two-tailed *t*-tests. Two-way analysis of variance with Bonforroni post hoc tests were used for all other comparisons.

RESULTS

VNS increases and decorrelates spontaneous firing

In order to determine the degree to which VNS altered synchronous firing, we calculated cross correlation histograms for 232 pairs of sites grouped by cortical separation (estimated by inter-electrode distance in our multi-electrode ar-

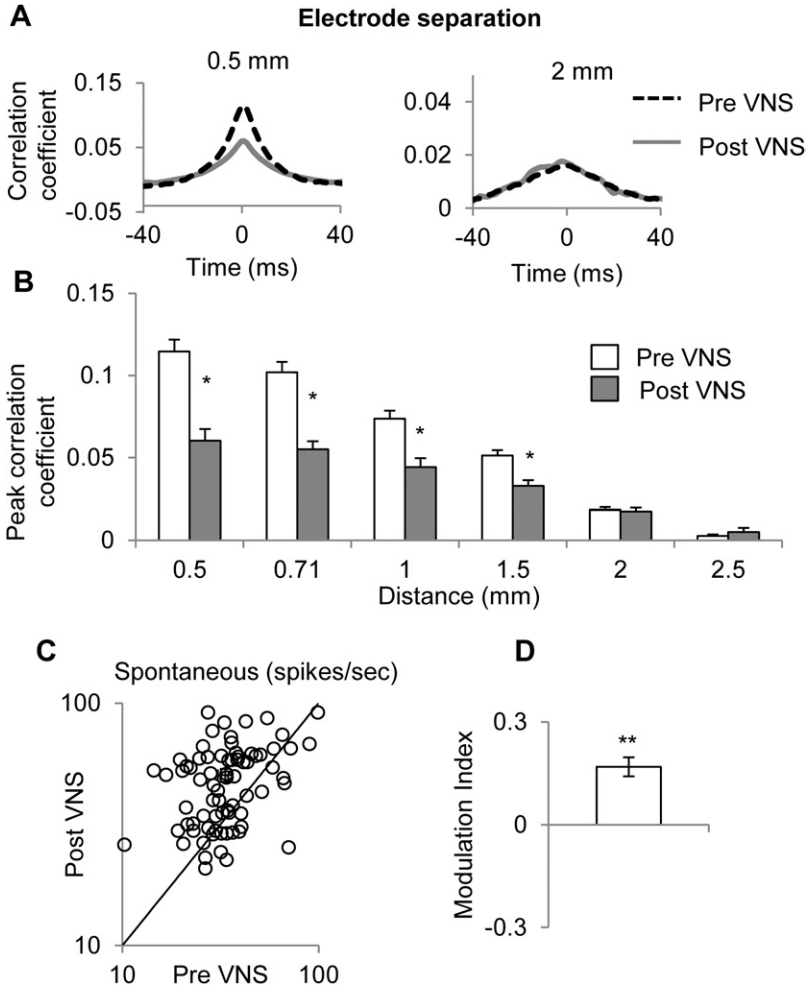

Fig. 2. VNS decorrelates and excites spontaneous firing rate. (A) Example cross-correlation histograms for a pair of cortical sites separated by 0.5 mm and another pair separated by 2 mm. (B) Correlated firing decreased with increased electrode separation however VNS decreased the average peak correlation coefficients for sites separated by 0.5–1.5 mm. Panel (C) shows a scatter plot summarizing the effects of VNS on spontaneous firing rate for a time period 100 ms after VNS compared to 100 ms before VNS. The increase in firing rate after VNS can be seen in control (a shift from unity towards upper left). This was quantified by creating a spontaneous firing rate modulation index (post-VNS−pre-VNS)/(post-VNS+pre-VNS) (D). The modulation index was significantly greater than zero for control conditions ($P<0.001$, 82 sites in six animals).

rays). As described previously (Eggermont, 1992) peak multi-unit correlation decreased with increasing distance (Fig. 2). Following VNS, spontaneous firing was significantly less correlated between sites separated by less than 2 mm, but was not different for sites separated by greater distances. Fig. 2A displays cross-correlograms for two pairs of sites separated by 0.5 mm and 2 mm respectively. Fig. 2B represents the average peak value of the cross-correlation amplitude for each intra-cortical distance (Fig. 2B, $P<0.05$).

In addition to its effects on correlated firing, VNS also had a significant excitatory effect on spontaneous firing rate. The increases in firing rate after VNS can be seen in control (a shift from unity towards upper left) for a time period 100 ms after VNS compared to 100 ms before VNS are summarized in Fig. 2C. This was quantified by creating a spontaneous firing rate modulation index (post-VNS−pre-VNS)/(post-VNS+pre-VNS) (Otazu et al., 2009) (Fig. 2D) and was significantly greater than zero ($P<0.001$, 82 sites in six animals).

VNS attenuates entrainment to repetitive noise burst stimulation at 6–8 Hz

Noise burst trains presented at specific repetition rates evoked multi-unit responses that increased substantially with each subsequent presentation in the train for many of the recorded sites. Similar to reports on the cortical augmenting response in rat somatosensory cortex (Castro-Alamancos and Connors, 1996a), this effect appeared to be dependent on post inhibitory rebound. Rebound excitation usually corresponded to a delay of approximately 111–166 ms, corresponding to an amplified response relative to the first for rates of ~6–9 Hz. An example peri-stimulus time histogram (PSTH) for a recording site expressing an augmenting response to a 7-Hz train is shown in Fig. 3A. When this stimulus was presented immediately after VNS the response to the first noise burst in the train of six was unaltered, but subsequent responses were significantly depressed or otherwise lost their augmenting dynamics (Fig. 3B). In order to evaluate temporal response characteristics we calculated RRTFs by presenting noise burst trains (4–30 Hz) and dividing the response to each noise burst by the response to the first in the train (see Experimental procedures). Values greater than 1 represent facilitation and values less than 1 represent depression (Kilgard and Merzenich, 1998b). VNS did not alter the evoked response to the first noise burst in the train of six; however, subsequent responses to noise bursts presented from 6 to 8 Hz were significantly attenuated as indicated by the population average response to each repetition rate (Fig. 3C) ($P<0.05$, 64 sites in five animals).

The muscarinic antagonist scopolamine blocks VNS-induced excitation and decorrelation

Scopolamine application alone (1 mg/kg, i.p.) did not alter intra-cortical synchrony or excitability in our preparation (possibly due to low levels of cholinergic activation present in the anesthetized state); however, it did suppress the effects of VNS. Correlated firing decreased with increased

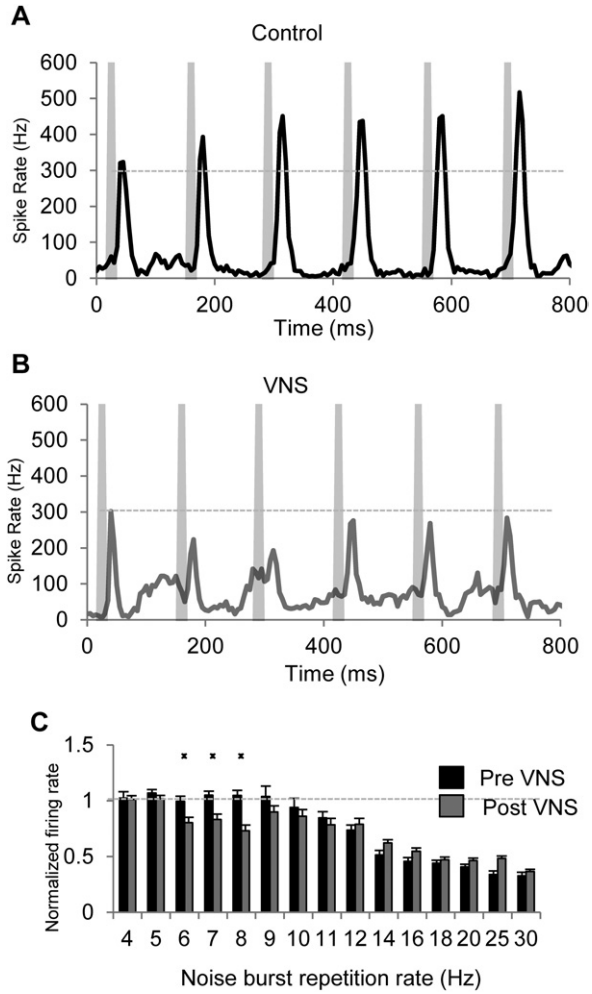

Fig. 3. VNS suppresses auditory entrainment to noise bursts presented at 6–8 Hz. (A) Peri-stimulus time histogram (PSTH) for an example site showing facilitation in response to a 7 Hz noise burst train in control conditions (shaded region marks noise burst onset). (B) When VNS was activated immediately before the noise burst train, the evoked response to the first noise burst in the series was unaffected however subsequent responses were depressed. (C) Group data displaying evoked responses to trains of six noise bursts presented at repetition rates from 4 to 30 Hz. Evoked responses were recorded and normalized by the response to the first in the series. Values greater than 1 represent facilitation, and values less than 1 represent depression. In pre-VNS conditions (black bars), responses were generally depressed at repetition rates greater than 10 Hz. When noise burst trains were presented immediately after VNS (gray bars) significant depression occurred from 6 to 8 Hz, $P<0.05$, 64 sites in five animals.

electrode separation; however, VNS had no effect on the average peak correlation coefficients in the presence of scopolamine ($P>0.05$). Example cross-correlation histograms for a pair of cortical sites separated by 0.5 mm and another pair separated by 2 mm are shown in Fig. 4A and population averages in (Fig. 4B). VNS also failed to significantly alter spontaneous firing rate in scopolamine treated animals. A scatter plot summarizing the effects of VNS in scopolamine pre-treated animals on spontaneous firing rate for a time period 100 ms after VNS compared to 100 ms before VNS in shown in Fig. 4C. No significant differ-

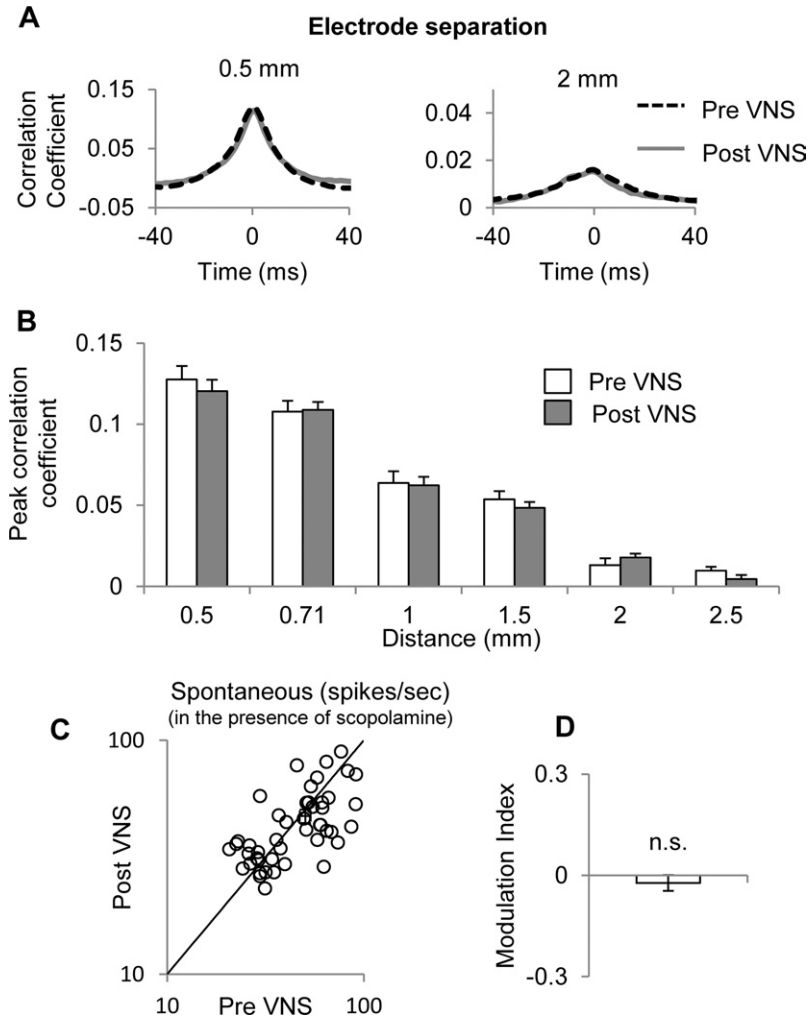

Fig. 4. The muscarinic antagonist scopolamine blocks VNS-induced excitation and decorrelation. (A) Example cross-correlation histograms for a pair of cortical sites separated by 0.5 mm and another pair separated by 2 mm. (B) Correlated firing decreased with increased electrode separation however VNS had no effect on the average peak correlation coefficients. Panel (C) shows a scatter plot summarizing the effects of VNS in scopolamine pre-treated animals on spontaneous firing rate for a time period 100 ms after VNS compared to 100 ms before VNS. No significant difference was observed. This was quantified by creating a spontaneous firing rate modulation index (post-VNS−pre-VNS)/(post-VNS+pre-VNS) shown in (D). The modulation index was not significantly different from zero ($P<0.05$, 49 sites in four animals).

ence was observed. The spontaneous firing rate modulation index (post-VNS−pre-VNS)/(post-VNS+pre-VNS) was not significantly different from zero ($P>0.05$, 49 sites in four animals, Fig. 4D).

The effect of VNS on temporal-tuning in scopolamine treated animals

Evoked responses to noise bursts repeated at rates less than 9 Hz were not significantly altered by VNS in scopolamine treated animals. A PSTH for an example site responding to a 7 Hz noise burst train in scopolamine pre-treated animals before and after VNS are shown in Fig. 5A and Fig. 5B. RRTFs in pre-VNS conditions were generally depressed at repetition rates greater than 14 Hz. When VNS was triggered immediately before noise burst train presentation, significant facilitation occurred at 9–10 Hz and significant depression occurred at 14 Hz (51 sites in four animals, $P<0.05$). To evaluate the muscarinic receptor contribution to the changes in temporal tuning induced by VNS, we subtracted the post-VNS RRTF from the pre-VNS RRTF in control animals and in scopolamine treated animals. The data shown in Fig. 6 indicate that scopolamine reversed the effects of VNS at some, but not all, repetition rates (8–10 Hz and 12–30 Hz, $P<0.05$). Note the nearly opposite profile for (post-VNS)−(pre-VNS) in the absence or presence of scopolamine.

DISCUSSION

In this study we first examined the acute effects of brief activation of VNS on intra-cortical multi-unit activity in anesthetized rat auditory cortex layers 4/5. VNS significantly increased and decorrelated spontaneous multi-unit firing rate and suppressed entrainment to repeated noise burst stimulation at 6–8 Hz. The muscarinic antagonist scopolamine attenuated these effects, strengthening the

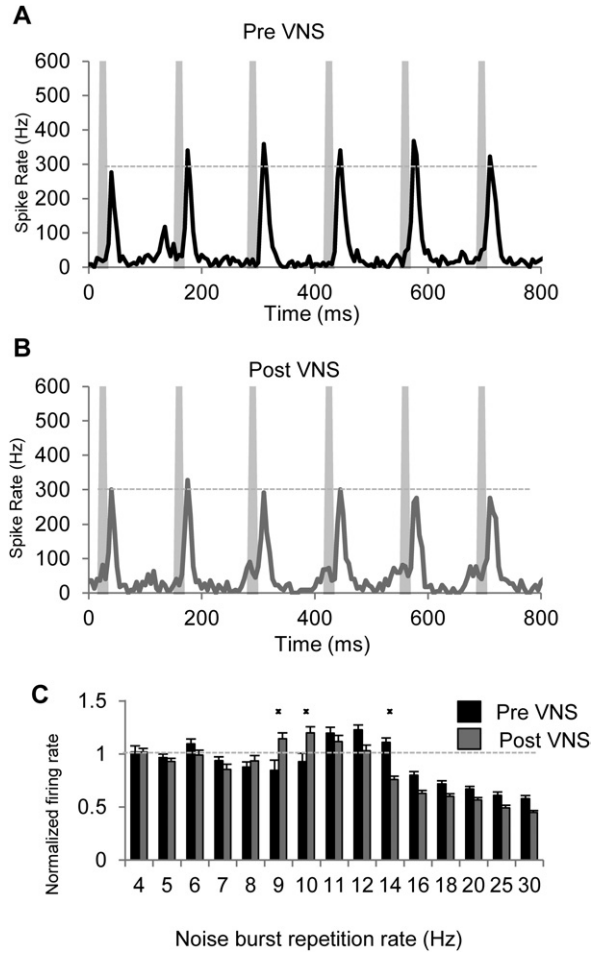

Fig. 5. The effect of VNS on temporal-tuning in scopolamine treated animals. (A, B) Peri-stimulus time histogram (PSTH) for an example site responding to a 7 Hz noise burst train in scopolamine pre-treated animals before and after VNS. (C) Responses to trains of six noise bursts presented at repetition rates from 4 to 30 Hz were recorded and normalized by the response to the first in the series (see methods). Values greater than 1 represent facilitation, and values less than 1 represent depression. In pre-VNS conditions (black bars), responses were generally depressed at repetition rates greater than 14 Hz. When VNS was triggered immediately before noise burst train presentation significant facilitation occurred at 9 Hz to 10 Hz and depression at 14 Hz, 51 sites in four animals.

hypothesis that VNS acutely alters cortical excitability and synchrony and that these effects are mediated in part through the action of acetylcholine on muscarinic receptors. Moreover, these results may explain common mechanisms between VNS induced plasticity, and the other therapeutic effects of VNS previously reported.

Although unknown, several prior studies have suggested that VNS mechanisms of action may be due to the increases in arousal associated with treatment (McLachlan, 1993; Malow et al., 2001; Rizzo et al., 2003; Jaseja, 2010). Aroused brain states are indeed associated with significantly increased seizure resistance (Kotagal and Yardi, 2008; Beenhakker and Huguenard, 2009) and there is a well-established relationship between arousal, cortical activation, and the cholinergic system. For example topically applied scopolamine to exposed feline cortex lead to the development of seizures but was prevented by application of the acetylcholinesterase inhibitor physostigmine (Tan et al., 1978). Systemic administration of scopolamine to healthy humans induces impairment to attentional processes, and memory, as well as decreases in higher frequency gamma/beta EEG power relative to lower frequency delta/theta power (Ebert and Kirch, 1998). Although not directly demonstrated in the current study, VNS has been shown to excite the nucleus basalis (NB) (Detari et al., 1983) and similarly to VNS, NB activation promotes arousal, suppresses seizure activity (Metherate et al., 1992; Berdiev et al., 2007), and promotes neural plasticity (Edeline et al., 1993; Engineer et al., 2011). The suppression of evoked responses to repetitive stimuli by brief activation of VNS we demonstrate are notably similar to the suppression induced by arousal (Castro-Alamancos and Connors, 1996b); however, their precise relationship remains unknown.

Several prior studies have attributed the effects of VNS to norepinephrine, which also contributes to arousal (Berridge and Foote, 1991). Among these, Smith et al., 2006 suggested that the therapeutic effects of VNS for the treatment of animals subjected to traumatic brain injury were due to enhanced noradrenergic activity. Other studies demonstrated increased activity of the noradrenergic locus coeruleus (LC) and central levels of norepinephrine following VNS as well as a reduction of VNS-induced seizure attenuation following LC lesions (Krahl et al., 1998; Groves et al., 2005; Roosevelt et al., 2006; Follesa et al., 2007). More recently, Raedt et al. (2011) further demonstrated that VNS-induced increases in norepinephrine release correlate with acute anti-seizure efficacy. Although these studies suggest that VNS mechanisms of action involve norepinephrine, they do not acknowledge that excessive noradrenergic activity leads to excessive synchrony and seizures (Noebels, 1984). Our demonstration that VNS alters cortical synchrony and excitability through muscarinic receptor activation suggests that the above studies should be interpreted with caution since lesions to the LC may also prevent subsequent release of acetylcholine (Berntson et al., 2003a,b). Consistent with this interpretation, systemic application of epinephrine activates the vagus nerve there by activating the nucleus tractus solitarius and the LC. The LC, through the release of norepinephrine activates the nucleus basalis, modulating sensory processing in the auditory cortex (“epinephrine priming”) in a cholinergic dependent manner, whereas cholinergic deafferentation induced through chemical lesions of basal forebrain cholinergic neurons prevents this effect (Berntson et al., 2003b).

Although the cholinergic system clearly contributes to seizure attenuation, demonstrated by lesions to the cholinergic system (Berdiev and van Luijtelaar, 2009), ACh also increases excitability due to the blockage of K^+-mediated conductances (Krnjevic, 1993). In fact, high concentrations of cholinergic agonists can lead to seizures formation (Turski et al., 1989). At the same time however, ACh also decreases the effectiveness of the excitatory network by greatly depressing the release of the excitatory trans-

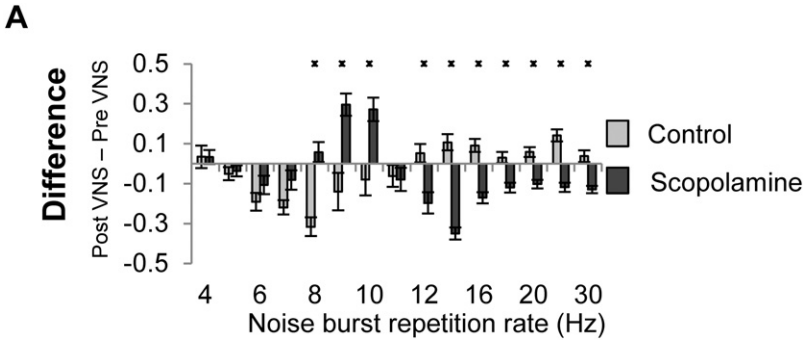

Fig. 6. Scopolamine reverses the effects of VNS on temporal tuning. To evaluate the muscarinic receptor contribution to the changes in temporal tuning induced by VNS, we subtracted the post-VNS RRTF from the pre-VNS RRTF in control animals and in scopolamine treated animals. (A) Repetition rate transfer function difference, scopolamine reversed the effects of VNS at some but not all repetition rates (7–10 Hz and 12–30 Hz, $P<0.05$). Note the nearly complimentary profile for VNS vs. VNS in scopolamine pre-treated animals. This suggests that muscarinic receptors contribute to the acute cortical effects of VNS on temporal processing.

mitter glutamate through activation of muscarinic receptors (Metherate and Ashe, 1991; Cox et al., 1992; Hasselmo and Cekic, 1996; Atzori et al., 2005; Kremin et al., 2006). Therefore, it is reasonable to speculate that this effect might supersede a cholinergic increase in excitability, and combined with the inhibitory effects of NE (Dinh et al., 2009), synergistically contribute to the various effects of VNS. Consistent with this possibility, muscarinic blockade prevented both the VNS-induced increase in cortical excitation, as well as the VNS-induced decorrelation. Although beyond the scope of the current study, our results do warrant future investigations utilizing recent developments in the sub-second and simultaneous measurement of multiple neurotransmitter levels (Parikh et al., 2007) combined with receptor specific antagonists and electrophysiological and behavioral assays to more precisely examine the complex mechanisms of action associated with VNS.

Limitations

Although our results suggest that acetylcholine, acting on muscarinic receptors contribute to the effects of VNS we observed, it should be noted that the present study does not demonstrate a specific site of action for scopolamine given systemically and the effects of muscarinic blockade are quite complex. For example Barnabi and Cechetto (2001) reported that VNS-induced excitation of insular cortex was attenuated by atropine (0.1 μM) injected into the ventroposterior parvocellular nucleus of the thalamus, while higher doses (1.0 μM) had no effect. Several other studies have demonstrated that muscarinic receptor blockade can increase the release of acetylcholine by preventing presynaptic m2 receptor activation (Quirion et al., 1995; Douglas et al., 2001). This may lead to muscarinic antagonist induced increases in nicotinic receptor activation further complicating any interpretation (Hasselmo and Sarter, 2011). Although VNS may also activate nicotinic acetylcholine receptors as well as noradrenergic, dopaminergic, and serotonergic activity, the muscarinic receptor antagonist scopolamine was sufficient to attenuate the effects of VNS we observed.

We have previously demonstrated that identical stimulation parameters were sufficient to acutely reduce cortical synchrony in awake animals (Engineer et al., 2011); however, anesthesia is known to alter levels of inhibition and synchrony suggesting that our results may not be identical to un-anaesthetized animals. It should be noted, however, that VNS-therapy is typically administered in combination with one or several anti-epileptic drugs, many with inherently sedative effects.

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