

Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression

Clinical article

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Object. Tinnitus is an auditory phantom percept related to tonic and burst hyperactivity of the auditory system. Two parallel pathways supply auditory information to the cerebral cortex: the tonotopically organized lemniscal system, and the nontopographic extralemniscal system, which fire in tonic and burst mode, respectively. Electrical cortex stimulation is a method capable of modulating activity of the human cortex by delivering stimuli in a tonic or burst way. Burst firing is shown to be more powerful in activating the cerebral cortex than tonic firing, and bursts may activate neurons that are not activated by tonic firing.

Methods. Five patients with an implanted electrode on the auditory cortex were asked to rate their tinnitus distress and intensity on a visual analog scale before and after 40-Hz tonic and 40-Hz burst (5 pulses at 500 Hz) stimulation. All patients presented with both high-pitched pure tone and white noise components in their tinnitus.

Results. A significantly better suppression for narrowband noise tinnitus with burst stimulation in comparison with tonic stimulation ($Z = -2.03$, $p = 0.04$) was found. For pure tone tinnitus, no difference was found between tonic and burst stimulation ($Z = -0.58$, $p = 0.56$). No significant effect was obtained for stimulation amplitude ($Z = -1.21$, $p = 0.23$) and electrical charge per pulse ($Z = -0.67$, $p = 0.50$) between tonic and burst stimulation. The electrical current delivery per second was significantly different ($Z = -2.02$, $p = 0.04$).

Conclusions. Burst stimulation is a new form of neurostimulation that might be helpful in treating symptoms that are intractable to conventional tonic stimulation. Further exploration of this new stimulation design is warranted. (DOI: 10.3171/2009.10.JNS09298)

KEY WORDS • lemniscal system • extralemniscal system •
 cortical stimulation • tinnitus • burst stimulation • tonic stimulation

TINNITUS is a distressing symptom affecting up to 10–15% of the population,^{3,23} and 2.4% are severely disabled due to their tinnitus, resulting in sleep disturbances, major depression, and a significant decrease in their quality of life.^{41,48} Tinnitus can be considered an auditory phantom phenomenon²⁸ similar to deafferentation pain seen in the somatosensory system,^{8,42,63} related to reorganization^{18,43} and hyperactivity^{32,53} of the auditory CNS.

No proven treatments exist for this population,¹⁴ but some promising results are being obtained by experimental neuromodulation in which both TMS^{13,16,34,36,37,40,49,50,57} and electrical stimulation via implanted electrodes are used.^{9,11,19,54}

Abbreviations used in this paper: fMR = functional MR; IPG = internal pulse generator; TMS = transcranial magnetic stimulation; VAS = visual analog scale.

Recently, it has been shown that stimulation of specific regions of the human brain can alter (suppress) tinnitus intensity^{10,11,54} as well as tinnitus distress in some patients, even without tinnitus intensity suppression.¹⁹ Auditory cortex stimulation can be performed with a strong impulse of magnetic field that induces an electrical current in the brain with TMS or with implanted electrodes.^{10,11,19,54} Initial results of auditory cortex stimulation via implanted electrodes by using tonic stimulation demonstrated that patients with pure tone tinnitus, but not noise-like tinnitus, benefit from this treatment.¹⁰ It was also shown that in patients who present with a combination of pure tone tinnitus and a noise-like component, both components had to be removed. Even completely removing the pure tone component does not result in a subjective amelioration as long as the second, noise-like component remains.¹⁰

Recently, a new stimulation design for TMS called theta burst stimulation was introduced,²⁶ and this has

been applied in tinnitus as well,^{12,13} and extended to alpha and beta burst stimulation.¹³ Burst TMS of the secondary auditory cortex is capable of suppressing noise-like tinnitus significantly better than tonic TMS.^{12,13} Based on these results, a custom-made program was developed that was capable of creating burst stimulation in a commercially available IPG (Eon, ANS/SJ Medical).

To investigate the differential effect of burst stimulation as compared with tonic stimulation, patients with tinnitus in whom electrodes had been implanted and whose tinnitus was intractable to tonic stimulation were analyzed using burst cortical stimulation. We report the first results of this new neurostimulation design in 5 patients with tinnitus who had electrodes implanted extradurally overlying the secondary auditory cortex and whose tinnitus was intractable to tonic stimulation for the noise-like component.

Methods

Patient Population

Five patients with implanted electrodes presenting with intractable tinnitus to tonic cortical stimulation were investigated in this study. All patients suffered from a combination of both pure tone and narrowband/white noise tinnitus, the latter of which has been demonstrated to be intractable to tonic electrical stimulation.¹⁰ All patients presented with Grade 4 tinnitus; that is, the worst grade according to the tinnitus questionnaire.²⁰ They all presented with a high-pitched pure tone component, the frequency of the pure tone either 4000 or 6000 Hz, and a noise-like component, a relatively rare combination. Tinnitus duration, patient sex and age, as well as tinnitus-matched loudness are described in Table 1. The study and treatment were approved by the ethics committee of the University Hospital Antwerp, Belgium.

Electrodes in all patients were implanted extradurally (Lamitorode 44, ANS Medical) on a target in the secondary auditory cortex by using a method previously described.^{8,10,11} In summary, patients intractable to any treatment for their tinnitus undergo a TMS of the secondary auditory cortex, both in burst and tonic mode, as previously described,^{12,13} by using a Super Rapid stimulator (Magstim Inc.), which is capable of repetitive pulse modes/tonic stimulation of up to 50 Hz as well as burst stimulation performed using a custom-made program. If the TMS can ameliorate the tinnitus transiently in a placebo-controlled way in 2 separate sessions, the patients are offered an implant of a Lamitorode 44 electrode on a predetermined area of the secondary auditory cortex. The target is selected with the aid of fMR imaging according to a method previously described.^{11,38,58} In the MR imaging unit (3T MR imaging machine; INTERA, Philips Medical Systems) the pitch and intensity of the tinnitus are matched to the tinnitus perceived by the patient. The electrode is implanted using a technique previously described as well.^{8,10,11} The Lamitorode 44 lead is made of 8 electrodes, with 28-mm electrode span and 60-cm lead length, configured with 2 offset rows of 4 electrodes, each 4 × 2.5 mm, with 3-mm spacing between the electrodes. A straight 6-cm-long incision is made overlying the audi-

TABLE 1: Characteristics of 5 patients with intractable tinnitus

Case No.	Age (yrs), Sex	Tinnitus Characteristic				
		Duration (yrs)	Side	Grade	Frequency (Hz)	Loudness (dB)
1	54, F	6	lt	4	4000	45
2	68, M	9	lt	4	6000	25
3	46, M	15	lt	4	6000	10
4	54, M	8	lt	4	4000	3
5	56, M	3	rt	4	6000	65

tory cortex, as determined by the fMR imaging-guided neuronavigation. The 6 × 2-cm craniotomy and the location for the electrode placement are tailored in the same fMR imaging-based navigated fashion. The lead, placed extradurally, is sutured to the coagulated dura mater and tunneled subcutaneously to the abdomen, where it is externalized.

On the 3rd postoperative day, trial stimulations are started. All patients undergo a tonic stimulation at 40 Hz and a burst stimulation at 40 Hz consisting of 5 spikes with 1-msec pulse width, and a 1-msec interspike interval in a charge-balanced way (Fig. 1); that is, at 40-Hz burst and 500-Hz spike frequencies in random order. The burst stimuli are delivered by a commercially available IPG (Eon, ANS/SJ Medical) capable of delivering tonic and burst mode stimulation by using a custom-made program.

The amount of electrical charge delivered to the auditory cortex is calculated by multiplying the current amplitude with the pulse width. Multiplying this electrical charge by the stimulation frequency yields the total amount of electrical current delivered to the auditory cortex per second (in other words, the electrically delivered dose). The difference in electrical current delivery is compared between tonic and burst stimulation, as are the current amplitudes used. The charge per pulse is also calculated by multiplying the pulse width with the current amplitude.

Results from burst and tonic stimulation are compared with each other and with preoperative scores, for both the pure tone component and the narrowband component separately. The 5 patients were asked to rate their tinnitus intensity on a VAS before (preoperative) and after (postoperative) tonic and burst stimulation, respectively. The effect of tinnitus suppression was analyzed by means of Wilcoxon signed-rank tests, with preoperative versus tonic, preoperative versus burst, and tonic versus burst as within-subjects variables. Because the stimulation does not generate sensory activation and thus cannot be perceived consciously, the data were obtained in a placebo-controlled way. Only patients who responded in a placebo-negative way to tonic stimulation for their pure tone component were included in this study comparing the effect of tonic versus burst stimulation for their noise-like component.

Results

Results of maximally obtained tinnitus suppression

Burst stimulation of auditory cortex for tinnitus suppression

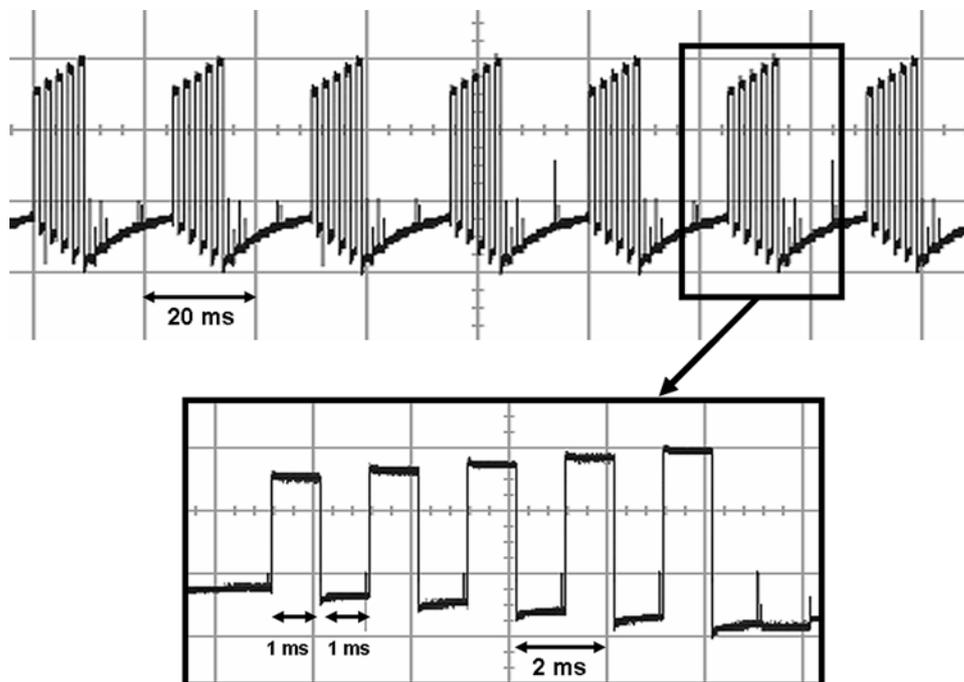


Fig. 1. Graphs showing burst mode: 1-msec spikes with 1-msec spike interval (500-Hz spike mode) and 5-msec charge balance firing at 40 Hz (40-Hz burst mode). Stimulation design was delivered by an IPG (Eon, ANS/SJ Medical) equipped with a custom-made stimulation program.

with 40-Hz tonic stimulation are compared with 40-Hz burst stimulation, both for the pure tone and the white noise component. For pure tone, results show a significantly better suppression when comparing preoperative VAS scores with postoperative tonic ($Z = -2.03$, $p = 0.04$; a reduction of 95.23%) and burst ($Z = -2.03$, $p = 0.04$; a reduction of 97.62%) stimulation on VAS. No significant effect was obtained between postoperative tonic and burst stimulation ($Z = -0.58$, $p = 0.56$).

For narrowband noise tinnitus, no differences were obtained between pre- and postoperative tonic stimulation ($Z = 0.0$, $p = 1.00$) on VAS. The data, however, revealed a significant effect for VAS when comparing pre- with postoperative tonic stimulation ($Z = -2.03$, $p = 0.04$; a reduction of 61.90%). A significant effect was also achieved on VAS scores in comparisons between postoperative tonic stimulation and burst stimulation ($Z = -2.03$, $p = 0.04$; a reduction of 61.90%) (Fig. 2).

None of the patients who received electrode implants developed an epileptic insult during the stimulation or during the follow-up period as of this writing. The average stimulation amplitude was 3.44 mA (range 2.00–6.00 mA) for tonic stimulation, and 2.34 mA (range 0.60–5.04 mA) for burst stimulation. No significantly lower amplitude for burst stimulation was obtained in comparison with tonic stimulation ($Z = -1.21$, $p = 0.23$).

The average electrical charge per pulse for tonic stimulation is 1644.80 μC , and for burst it is 2286 μC , a nonsignificant difference ($Z = -0.67$, $p = 0.50$). The average electrical current delivery per second for tonic stimulation is 65,792 mA (range 24,960–120,000 mA) versus 457,200 mA (range 120,000–1,008,000 mA) for burst, a significant difference ($Z = -2.02$, $p = 0.04$).

Discussion

The human auditory system consists of 2 main parallel pathways supplying auditory information to the cerebral cortex: the parvalbumin-staining lemniscal (classical) and calbindin-staining extralemniscal (nonclassical) systems.⁷ In animals the parvalbumin pathway, ascending from the central nucleus of the inferior colliculus, is the more direct, and terminates in the ventral part of the medial geniculate body. Its neurons are sharply tuned, tonotopically organized, and consistent in their responses,^{17,31} and they fire predominantly in tonic mode^{22,25} when sounds are consciously perceived.⁶² They project to core areas of the auditory cortex characterized by high parvalbumin immunoreactivity and by similar neuronal properties. The calbindin pathway is more diffuse in its origins and terminates in the dorsal and medial nuclei.³¹ Neurons in the dorsal and medial nuclei are not frequency-specific or tonotopic, and are labile in their responses.^{4,31} They fire more in burst mode^{22,25} and project more diffusely to belt areas of the auditory cortex, in which parvalbumin immunoreactivity is reduced and in which neuronal responses are less specific than in the core. The belt areas are the origins of streams of corticocortical connections leading into the temporal, parietal, and frontal lobes.³¹

Some neurons fire in packets of action potentials followed by periods of quiescence (bursts), whereas others within the same stage of sensory processing fire in a tonic manner.⁵ Information theory suggests that both bursting and tonically firing model neurons efficiently transmit information about the stimulus.^{5,47} Burst and tonic firing might be parallel computations in certain sensory systems.

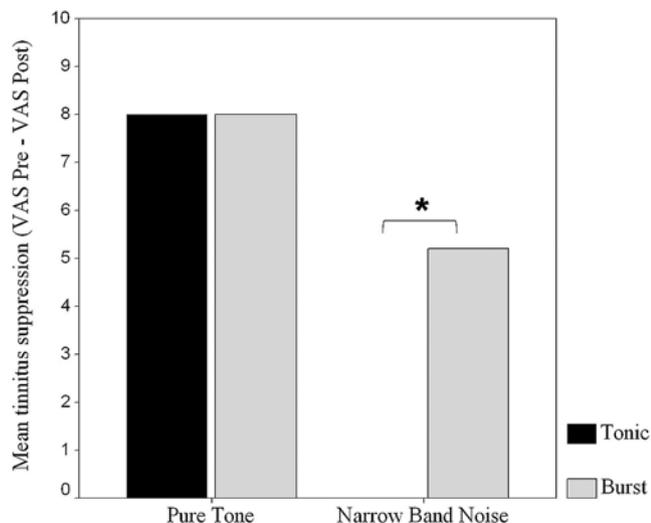


Fig. 2. Bar graph showing mean tinnitus suppression after tonic and burst stimulation for pure tone and narrowband noise tinnitus component (* $p < 0.05$).

Tinnitus is related to reorganization^{18,43} and hyperactivity^{32,53} of the auditory CNS, most commonly related to decreased input (that is, hearing loss).^{44,45} Diminished output from the affected cochlear region causes reduced inhibition in central auditory structures,^{1,61} leading to hyperexcitability of the central auditory system.^{52,53} This is characterized by increased spontaneous firing of neurons in the lemniscal central and extralemniscal external nuclei of the inferior colliculus^{6,29} as well as in the primary⁴⁶ and secondary auditory cortex.¹⁵

Based on these data it was hypothesized that white noise tinnitus may be caused by increased burst firing in the nontonotopic (extralemniscal) system, whereas pure tone tinnitus may be the result of increased tonic firing in the tonotopic (lemniscal) system.^{12,13} Narrowband tinnitus could be the result of a coactivation of both pathways.

Burst firing has been studied predominantly in the thalamus. Thalamic neurons can respond to inputs in 2 distinct modes, known as burst or tonic.²⁷ A burst is a cluster of action potentials with interspike intervals ≤ 4 msec occurring on a plateau phase. As soon as the interspike interval becomes > 4 msec, the burst is considered complete.²¹ This should be differentiated from clustered tonic firing, without a plateau phase, where the interspike interval is > 4 msec, because reliability of signal transmission is greater for burst spikes than for tonic spikes with similar preceding interspike intervals.² It was shown that in the awake state the first action potential of a burst is more than twice as likely to evoke an action potential than is an action potential during tonic firing, and later spikes in the burst further raise the probability of eliciting postsynaptic action potentials,⁶⁰ suggesting that burst firing is a wake-up call from the thalamus.⁵⁶ The cortical responses to thalamic bursts are larger in amplitude than those to tonic firing, and the increased amplitude of the burst-evoked excitatory postsynaptic potentials is due to both a larger initial excitatory postsynaptic potential and temporal summation. This is related to the fact that tonic firing generates a linear response, whereas burst

firing generates a nonlinear response,⁵ and results in a better signal-to-noise ratio than tonic firing.⁵⁶ The switch from tonic to burst can be elicited by modulatory cortical feedback.⁵⁵ It has furthermore been shown that electrical auditory cortex burst stimulation exerts its effect predominantly on the extralemniscal medial geniculate body,^{65,66} which fires predominantly in burst mode.^{22,25} These thalamic high-frequency burst discharges are particularly effective in activating large inhibitory postsynaptic potentials, whereas tonic firing is not,³⁵ suggesting that burst firing could be particularly effective in suppressing hyperactivity-related pathological conditions in the brain. Thus, cortical burst stimulation might predominantly modulate the extralemniscal thalamus and could be particularly effective in suppressing thalamocortical hyperactivity syndromes via a nonlinear effect, which is more potent than tonic firing.

Based on these data, and the idea that neurostimulation should aim at mimicking neural firing as closely as possible, the authors attempted to use burst neurostimulation in 5 patients in whom tonic neurostimulation for narrowband tinnitus had failed. This resulted in a statistically significantly better suppression of noise-like tinnitus in comparison with tonic stimulation. However, for the pure tone tinnitus component, no difference in suppression rate could be demonstrated between the 2 stimulation designs, similarly to what has been demonstrated for TMS.^{12,13} From these data it cannot be concluded that the differential effect is solely due to the stimulation design (burst), because the burst design resulted in a significantly higher total amount of electrical current per second being delivered, which could be a reason as well. A study comparing burst stimulation to high-frequency tonic stimulation with the same frequency and the same amount of current applied should be performed to clarify this possibility. Because the amplitude and electrical charge per pulse are not significantly different, it could be the design itself and not the total amount of electrical current delivered per second that is important, in accordance with the physiological differences described above.

Whether other pathological conditions characterized by increased burst firing, such as phantom pain,^{30,39,51} Parkinson disease^{30,64,67} and other movement disorders,³³ epilepsy,^{24,30} addiction,⁵⁹ and clinical depression³⁰ (some of which are also being treated by neurostimulation), are amenable to burst stimulation remains a challenging question.

Conclusions

A new clinical electrical neurostimulation design is presented, consisting of bursts of high-frequency stimuli. Burst stimulation might exert its effect either by being more powerful than tonic stimulation or by having a differential effect on the topographic versus nontopographic pathways. This first clinical report warrants further research to explore the full capacity of burst stimulation.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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