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Targeting the Parahippocampal Area by Auditory Cortex Stimulation in Tinnitus

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ABSTRACT

Background: The final common pathway in tinnitus generation is considered to be synchronized auditory oscillatory hyperactivity. Intracranial auditory cortex stimulation (iACS) via implanted electrodes has been developed to treat severe cases of intractable tinnitus targeting this final common pathway, in the hope of being a panacea for tinnitus. However, not everybody responds to this treatment. Objective: The electrical brain activity and functional connectivity at rest might determine who is going to respond or not to iACS and might shed light on the pathophysiology of auditory phantom sound generation.
Method: The resting state electrical brain activity of 5 patients who responded and 5 patients who did not respond to auditory cortex implantation are compared using source localized spectral activity (*Z*-score of log transformed current density) and lagged phase synchronization.
Results: sLORETA source localization reveals significant differences between responders vs non-responders for beta3 in left posterior parahippocampal, hippocampal and amygdala area extending into left insula. Gamma band differences exist in the posterior parahippocampal areas and BA10. Functional connectivity between the auditory cortex and the hippocampal area is increased for beta2, delta and theta2 in responders, as well as between the parahippocampal area and auditory cortex for beta3.
Conclusion: The resting state functional connectivity and activity between the auditory cortex and parahippocampus might determine whether a tinnitus patient will respond to a cortical implant. The auditory cortex may only be a functional entrance into a larger parahippocampal based tinnitus network.

Introduction

Non-pulsatile tinnitus is considered to be an auditory phantom percept [1] analogous to phantom pain [2,3]. Both phantom percept disorders have been considered persisting aversive memory traces [4] and share similar clinical features, pathophysiological mechanisms and treatment approaches [2–5]. It is a frequent symptom with an incidence of about 1% and prevalence of 10–15% in the western world [6,7]. There are little to no effective evidence-based treatments [8]. It severely impairs the quality of daily life in 2–3% of the population [7], and is often associated with insomnia [9], anxiety [10,11] and depression [11,12].

A pathophysiological model, called thalamocortical dysrhythmia, based on sensory deprivation, has been proposed both for pain and tinnitus [13]. At rest, in a normally functioning auditory system without deafferentation, the auditory thalamocortical columns oscillate at alpha frequencies (8–12 Hz). When there is deafferentation (hearing loss) alpha oscillations decrease to theta (4–7 Hz), possibly because there is less information to be processed [14]. This increased hearing loss associated theta activity results in decreased GABAa (gamma amino butyric acid) mediated lateral inhibition [13,15] leading to a halo of faster gamma band activity (30–80 Hz) at the lesion edge, generating the positive symptoms (tinnitus, pain). This pathologically persisting coupled theta-gamma rhythm is called thalamocortical dysrhythmia [13].

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Magnetoencephalography (MEG) studies have demonstrated that tinnitus is indeed correlated to decreased alpha [16] and associated increased gamma band activity in the contralateral auditory cortex [13,17]. Furthermore, the amount of contralateral gamma band activity correlates with the perceived intensity of the phantom sound [18]. Gamma band activity (local field potentials and firing rate) in the auditory cortex correlates to the BOLD signal on fMRI [19,20], and recordings from implanted electrodes overlying the secondary auditory cortex in a tinnitus patient has demonstrated that gamma activity correlates with the BOLD signal and that theta and gamma are coupled in the tinnitus state [21]. Based on the above data it has been suggested that fMRI can be used clinically as an indirect way of looking at the neural signature of tinnitus [22]. And indeed, recordings from an implanted electrode have revealed that maximal tinnitus suppression is obtained by current delivery exactly at the BOLD spot, which co-localizes with increased spatially coupled gamma and theta activity in contrast to the other electrode poles demonstrating a normal alpha peak. These spectral changes normalize when stimulation induces tinnitus suppression, both on electrode and source localized EEG recordings. These data suggest that theta-gamma coupling as proposed by the thalamocortical dysrhythmia model might be causally related to a conscious auditory phantom percept [21].

It has been demonstrated that electrical stimulation via implanted electrodes [5,23–28] on the auditory cortex in humans can benefit some patients suffering from tinnitus by interfering with the proposed thalamocortical dysrhythmia model [21,28]. However, in a recent evaluation of more than 40 implanted tinnitus patients it was shown that only 1 out of 3 of these patients responded to tonic stimulation and that 50% of non-responders to tonic stimulation could be rescued by applying burst stimulation, still resulting in 1/3 patients not responsive to the implant [29]. Since all implanted patients responded twice to a TMS session in a placebo-controlled way, this TMS test is not ideal as a predictive test for selecting patients for surgical implantation. On the other hand, if a patient responds to the implant, the amount of tinnitus suppression obtained by TMS does correlate with the amount of tinnitus suppression obtained by the implant [29].

It remains elusive why some patients do respond to the implant and others do not, even though correct surgical positioning is verified by fusion of the postoperative CT scan (demonstrating the exact localization of the electrode) with the preoperative fMRI (demonstrating the most likely auditory cortex generator of the tinnitus). One can hypothesize that some people are more resistant to electrical stimulation than others. This is in accordance with data from transcranial direct current stimulation [30,31], transcranial magnetic stimulation [32–34] and transcutaneous electrical nerve stimulation [35] in tinnitus, with a response rate of 30–50% of patients. The aim of the study is to determine whether differentiating the resting state brain activity and functional connectivity on a preoperative EEG with source analysis might help to predict successful implantation for tinnitus suppression, and might be clinically relevant as an adjunct for selecting future candidates for implants.

Methods and materials

Participants

Participants were selected from a group of patients who had been implanted with an electrode overlying the posterior part of the superior temporal gyrus, i.e. the secondary auditory cortex in an attempt to treat their tinnitus. Details about the selection criteria and surgical technique have been published before [23,24,29,36]. In brief, if a treatment intractable patient responds on two separate days to transcranial magnetic stimulation in a placebo-controlled way, targeting the superior temporal gyrus, the patient was eligible for an extradural implant. Intractable means the patient has no lasting benefit from audiological or ENT treatments and has no improvement from medication (flupentixol, melitracen and clonazepam) [37]. The electrode was targeting the area of BOLD activation on fMRI, elicited by presenting tinnitus matched sound in the MRI scanner, as described before [29]. The surgery is aided by fMRI guided intraoperative neuronavigation [21,22,24,29]. The side of the implant was contralateral for unilateral tinnitus and the side that yielded most suppression for bilateral tinnitus. One patient underwent bilateral implantation (patient no. 8). The BOLD spot used as the surgical target correlates to theta-gamma band coupled activity on source analyzed EEG [21] (group data submitted).

Ten patients (6 male, 4 female, mean age = 47 years, range = 26–63 years, see Table 1 for detailed information) who had preoperative EEGs performed were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the University Hospital of Antwerp, Belgium. Data were retrospectively collected that detailed the patients' gender, age, tinnitus type, tinnitus side,

Table 1
Patient characteristics.

Subject	Responder	Sex	Age	Tinnitus type	Tinnitus side	Tinnitus pitch (Hz)	Tinnitus intensity (dB SL)	Tinnitus loudness (VAS)	Tinnitus grade	Side of implant	Tinnitus duration (years)
1	R	M	54	PT + NBN	R	6000	7	9	III	L	1
2	R	M	34	NBN	R	6000	0	8	IV	R	3
3	R	V	63	NBN	R > L	6000	0	9	IV	L	17
4	R	M	45	NBN	L > R	3000 L	5	9	IV	R	18
						4000 R	5	6			
5	R	M	45	NBN	R	6000	10	9	III	R	1
Responders	*Mean*		48.20			5166.67	4.50	8.33			8.00
	SD		11.55			1329.16	3.93	1.12			8.17
6	NR	M	49	PT	BIL	6000	3	9	IV	L	3
7	NR	V	42	PT	L	2000	20	10	II	R	4
8	NR	M	52	NBN	R > L	16000	10	7	III	L + R	3
9	NR	V	62	PT	BIL	8000	X	8	X	R	1
10	NR	V	26	PT	R	8000	65	8	III	L	1
Non-responders	*Mean*		46.20			80,000	19.60	8.40			2.40
	SD		13.38			5099.02	26.52	1.14			1.34
R vs NR			$U = 11$			$U = 8$	$U = 9.5$	$U = 14$	$\chi^2 = 5.11$		$U = 10$
			$P = .84$			$P = .25$	$P = .33$	$P = .93$	$P = .28$		$P = .69$

R = responder, NR = non-responder, PT = pure tone tinnitus, NBN = narrow band noise tinnitus, L = left, R = right, BIL = bilateral.