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Acute effects and after-effects of acoustic coordinated reset neuromodulation in patients with chronic subjective tinnitus

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ABSTRACT

Chronic subjective tinnitus is an auditory phantom phenomenon characterized by abnormal neuronal synchrony in the central auditory system. As shown computationally, acoustic coordinated reset (CR) neuromodulation causes a long-lasting desynchronization of pathological synchrony by downregulating abnormal synaptic connectivity. In a previous proof of concept study acoustic CR neuromodulation, employing stimulation tone patterns tailored to the dominant tinnitus frequency, was compared to noisy CR-like stimulation, a CR version significantly detuned by sparing the tinnitus-related pitch range and including substantial random variability of the tone spacing on the frequency axis. Both stimulation protocols caused an acute relief as measured with visual analogue scale scores for tinnitus loudness (VAS-L) and annoyance (VAS-A) in the stimulation-ON condition (i.e. 15 min after stimulation onset), but only acoustic CR neuromodulation had sustained long-lasting therapeutic effects after 12 weeks of treatment as assessed with VAS-L, VAS-A scores and a tinnitus questionnaire (TQ) in the stimulation-OFF condition (i.e. with patients being off stimulation for at least 2.5 h). To understand the source of the long-lasting therapeutic effects, we here study whether acoustic CR neuromodulation has different electrophysiological effects on oscillatory brain activity as compared to noisy CR-like stimulation under stimulation-ON conditions and immediately after cessation of stimulation. To this end, we used a single-blind, single application, cross over design in 18 patients with chronic tonal subjective tinnitus and administered three different 16-minute stimulation protocols: acoustic CR neuromodulation, noisy CR-like stimulation and low frequency range (LFR) stimulation, a CR type stimulation with deliberately detuned pitch and repetition rate of stimulation tones, as control stimulation. We measured VAS-L and VAS-A scores together with spontaneous EEG activity pre-, during- and post-stimulation. Under stimulation-ON conditions acoustic CR neuromodulation and noisy CR-like stimulation had similar effects: a reduction of VAS-L and VAS-A scores together with a decrease of auditory delta power and an increase of auditory alpha and gamma power, without significant differences. In contrast, LFR stimulation had significantly weaker EEG effects and no significant clinical effects under stimulation-ON conditions. The distinguishing feature between acoustic CR neuromodulation and noisy CR-like stimulation were the electrophysiological after-effects.

Acoustic CR neuromodulation caused the longest significant reduction of delta and gamma and increase of alpha power in the auditory cortex region. Noisy CR-like stimulation had weaker and LFR stimulation hardly any electrophysiological after-effects. This qualitative difference further supports the assertion that long-term effects of acoustic CR neuromodulation on tinnitus are mediated by a specific disruption of synchronous neural activity. Furthermore, our results indicate that acute electrophysiological after-effects might serve as a marker to further improve desynchronizing sound stimulation.

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1. Introduction

A widely accepted consensus guideline (Tunkel et al., 2014) provides current tinnitus definitions. Secondary (objective) tinnitus is defined as tinnitus associated with an identifiable organic condition other than sensorineural hearing loss. In contrast, primary (subjective) tinnitus is an idiopathic symptom that may or may not be associated with sensorineural hearing loss. However, primary tinnitus is typically initiated by damage to the peripheral hearing system (Eggermont and Roberts, 2004; Irvine et al., 2001; Lockwood et al., 2002; Norena et al., 2002; Weisz et al., 2006) that leads to a sequence of structural and functional changes in the central hearing system (Eggermont, 2007; Eggermont and Roberts, 2004; Lockwood et al., 2002; Moller, 2003). The latter give rise to a phantom auditory perception, i.e. a conscious awareness of an internally generated sensory percept when no corresponding auditory stimulus is present (Eggermont and Roberts, 2004; Snow, 2004). In recent years, there is a growing body of evidence for a critical role of pathological neuronal synchronization in the auditory system in tinnitus pathophysiology (Eggermont and Tass, 2015; Shore et al., 2016). An increase of neuronal synchrony has been described both in animal studies after noise trauma (Norena and Eggermont, 2003; Ochi and Eggermont, 1997; Seki and Eggermont, 2003) and in tinnitus patients (Norena and Eggermont, 2003; Ochi and Eggermont, 1997; Seki and Eggermont, 2003; Weisz et al., 2005, 2007b). Magnetoencephalography (MEG) and electroencephalography (EEG) studies revealed specific alterations of oscillatory power in particular frequency bands (Llinas et al., 1999; Weisz et al., 2005, 2007b) in patients with chronic subjective tinnitus. Specifically, increase of the oscillatory power in the delta, theta, and gamma frequency ranges as well as reduction of alpha power in the auditory cortex region were associated with the presence of tinnitus and its intensity (Adamchic et al., 2014a; Adjamian et al., 2012; De Ridder et al., 2011; De Ridder et al., 2014; De Ridder et al., 2015; Elgoyhen et al., 2015; Llinas et al., 2005; Llinas et al., 1999; Tass et al., 2012a; Van der Loo et al., 2009; Weisz et al., 2005, 2007b). An increase of oscillatory EEG power is typically interpreted as an increase in neuronal synchronization in terms of coincident firing within neuronal populations (Hamalainen et al., 1993; Klass and Daly, 1979; Niedermeyer and Da Silva, 1999; Nunez, 1981).

Studies in cortical primary sensory areas have revealed that neuronal plasticity is not restricted to periods early in life, but is present and can be reactivated in the mature brain, too [for review see (Hübener and Bonhoeffer, 2014)]. The neuronal timing pattern plays a key role in shaping synaptic connectivity (Hebb, 1949; Bliss and Lomo, 1973). Neurons adapt the strength of their synapses to the relative timing of their action potentials according to the fundamental mechanism of spike timing-dependent plasticity (STDP) (Gerstner et al., 1996; Markram, 1997). Computationally it was shown that in networks with STDP stable synchronized states with up-regulated strength of synaptic connectivity and stable desynchronized states with down-regulated synaptic connectivity may generically coexist (Tass and Majtanik, 2006; Tass and Hauptmann, 2006, 2007, 2009; Hauptmann and Tass, 2007). Along the lines of a computational approach (Tass, 1999; Tass, 2002) coordinated reset (CR) stimulation (Tass, 2003a, 2003b) was developed to specifically counteract abnormal neuronal synchrony by desynchronization. To this end different neuronal subpopulations of a target population are stimulated through different stimulation sites sequentially at different times in order to reset the phases of the different subpopulations equidistantly in time (Tass, 2003a, 2003b). CR stimulation causes a desynchronization and, hence, a reduction of the strength of the synaptic connections, which ultimately results in an anti-kindling, i.e. an unlearning of abnormally up-regulated synaptic connectivity and neural synchrony (Tass and Majtanik, 2006; Tass and Hauptmann, 2006, 2007, 2009; Hauptmann and Tass, 2007, 2009). The network is shifted from a pathological model state with abnormally strong synapses to a desynchronized state with weaker synapses, and the stimulation effect outlasts the cessation of stimulation (Tass and Majtanik, 2006; Tass and Hauptmann, 2006, 2007, 2009; Hauptmann and Tass, 2007, 2009).

CR stimulation was first developed computationally for electrical deep brain stimulation (DBS) for the treatment of Parkinson's disease (Tass, 2003a, 2003b), computationally studied in networks with (Tass and Majtanik, 2006; Tass and Hauptmann, 2006, 2007, 2009; Hauptmann and Tass, 2007, 2009) and without (Lysyansky et al., 2011, 2013) STDP and later on successfully applied in pre-clinical (Tass et al., 2012b; Wang et al., 2016) and clinical (Adamchic et al., 2014b) proof of concept studies. In addition, the CR concept was extended to sensory stimulation (Popovych and Tass, 2012), especially acoustic CR stimulation for the treatment of chronic primary tinnitus (Tass and Popovych, 2012; Tass et al., 2012a). In a prospective, randomized, single blind, placebo-controlled proof of concept study in 63 patients acute and long lasting clinical effects of a 12-week treatment with CR neuromodulation and noisy CR-like stimulation were assessed with visual analogue scale (VAS) scores for loudness (VAS-L) and annoyance (VAS-A) as well as with the TF score (Tass et al., 2012a). The TF ("Tinnitus-Fragebogen") (Goebel and Hiller, 1993) is the German adaptation of the tinnitus questionnaire (TQ) (Hallam et al., 1984). Acoustic CR neuromodulation and noisy CR-like stimulation share the basic rhythmic CR pattern and employ tones that are tailored to the patient's dominant tinnitus frequency. *Acoustic CR neuromodulation* uses a template of four stimulation tones with fixed frequency ratios with respect to the tinnitus frequency. In contrast, *noisy CR-like stimulation* is characterized by randomly selecting the actual four stimulation tones during each stimulation cycle from a larger set of tones, sparing the tinnitus-related pitch range and including substantial random variability of the tone spacing on the frequency axis where all stimulation tones were defined by frequency ratios with the tinnitus frequency (Tass et al., 2012a). In the proof of concept study CR stimulation turned out to be safe and well-tolerated and led to a significant decrease of tinnitus symptoms as assessed by VAS and TF scores (Tass et al., 2012a). EEG recordings performed before and after 12 weeks of treatment with acoustic CR neuromodulation revealed a significant reduction of pathologically elevated delta and gamma activity together with an increase of pathologically reduced alpha activity in a network of brain areas comprising auditory as well as non-auditory cortices (Adamchic et al., 2014a; Silchenko et al., 2013; Tass et al., 2012a).

The starting point of this paper is the significant difference of the clinical effects of the two stimulation protocols: Acoustic CR neuromodulation and noisy CR-like stimulation both had acute effects (with respect to baseline) as assessed with VAS-L and VAS-A scores in the *stimulation-ON condition* (i.e. 15 min after turning on stimulation), but only acoustic CR neuromodulation had sustained long-lasting effects as assessed in the *stimulation-OFF condition* (i.e. after having turned off stimulation for at least 2.5 h) after 12 weeks of treatment (Tass et al., 2012a). As yet, electrophysiological effects during and shortly after cessation of acoustic CR neuromodulation have not been studied. Accordingly, we here set out to study acute effects and acute after-effects of both stimulation protocols with VAS scores and, in particular, with EEG recordings. This is to elucidate acute electrophysiological stimulation responses and mechanisms that might lead to therapeutic sustained long-lasting effects. Specifically, based on computational studies (Tass and Majtanik, 2006; Tass and Popovych, 2012; Tass et al., 2012b) we hypothesize that acoustic CR neuromodulation causes a desynchronization of delta oscillations followed by a desynchronizing after-effect, provided the stimulation duration is sufficient. Since our computational predictions are based on qualitative rather than quantitative models, it remains to be tested, whether the selected 16 min stimulation duration is appropriate. We have selected a 16 min duration, since in a previous proof of concept study (Tass et al., 2012b) this dose was sufficient to at least induce acute clinical CR effects. Note, based on previous clinical (Tass et al., 2012b) and computational (Tass and Majtanik, 2006; Tass and Popovych, 2012; Tass et al., 2012b) findings, we would hypothesize acutely delivered acoustic CR neuromodulation