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ORIGINAL PAPER

The Use of Alcohol as a Moderator for Tinnitus-Related Distress

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Abstract Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source. Persons with tinnitus engage in a number of health behaviors to manage tinnitus. This can go from prescription medication, masking devices, behavioral training techniques to cortical implants. Potentially less adaptive methods of coping with tinnitus, such as the use of alcohol, are poorly studied. The purpose of this study was to further explore the neurobiological mechanism of tinnitus improvement by the use of alcohol. We observed differences in the alpha, beta and gamma frequency band when comparing resting-state EEG before and after alcohol intake. More precisely increased synchronized alpha1 activity was found in the posterior cingulate cortex and decreased synchronized alpha2 activity was demonstrated in orbitofrontal cortex, ventrolateral prefrontal cortex and subcallosal anterior cingulate cortex after alcohol intake. Increased synchronized activity was found in a region between the pregenual and dorsal anterior cingulate cortex and the left insula for beta and decreased activity in the precuneus after alcohol intake. For the gamma frequency band decreased synchronized activity in the precuneus and the posterior cingulate cortex was demonstrated after alcohol intake. Region of interest analyses in auditory cortices and parahippocampal area revealed however no differences in the different frequency bands before and after alcohol consumption.

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Introduction

Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source. The American Tinnitus Association estimates 50 million Americans are affected by it, and that 12 million of these people have chronic tinnitus that prompts them to seek medical attention (Moller 2007). About 6–25% of the affected people report that tinnitus causes a considerable amount of distress (Baguley 2002; Eggermont and Roberts 2004; Heller 2003), with 2–4% suffering in the worst degree (Axelsson and Ringdahl 1989). Severe tinnitus can be so severe that it becomes disabling, interfering with sleep and concentration, social interaction and work and results in major depressions (Erlandsson and Holgers 2001; Scott and Lindberg 2000).

People with tinnitus engage in a number of health behaviors to manage tinnitus. This can be prescription medication (Elgoyhen and Langguth 2009; Langguth et al. 2009), hearing aids and masking devices (Moffat et al. 2009), cognitive and behavioral training techniques (Jastreboff and Jastreboff 2000). But also surgical solutions and neuromodulation such as cochlear (Van de Heyning et al. 2008) or cortical (De Ridder et al. 2007) implants, rTMS (Khedr et al. 2009) and tDCS (Vanneste et al. 2010b) are applied to manage tinnitus. Potentially less adaptive methods of coping with tinnitus, such as the use of alcohol, are poorly studied. Studies have shown individuals often use alcohol to cope with stress (Pohorecky 1991). Also tinnitus patients sometimes use alcohol as a coping strategy for tinnitus. Research showed a mixed effect of

alcohol on tinnitus with 22% of the sample reporting that drinking worsened tinnitus, 62% reporting no effect of alcohol on tinnitus and 16% reporting that alcohol improved tinnitus (Pugh et al. 1995). Whether and to what extent a person drinks alcohol in response to a stressor depends on many factors including severity, chronicity and impact of the stressor, the lack of other methods for managing the stressor, and the availability of social support to buffer the stressful events (Riley and King 2009).

Like auditory hallucinations, tinnitus is also considered an auditory phantom percept related to plastic alterations in the auditory cortex (Muhlnickel et al. 1998) and the parahippocampus (Landgrebe et al. 2009; Vanneste et al. 2010c, d). Neuroimaging and electrophysiologic studies indicate an excessive spontaneous activity in the central auditory nervous system and changes in the tonotopic map of the auditory cortex as the neurobiological basis of tinnitus (Lockwood et al. 1998; Salvi et al. 2000; Schlee et al. 2009; Smits et al. 2007; Weisz et al. 2007). Whereas more people experience a phantom sound, only 1 in 5 of the people who perceive tinnitus is emotionally affected by it. Hence the sound perception and the distress caused by tinnitus might be related to two separate mechanisms/networks in the brain. Recent research on the neurobiology of tinnitus-related distress revealed that the subcallosal and dorsal anterior cingulate cortex, posterior cingulate cortex, precuneus and insula (Vanneste et al. 2010a) are important areas related to tinnitus-related distress similar to the areas involved in the emotional component of the pain matrix (Craig 2003; Critchley 2005; Peyron et al. 2000; Phan et al. 2002) and the distress related areas in asthmatic dyspnea (von Leupoldt et al. 2009). Interestingly these areas are also involved in alcohol consumption. Contrasting between alcoholic drink odors (e.g. subjects' drinks of choice) and non-appetitive odors (e.g. grass, leather) is characterized by activity in the orbitofrontal cortex, ventromedial frontal cortex, subcallosal anterior cingulate cortex, posterior cingulate cortex, retrosplenial area, and the precuneus in heavy drinkers (Bragulat et al. 2008). Visual images of alcoholic beverages induced activity in the orbitofrontal cortex, ventromedial frontal cortex, and posterior cingulate (Hermann et al. 2006). In addition to these regions, also the dorsal and subcallosal anterior cingulate cortex, precuneus and precuneus are involved (Tapert et al. 2003). However we expect brain areas involved in the tinnitus intensity (i.e. loudness) such as the auditory cortex and parahippocampus not to differ when comparing before and after alcohol intake as these area are not related to alcohol intake (van der Loo et al. 2009; Vanneste et al. 2010c, d).

As brain areas involved in tinnitus-related distress and in alcohol use partially overlap, it is conceivable that in some patients alcohol can modulate the tinnitus distress network and thereby ameliorate the tinnitus percept. The purpose of this study was to explore the neurobiological mechanism underlying alcohol mediated tinnitus improvement. We therefore focus on the differences in cortical sources of the resting-state EEG (eyes closed) in tinnitus patients before and after alcohol intake. Using continuous scalp EEG recordings and standardized Low Resolution Electromagnetic Tomography (sLORETA), a tomographic inverse solution imaging technique (Pascual-Marqui et al. 1994), we analyzed differences before and after alcohol consumption within a group of selected ROIs were calculated.

Methods

Participants

Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were excluded from the study in order to obtain a more homogeneous sample. All patients were investigated for the extent of hearing loss using audiograms. Tinnitus intensity was matched both for frequency and intensity above hearing threshold. They were interviewed as to their perceived location of the tinnitus (exclusively in the left ear, predominantly in the left ear, in both ears, and centralized in the middle of the head (bilateral), predominantly in the right ear, exclusively in the right ear).

Five patients ($N = 5$; all males) with chronic tinnitus participated in this study, with a mean age of 54.25 ($SD = 3.15$). Tinnitus was considered chronic if its onset dated back 1 year or more. The mean tinnitus duration was 4.5 years ($SD = 0.98$). All patients had narrow band noise tinnitus. Two patients perceived tinnitus unilaterally, while three patients perceived tinnitus bilaterally. All patients drink alcohol on daily bases to cope with their tinnitus and to decrease the perceived tinnitus intensity. The daily amount depends on the quantity required to obtain suppression of their tinnitus. For this study all patients drank alcohol until they perceived their usual tinnitus suppression. All patients were after alcohol intake still aware and able to correctly judge their tinnitus perception.

All patients were requested to arrive sober to the clinic. As some of these patients are probably depending on their alcohol, all patients were invited in the morning to prevent alcohol craving to a minimum. After a resting state EEG was taken, patients had time to drink alcohol as needed and were asked to report when there tinnitus distress and tinnitus intensity was reduced by minimum 30%. Immediately after reporting a resting state EEG was taken.

A visual analogue scale for tinnitus intensity ('How loud is your tinnitus?: 0 = no tinnitus and 10 = as loud as imaginable') and tinnitus distress ('How stressful is your

tinnitus? 0 = no distress and 10 = suicidal distress') was asked before (pre) and directly after (post) alcohol consumption. For comparing pre en post alcohol consumption a Wilcoxon Sign Ranking test was performed as our results are normally distributed due to a small sample size.

The study was approved by the Ethical Committee of the Antwerp University Hospital, Belgium.

EEG Data Collection

EEGs were obtained in a fully lighted room with each participant sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 min. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10–20 International placement referenced to linked ears and impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 1024 Hz, band passed 0.15–200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software (Congedo 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact were removed from the stream of the EEG. Average cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz).

Control Subjects with Tinnitus Patients

Similar to the tinnitus patients, EEGs (Mitsar, Nova Tech EEG, Inc, Mesa) were obtained for an age- and gender-matched control group (N = 5) in a fully lighted room with each participant sitting upright in a comfortable chair. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10–20 International placement referenced to linked lobes and impedances were checked to remain below 5 kΩ. Data were collected for 100 2-s epochs eyes closed, sampling rate = 1024 Hz, and band passed 0.15–200 Hz. Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz.

Source Localization

Based on the scalp-recorded electric potential distribution, the standardized low resolution brain electromagnetic tomography (sLORETA) software can be used to compute the cortical three-dimensional distribution of current density. This method is a properly standardized discrete, three-dimensional (3D) distributed, linear, minimum norm inverse solution. The particular form of standardization used in sLORETA endows the tomography with the property of exact localization to test point sources, yielding images of standardized current density with exact localization albeit with low spatial resolution (i.e. neighboring neuronal sources will be highly correlated). It is also important to emphasize that sLORETA has no localization bias even in the presence of measurement and biological noise.

It should be emphasized that the localization properties of any linear 3D inverse solution (i.e. tomography) can always be determined by the localization errors to test point sources. If such a tomography has zero localization error to such point sources located anywhere in the brain, then, except for low spatial resolution, the tomography will localize correctly any arbitrary 3D distribution. This is due to the principles of linearity and superposition. These principles do not apply to non-linear inverse solutions, nor do they apply to schemes that are seemingly linear but are not 3D inverse solutions (e.g. one-at-a-time best fitting dipoles).

The tomography LORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) (Mulert et al. 2004; Vitacco et al. 2002), structural MRI (Worrell et al. 2000), Positron Emission Tomography (PET) (Dierks et al. 2000; Pizzagalli et al. 2004; Zumsteg et al. 2005). Further LORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (Zumsteg et al. 2006a; Zumsteg et al. 2006c) and cognitive ERPs (Volpe et al. 2007). It is worth emphasizing that deep structures such as the anterior cingulate cortex (Pizzagalli et al. 2001), and mesial temporal lobes (Zumsteg et al. 2006b) can be correctly localized with these methods.

Statistics

The sLORETA software package was used to perform the statistical analyses. The methodology used is non-parametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic (e.g. the maximum of a t or an F statistic), under the null hypothesis. This methodology corrects for multiple testing (i.e., for the collection of tests performed for all voxels and frequencies bands. Due to the non-parametric nature of the method, its validity need not rely on any assumption of Gaussianity. The interested reader is referred to for Nichols and Holmes (2002) a complete overview of the methodology, where details about the properties (e.g. pertaining to

its non-parametric nature, and pertaining to how it properly corrects for multiple testing) can be found (Nichols and Holmes 2002). We performed one voxel-by-voxel test (comprising 6,239 voxels each) for the difference frequency bands.

In addition, we made a comparison between tinnitus patients that use alcohol as a coping mechanism but where sober and compare these with patients that do not use alcohol as a coping mechanism using a contrast employing a t-statistic for unpaired groups and a corrected ($P < 0.05$).

Region of Interest

Furthermore, the log-transformed electric current density was averaged across all voxels belonging to the region of interest, for respectively the left and right auditory cortex ((BA21, BA22, BA40 and BA41) and the left and right parahippocampus (BA27 and BA29) for delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz) frequency band.

For comparing pre en post alcohol consumption log transformed current densities a Wilcoxon Sign Ranking test was perform as our results are normal distributed due to a small sample size.

Results

Pre and Post Alcohol Consumption

The analysis indicated a significant effect for tinnitus distress ($Z = -2.21$, $P < 0.05$) and tinnitus intensity ($Z = -2.21$, $P < 0.05$) (Fig. 1). The amount of improvement for tinnitus distress and tinnitus intensity is 61.53% (range from 33% - 100%) and 57.88% (range from 33% - 100%) respectively.

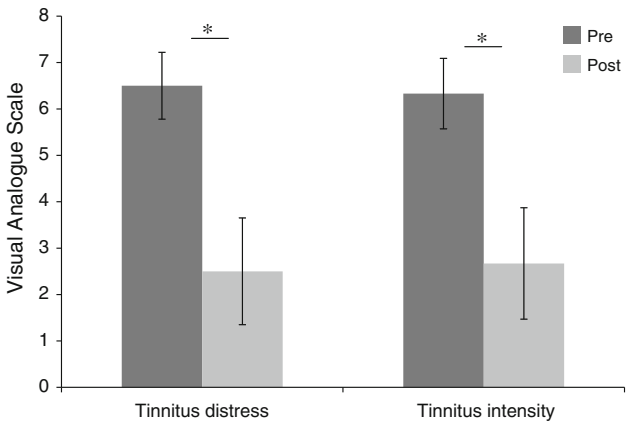

Fig. 1 Pre- and Post Alcohol consumption Visual Analogue scale for tinnitus distress and tinnitus intensity (*$P < 0.05$; **$P < 0.01$)

Contrast Analysis

The frequency band parameters delta (2–3.5 Hz), theta (4–7.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz) were similar before and after alcohol intakes. Figure 2 illustrates that the sLORETA current source density in the alpha1 (8–10 Hz) band was higher after alcohol intake in posterior cingulate cortex (BA 31). For alpha2 (10.5–12.5 Hz), decreased synchronized activity was found in the subcallosal anterior cingulate cortex (BA25), orbitofrontal cortex (BA10), ventrolateral prefrontal cortex (BA47) after alcohol intake. Analysis further revealed increased synchronized activity in a region between the pregenual and dorsal anterior cingulate cortex (BA24) and the left insula (BA13) for beta3 (21.5–30 Hz) after alcohol intake. In the same frequency band also decreased synchronized activity was found in the precuneus (BA7, BA31) extending into the posterior cingulate cortex (BA31). For gamma (30.5–44 Hz), analysis yielded decreased synchronized activity in the precuneus (BA 7, BA31) and the posterior cingulate cortex (BA 31) after alcohol intake.

Region of Interest Analysis

A region of interest analysis was conducted to verify if there was also a changes related to tinnitus intensity, next to tinnitus related distress areas. Hence an extra analysis was conducted demonstrating no significant differences ($P > 0.30$) for the right parahippocampus, left parahippocampus, left auditory cortex, right auditory cortex,before and after alcohol intake in delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma.

Alcohol Consumption Tinnitus Patients Versus Tinnitus Control Patients

A contrast analysis obtained no significant effect for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz).

Discussion

This is the first study observing the effect of alcohol as a coping mechanism for tinnitus-related distress and tinnitus intensity. We observed differences in alpha, beta and gamma frequency bands when comparing resting-state EEG before and after alcohol intake. More precisely increased synchronized alpha1 activity was found the

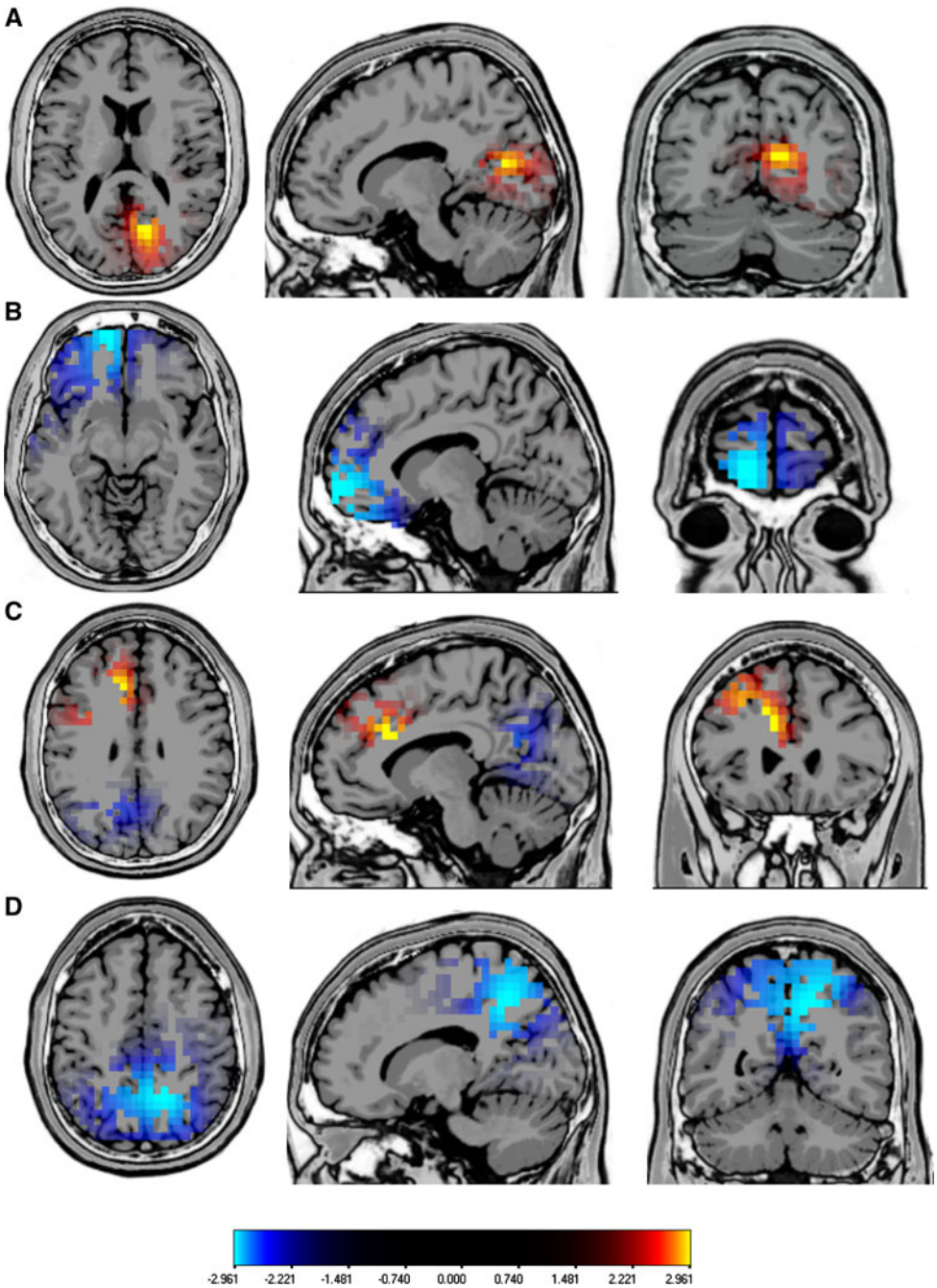

Fig. 2 sLORETA contrast analysis before and after alcohol intake ($P < 0.05$). **a** Alpha1, **b** alpha2, **c** beta3 and **d** gamma

posterior cingulate cortex and decreased synchronized alpha2 activity was demonstrated in orbitofrontal cortex, ventrolateral prefrontal cortex and subcallosal anterior cingulate cortex after alcohol intake. Increased synchronized activity was found dorsal anterior cingulate cortex and the left insula for beta and decreased activity in the precuneus. For the gamma frequency band decreased synchronized activity in the precuneus and the posterior cingulate cortex was demonstrated after alcohol intake. Region of interest analyses revealed however no differences in the different frequency bands before and after alcohol consumption. In addition a comparison between tinnitus patients that use alcohol as a coping mechanism but were sober and compare these with patients that do not use alcohol, revealed no significant effect. This latter finding indicates that the tinnitus patients that use alcohol as a coping mechanism do not have different brain activity in comparison to control tinnitus patients before alcohol consumption.

The observations are in accordance with studies on alcohol drinking which show that the orbitofrontal cortex, ventromedial frontal cortex, subcallosal anterior cingulate

cortex, posterior cingulate cortex, retrosplenial area, and the precuneus are influenced by seeing or smelling alcohol cues (Bragulat et al. 2008; Hermann et al. 2006; Tapert et al. 2003). Previous studies also showed that these brain areas, namely orbitofrontal cortex, ventromedial frontal cortex, subcallosal anterior cingulate cortex, posterior cingulate cortex, retrosplenial area, and the precuneus are also important in distress in general (Blood et al. 1999; Damasio 1996; Dias et al. 1996; Wheeler et al. 1993) and also for tinnitus-related distress (Muhlau et al. 2006; Vanneste et al. 2010a).

The results of this study reveal that after alcohol intake spontaneous activity is decreased for beta and gamma activity and increased for alpha activity in the posterior cingulate cortex extending into the precuneus. In highly distressed tinnitus patients typically the posterior cingulate cortex and precuneus shows decreased synchronized alpha activity (Vanneste et al. 2010a–d). Specifically, greater negative emotional intensity was associated with longer duration of activation in regions along the anterior medial prefrontal cortex and the posterior cingulate cortex in functional MRI (Waugh et al. 2010.). The posterior cingulate cortex has been proposed to be involved in cognitive evaluation and memorization of sensory input (Vogt et al. 1992). Hence, it can be hypothesized that alcohol intake might reduce the cognitive evaluation and/or the emotional intensity leading to stress release in highly distressed tinnitus patients.

Functional connectivity has shown that the dorsal anterior cingulate cortex is anticorrelated to the posterior cingulate (Margulies et al. 2007). Our results indicate that for the beta frequency band a decrease in the posterior cingulate cortex goes along with a decrease in the anterior cingulate cortex. Research already demonstrated that the anterior cingulate cortex is important for attentional control in a Stroop task (Aarts and Roelofs 2011; Bush et al. 2000; Bush et al. 1998; MacDonald et al. 2000; Pardo et al. 1990; Whalen et al. 1998) and that patients with severe tinnitus respond more slowly to a Stroop task paradigm than controls, indicating sustained selective and divided attention (Andersson et al. 2005; Andersson et al. 2000; Stevens et al. 2007). Based on this concept activation of the anterior cingulate cortex might keep the tinnitus out the focus of attention which ultimately can reduce distress.

Previous research has already shown that the orbitofrontal cortex is important for emotional processing of sounds (Blood et al. 1999; Damasio 1996; Dias et al. 1996; Wheeler et al. 1993). For example, patients with orbitofrontal cortex lesions had reduced self-evaluated perception of the unpleasantness of the acoustic probe stimulus (Angrilli et al. 2008). The orbitofrontal cortex is known to serve as a store of implicitly acquired linkages between factual knowledge and bio-regulatory states, including those that constitute feelings and emotions (Volz and von Cramon 2009). Furthermore, research showed more alpha activity in subcallosal anterior cingulate cortex for highly distressed tinnitus patients (Vanneste et al. 2010a). Increased activity in posterior subcallosal anterior cingulate cortex extending into nucleus accumbens-ventral tegmental area is involved in processing of aversive sounds (Zald and Pardo 2002) and unpleasant music (Blood et al. 1999) as well as tinnitus (Muhlau et al. 2006). It has also been implicated as the key component of social distress (Masten et al. 2009), suggesting activity in this area might not be specific for tinnitus. The subcallosal anterior cingulate and the ventromedial prefrontal cortex have been implicated in negative feedback regulation of the amygdala and arousal (Maren and Quirk 2004). The same brain regions, which are rich in μ opioid receptors, have been implicated in the regulation of endogenous pain inhibition circuits (Zubieta et al. 2001). Also the subcallosal anterior cingulate cortex and the ventromedial prefrontal cortex play important roles in the regulation of emotional arousal and of pain perception (Valet et al. 2004). In line with these findings the results of this study showed decreased synchronized alpha activity in the orbitofrontal cortex, subcallosal anterior cingulate cortex after alcohol intake suggesting that the tinnitus might become emotionally less relevant and less stressful leading to reduction of both the tinnitus distress and intensity perception.

Analysis of the auditory cortex and parahippocampus before and after alcohol intake revealed no significant differences for the different frequency bands. In particular, the gamma band is of interest, as previous research already illustrated that tinnitus perception correlates to sustained high frequency gamma band activity in auditory cortex (Weisz et al. 2007) and that tinnitus intensity correlates with gamma band current density in the contralateral auditory cortex (van der Loo et al. 2009). The involvement of the parahippocampal area might be related to the constant updating of the tinnitus percept, and as such preventing habituation (De Ridder et al. 2006). As our results indicate that after alcohol consumption no differences occur within this region, this might suggest that tinnitus is still present, but might be less distressing or less perceived consciously. Previous research already demonstrated that the precuneus and dorsal anterior cingulate cortex are important in conscious awareness and show significantly greater gamma band synchronization power during conscious awareness (Dehaene and Naccache 2001; Rees et al. 2002; Stephan et al. 2002; Tsuchiya and Adolphs 2007). Our results indicate a decrease in gamma band activity in the precuneus extending in the posterior cingulate cortex, which might suggest a decrease in conscious awareness of the tinnitus. However further research is needed to further confirm this hypothesis.

One limitation of the current study was that patients were aware of the aim of the study. However, the patients used alcohol as a coping mechanism on a daily basis. We furthermore want to clearly state that alcohol consumption is not encouraged are a viable method to manage the distressing effect of tinnitus as there are potential risk involved (i.e. addiction…).

In conclusion, the results of this study demonstrate that for some patients alcohol can help in coping with tinnitus transiently and has a clear impact on orbitofrontal cortex, ventromedial frontal cortex, subcallosal anterior cingulate cortex, posterior cingulate cortex, and the retrosplenial area. These brain areas are important in distress in general and in tinnitus related distress specifically. Alcohol consumption does change these distress related brain areas leading to a reduction in tinnitus related distress. However, brain areas involved in the tinnitus perception such as the auditory cortex and parahippocampus did not show any differences before and after alcohol intake, a feature which requires elucidation by further studies.

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