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Research paper

Top-down and bottom-up neurodynamic evidence in patients with tinnitus

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ABSTRACT

Although a peripheral auditory (bottom-up) deficit is an essential prerequisite for the generation of tinnitus, central cognitive (top-down) impairment has also been shown to be an inherent neuropathological mechanism. Using an auditory oddball paradigm (for top-down analyses) and a passive listening paradigm (for bottom-up analyses) while recording electroencephalograms (EEGs), we investigated whether top-down or bottom-up components were more critical in the neuropathology of tinnitus, independent of peripheral hearing loss. We observed significantly reduced P300 amplitudes (reflecting fundamental cognitive processes such as attention) and evoked theta power (reflecting top-down regulation in memory systems) for target stimuli at the tinnitus frequency of patients with tinnitus but without hearing loss. The contingent negative variation (reflecting top-down expectation of a subsequent event prior to stimulation) and N100 (reflecting auditory bottom-up selective attention) were different between the healthy and patient groups. Interestingly, when tinnitus patients were divided into two subgroups based on their P300 amplitudes, their P170 and N200 components, and annoyance and distress indices to their tinnitus sound were different. EEG theta-band power and its Granger causal neurodynamic results consistently support a double dissociation of these two groups in both top-down and bottom-up tasks. Directed cortical connectivity corroborates that the tinnitus network involves the anterior cingulate and the parahippocampal areas, where higher-order top-down control is generated. Together, our observations provide neurophysiological and neurodynamic evidence revealing a differential engagement of top-down impairment along with deficits in bottom-up processing in patients with tinnitus but without hearing loss.

1. Introduction

Tinnitus is the illusory perception of sound in the absence of an external sound (Jastreboff and Sasaki, 1994; Mohamad et al., 2016). People with tinnitus experience difficulties in mental concentration and impaired cognitive efficiency (Hallam et al., 2004). Based on functional imaging studies, it is generally accepted that tinnitus is associated with maladaptive neuro-plasticity because of impairment in the auditory system (Faber et al., 2012). Most symptoms of tinnitus can be attributed to hyperactivity and reorganization in the auditory central nervous system (Eggermont and Roberts, 2004; Kaltenbach and Afman, 2000; Muhlnickel et al., 1998; Salvi et al., 2000) with coactivation of non-auditory brain structures such as the dorsolateral prefrontal cortex (DLPFC; Schlee et al., 2009b; Vanneste et al., 2010) and anterior cingulate cortex (ACC; Muhlau et al., 2006; Vanneste et al., 2010). The DLPFC is essential for higher-order cognitive control functions and goal-directed behaviors (Fuster, 2008; McNamee et al., 2015; Miller and Cummings, 2007), and the ACC executes top-down inhibitory control (Johnston et al., 2007; Silton et al., 2010). These prefrontal areas have also been found to be involved in auditory attention (Alain et al., 1998; Lewis et al., 2000; Voisin et al., 2006), thus resulting in top-down modulation of auditory processing (Mitchell et al., 2005). This has been further confirmed by an electrophysiological study indicating that tinnitus might occur as a result of dysfunctional top-down inhibitory processes (Norena et al., 1999).

Although it has been reported that tinnitus influences auditory selective attention (Andersson et al., 2000), with patients reporting

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Abbreviations

ABR	auditory brainstem response
ACC	anterior cingulate cortex
ANOVA	analysis of variance
BA	Brodmann area
CNV	contingent negative variation
DP	distortion product
DPOAE	distortion product otoacoustic emission
DTF	directed transfer function
EEG	electroencephalogram
EOG	electrooculogram
ERP	event-related potential
FDR	false discovery rate
HL	hearing level
ICA	independent component analysis
ISI	inter-stimulus interval
K-THI	Korean version-tinnitus handicap inventory
nHL	normal hearing level
OAE	otoacoustic emission
PTA	pure tone audiometry
ROI	region of interest
SD	standard deviation
SNR	signal-to-noise ratio
SPL	sound pressure level
TE	transient evoked
TEOAE	transient evoked otoacoustic emission
VAS	visual analog scale

concentration difficulties due to their tinnitus (Andersson et al., 1999; Heeren et al., 2014), uncertainty still exists regarding the direction of causation between tinnitus and cognitive processes of attention (Andersson and McKenna, 2006; Mohamad et al., 2016). This is because of a lack of evidence supporting the claim that tinnitus severity negatively influences sustained attention (Hallam et al., 2004; McKenna and Hallam, 1999; McKenna et al., 1995). Moreover, while some studies showed that tinnitus leads to altered performance on attention-related tasks (Hallam et al., 2004; Rossiter et al., 2006; Stevens et al., 2007), others have suggested that these alterations might rely on reduced top-down executive control (i.e., the ability to resolve conflicts among responses and voluntarily regulate the allocation of attention resources) rather than on attentional processes per se (Andersson et al., 2000; Rossiter et al., 2006). Accordingly, it is still debatable whether these deficits are the consequence of general changes in the executive control of attention, the consequence of genuine alterations in a specific attentional ability, or simply the result of a general slowdown in cognitive processing (Heeren et al., 2014).

Nevertheless, among several cognitive processes putatively responsible for the generation of tinnitus, attention has been considered to be one of the most potent factors contributing to both its development and modulation (Gu et al., 2010; Hoare et al., 2012; Husain et al., 2011; Jastreboff and Jastreboff, 2006; Searchfield et al., 2012; Zenner et al., 2006). Preliminary evidence has consistently supported the claim that the severity of self-reported tinnitus symptoms negatively influences 'executive' attention (Heeren et al., 2014; Jackson et al., 2014). For example, Heeren et al. (2014) reported that the degree of executive control impairment was correlated with the duration of tinnitus. Accordingly, tinnitus seems to specifically alter the top-down 'executive' control subcomponent of attention. Tinnitus perception can also be subject to attentional bottom-up processes that are influenced by stimulus salience. Interactions between top-down and bottom-up processes contribute to the allocation of limited perceptual processing resources to one or more sound-parameter dimensions (Caporello Bluvas and Gentner, 2013). In general, active redirection of attention, embedded in a top-down process, may precede an event or stimulus, and bottom-up sensory processing is then guided by such top-down processing as a specific reallocation of attention relevant to the type of stimulus to follow or task to be performed. In this way, top-down modulation can increase the efficiency of perceptual identification in response to directed attention. Presumably, top-down and bottom-up processes of attention may share neural resources, although their expression in brain networks may depend on the specific types of task stimuli and the behavioral and cognitive performance requirements of the task procedure (Roberts et al., 2013).

Based on these perceptual processes, lower level acoustic stimuli are modulated by sensory-driven bottom-up processing for the transmission of an auditory cue to higher level processes, and top-down processes selectively direct it to objects of interest in an ambiguous situation. Neural mechanisms that direct the focus of awareness are commonly described as those responsible for top-down attention-like functions (Roberts et al., 2013). As top-down attentional processes are strongly associated with the prediction of an internal model through prior knowledge of sound sources (Bayat et al., 2013), the mismatch between predicted and experienced inputs due to peripheral auditory deafferentiation facilitates neuroplastic changes in the subcortical neuro-modulatory system (Vanneste and De Ridder, 2016). These changes result in persistent activation of the central attention network, which underlies tinnitus (De Ridder et al., 2011; Jastreboff and Hazell, 1993, Jastreboff and Jastreboff, 2000; Roberts et al., 2013; Weisz et al., 2005). In fact, an attentional network involving the auditory cortex has been regarded as a possible candidate for the generation and modulation of tinnitus (Brennan and Jastreboff, 1989; Jastreboff, 1990, 2007; Jastreboff et al., 1996). For instance, the ACC and fronto-parieto-temporal areas are known to be the anatomical bases of an awareness network that functionally connects to sensory cortices, such as the primary auditory cortex (Boly et al., 2004). Similarly, persistent tinnitus (chronic ringing of the ears) tends to consciously decrease while people with tinnitus focus on daily activities that require attention and do not require auditory processing (Roberts et al., 2013). In addition, more than 80% of people with normal hearing experience tinnitus in a soundproof room (De Ridder et al., 2011), and some patients with peripheral auditory impairment often do not complain of tinnitus. Accordingly, it seems that high-order auditory attention processing may play an important role in the generation of tinnitus.

It is not yet clear how such early perceptual processes solely contribute to the generation or modulation of tinnitus, as most earlier studies did not exclude tinnitus patients with peripheral auditory disorders (Moazami-Goudarzi et al., 2010; Schlee et al., 2009a; Song et al., 2015b), which subsequently resulted in inconsistencies due to a failure of isolating a central auditory perceptual process from peripheral auditory deficits. It is obvious that most cases of tinnitus are typically associated with a hearing threshold shift (Emmerich et al., 2002). Even patients with tinnitus have apparently normal hearing on conventional tests, but a marked reduction of auditory nerve output at high frequency sound levels has been reported (Schaette and McAlpine, 2011). This

indicates that damage to the peripheral auditory system is an essential prerequisite for the generation of tinnitus. In particular, considering that patients with tinnitus perceive the phantom sound in the deafferented frequencies (Norena et al., 2002), it is reasonable that peripheral cochlear damage would be a main trigger for the generation of tinnitus. Moreover, studies of neural plasticity in the auditory cortex (Fritz et al., 2003; Weinberger, 2007) demonstrate that cholinergic neuromodulators gate synaptic plasticity for unexpected and behaviorally relevant stimuli, which accounts for a bottom-up attention-like function (Roberts et al., 2013). Taken together, the above observations indicate that the mechanisms by which attention (top-down or bottom-up) is involved and how it is engaged in the neuroplastic changes underlying tinnitus remain to be further discussed (Roberts and Bosnyak, 2010).

Using a classical oddball paradigm (as a top-down directed task) in comparison to a passive listening paradigm (as a bottom-up directed task), we investigated whether the top-down or the bottom-up component is significantly modulated in patients with tinnitus but without hearing loss, depending on the experimental conditions. These modulations may be reflected in both event-related potentials (ERPs) and event-related oscillations. In particular, to avoid possible confounding effects of distorted auditory input (bottom-up) features due to peripheral auditory damage, only patients with tinnitus but without hearing loss were recruited for the present study. The oddball paradigm is traditionally assessed by the P300 (Katayama and Polich, 1999), which is a positive ERP peak typically observed between 350 and 600 ms poststimulus (Picton, 1992; Sutton et al., 1965). In classical ERP studies, it has been shown that the P300 amplitude is positively related to the degree of attention required (Johnson, 1988; Lammers and Badia, 1989; Polich and Mcisaac, 1994). Since the present study focused on both top-down and bottom-up attentional processes, we wanted to further investigate whether the EEG neurodynamics of higher attentional resourcing group (i.e., T1) behave differently from those of the lower attentional resourcing group (i.e., T2) in both top-down and bottom-up processes. Thus, we simply divided all the tinnitus patients into two subgroups by a median-split based on their P300 amplitudes. If a double dissociation is observed in the results, a compelling differential effect of tinnitus on top-down or bottom-up processing could be shown. Our study may therefore provide one of the significant rationales for studying tinnitus pathology with joint top-down and bottom-up processing concerns, rather than either one independently.

In order to investigate the neurodynamic causal connectivity across principal brain regions in auditory processes, we also performed Granger causality analysis. Brain causal connectivity during the assessment of auditory stimuli may provide more advanced understandings of communicative directional flow (He et al., 2011; Ioannides, 2007) of auditory information in healthy controls vs. patients with tinnitus. To date, there has been a lack of neurodynamic evidence showing that subcortical top-down regions (e.g., hippocampus) causally influence the auditory cortex within attentional networks. Since EEG theta activity has been considered to be a possible electrophysiological correlate of top-down regulation in memory systems (Sauseng et al., 2008), such as short-term memory (Vertes, 2005), and ongoing EEG alpha activity is associated with sustained attention (Orekhova et al., 2001), we investigated both theta and alpha oscillations. EEG alpha and theta oscillations reflect cognitive and memory performance (Klimesch, 1999). Furthermore, since prestimulus EEG alpha activity has been known to reflect prestimulus top-down processing (Min and Herrmann, 2007, Min and Park, 2010) and inhibitory control of task-irrelevant processing (Klimesch et al., 2007; Min and Park, 2010), we performed EEG spectral analysis during both prestimulus and poststimulus periods.

2. Materials and methods

2.1. Participants

EEG data were recorded from 15 patients with tinnitus (7 women; mean age, 30.2 years; age range, 17–41 years) and 15 age/sex-matched healthy volunteers (7 women; mean age, 28.7 years; age range, 20–43 years), in accordance with the ethics guidelines established by the Institutional Review Board of Hallym University College of Medicine (IRB No. 2016-I013) and the Declaration of Helsinki (World Medical Association, 2013). The study was undertaken with the understanding and written consent of each participant. All of the patients exhibited definite tinnitus for at least 3 months, and normal hearing on conventional hearing testing. Normal hearing was defined as subjects possessing (1) pure tone audiometry (PTA) thresholds of 25 dB hearing level (HL) or better at all octave frequencies from 250 to 8000 Hz, (2) a transient evoked (TE) otoacoustic emission (OAE) with a signal-to-noise ratio (SNR) of more than 5 dB and distortion product (DP) OAEs with SNR of more than 3 dB on OAE tests, (3) waves I-III inter-peak latency of less than 2.4 ms and wave V latency of less than 6.2 ms on auditory brainstem response (ABR) tests, and (4) a normal tympanic membrane on otoscopy. To minimize the possibility of hidden hearing loss at high frequencies, and normalize the patients' cognitive ability with that of the healthy volunteers, patients were excluded from our study if they (1) were older than 50, (2) showed active or prior history of vertigo, Meniere disease, noise exposure, hyperacusis or psychiatric problems, (3) used ototoxic drugs, and (4) had poorly defined or complex tinnitus (failure of tinnitus pitch matching). In addition, the patients filled in a tinnitus questionnaire, including a visual analog scale [VAS, ranging from 0 to 10 (0: not annoyed, 10: extremely annoyed)] and a Korean version-tinnitus handicap inventory (K-THI) questionnaire, translated from the original THI of the American tinnitus association (Newman et al., 1996). For the control group, it was confirmed that the healthy participants did not exhibit tinnitus or evidence of cochlear damage, as assessed by the PTA, OAE, and ABR tests. The control group was thus otolaryngologically and audiologically normal.

2.2. Audiometric evaluation and tinnitus test

Clinically detailed audiometric and otoscopic evaluations were performed in all participants. Hearing was measured at a frequency range of 250–8000 Hz with calibrated pure tone audiometry (GSI AudioStar Pro™, Grason Stadler, Eden Prairie, MN) in a soundproof audio booth. Recording of OAEs and their spectrum analysis were carried out using an OAE measuring device (Echoport ILO-292®, Otodynamics Ltd., Hatfield Herts, UK). For the clinical documentation of TEOAEs, nonlinear click stimuli (80 μs, rate of 50/s using the nonlinear mode) were presented at a level adjusted to an 84.5 dB peak. Each accepted sweep averaged the response to two interleaved waveforms, which were combined in a single OAE result. The SNR and reproducibility were displayed in the response window. For the clinical documentation of DPOAEs, two continuous primary tones were presented ($f1<f2$, 1.21 frequency ratio) at a stimulus level of 70 dB sound pressure level (SPL). DP-grams were displayed in ¼ octave steps over a frequency range of the $f2$ that extended from 1001 to 8008 Hz (i.e., 1001, 2002, 3003, 4004, 5005, 6006, 7007, and 8008 Hz). SNRs were obtained from each DPOAE measure. ABRs were measured by a Navigator® Pro system (Bio-Logic Systems Corp., Mundelein, IL). Click sound of alternating

polarity (50 μsec, 11/s stimulation rate) was presented through insert-earphones at a level of 90 dB normal hearing level (nHL). The amplifier bandwidth ranged from 100 to 3000 Hz with amplification of 100,000 times. The number of sweeps for a reliable averaged response to each click sound was between 1000 and 1500. The latencies of waves I, III, and V, and the inter-aurally inter-peak time intervals of I–III and III–V were used as parameters for assessing the integrity of the peripheral auditory system.

For tinnitus pitch matching in the patients with tinnitus, a two alternative forced choice method (Goldstein and Shulman, 1997) was employed. Pulsed pairs of tone ranging from 125 Hz to 12 kHz were alternatively presented at 10–15 dB above the patient's hearing threshold (i.e., a comfortable level for the patient) to the affected ear. Subsequently, patients with tinnitus were asked to choose which one most closely matched their tinnitus. These procedures were repeated seven to nine times for a correct match. After patients determined which stimulus was closest to the pitch of their tinnitus, the same two alternative forced choice procedure was repeated with the tinnitus matched tone and the octave above and below it to avoid octave confusion. If patients describe their tinnitus as hissing or swishing, various sounds including narrowband noise or white noise as well as a pure tone were presented to judge the tinnitus quality. In patients with bilateral tinnitus (patient ID 3, 6, and 11; Table 1), the tinnitus matching procedure was performed on each ear individually. If the patient exhibited differences in tinnitus between the two ears, the tinnitus pitch was decided based on the side considered more annoying by the patient.

However, it is possible that peripheral damage, especially at high frequencies, could be present, but not detected by routine audiometry (Adjamian et al., 2012). For example, some patients with high-frequency tinnitus, despite having audiometrically normal thresholds, are not necessarily free of any deafferentiation in the cochlea (Weisz et al., 2006). Kujawa and Liberman (2009) have shown that the recovery of audiometric thresholds to normal levels from temporary hearing loss does not indicate the reversal of damage to inner ear structures. Schaette and McAlpine (2011) also suggest that tinnitus patients with apparently normal audiograms may have 'hidden hearing loss', which is defined as damage to the auditory nerve fibers. Hence, although all the tinnitus patients in the present study showed normal latencies in waves I-III on ABRs, and normal OAEs [generally indicating the integrity of peripheral auditory nerves (Moller and Jannetta, 1982; Moller et al., 1981), and normal function in their cochlear hair cells (Kemp, 1978; Mills and Rubel, 1994)], 'normal hearing' in this paper refers to participants who had normal hearing ability in the typical frequency range of 250–8000 Hz using conventional tests (e.g., PTA, OAE, ABR, and otoscopic examination). We are also aware that this classification does not indicate the absence of deafferentiation altogether.

2.3. Experimental design

During EEG acquisition, the participants performed the following two tasks: (1) an auditory oddball task and (2) a passive listening task (see Fig. 1). In the oddball paradigm, two stimuli were presented in random order. One stimulus occurred less frequently than the other (i.e. the oddball). The participant was required to discriminate the rare stimulus (target) from the frequent one (standard) by noting the occurrence of the target, typically by pressing a button (Duncan-Johnson and Donchin, 1977; Polich, 1989; Verleger and Berg, 1991). Because the P300 component of ERP reflects fundamental cognitive processes (Donchin and Coles, 1988; Johnson, 1988; Picton, 1992; Polich, 1993) and is often obtained using the oddball paradigm (Katayama and Polich, 1999), the oddball task was employed in the present study. The P300 elicited by the target in this task is a large, positive-going potential that is largest over the parietal electrode sites and occurs at about 300 ms poststimulus in normal young adults.

During the auditory oddball task, participants were instructed to respond by pressing a button with one hand whenever the rarely presented auditory target stimulus was detected and to press another button with the opposite hand if the frequently presented auditory standard stimulus was detected. Response hands were counterbalanced across participants. The auditory stimuli were presented to participants using binaural insert earphones (EARTONE 3A®, 3M Company, Indianapolis, IN). The oddball task consisted of 80 target stimuli (20% occurrence probability in the stimulus set) and 320 standard stimuli (80% occurrence probability in the stimulus set), which were presented in random order. Because the oddball task required participants' active responses based on a cognitive decision regarding the presented stimulus types during the performance of the task, the results from this oddball task were interpreted principally as auditory top-down effects. The frequency of target stimuli for healthy participants was 8 kHz, which was the dominant tinnitus frequency of the patients. The frequency of the standard stimulus was 500 Hz. The length of each auditory stimulus was 200 ms, with 10 ms for each rising and falling phase. All the auditory stimuli were generated using the Adobe Audition software (version 3.0, Adobe Systems Incorporated, San Jose, CA). Each auditory stimulus was presented for 200 ms with a variable inter-stimulus interval, ranging randomly between 1300 ms and 1700 ms, and centered at 1500 ms. The acoustic intensities of the stimuli were controlled and were set

Table 1
Overview of the patients with tinnitus.

ID	Subgroup	Sex	Age (yrs.)	Tinnitus frequency (kHz)	Deficit side of ear	Etiology	Right[a] (dB HL)	Left[a] (dB HL)
1	T2	F	22	8	Left	Idiopathic	−2	2
2	T1	F	30	8	Right	Idiopathic	5	5
3	T2	F	35	8	Both	Idiopathic	10	9
4	T1	M	23	8	Left	Idiopathic	14	10
5	T1	M	32	2	Left	Idiopathic	2	−1
6	T2	M	19	8	Both	Idiopathic	5	5
7	T1	M	26	8	Left	Idiopathic	0	−1
8	T2	M	26	8	Left	Idiopathic	2	1
9	T1	M	17	8	Left	Idiopathic	5	6
10	T1	M	35	8	Left	Idiopathic	4	2
11	T2	F	40	0.25	Both	Idiopathic	9	11
12	T1	F	41	8	Left	Idiopathic	0	0
13	T2	F	28	0.125	Right	Idiopathic	4	5
14	T2	M	41	0.125	Right	Idiopathic	9	8

[a] Pure tone audiometry (PTA) threshold.

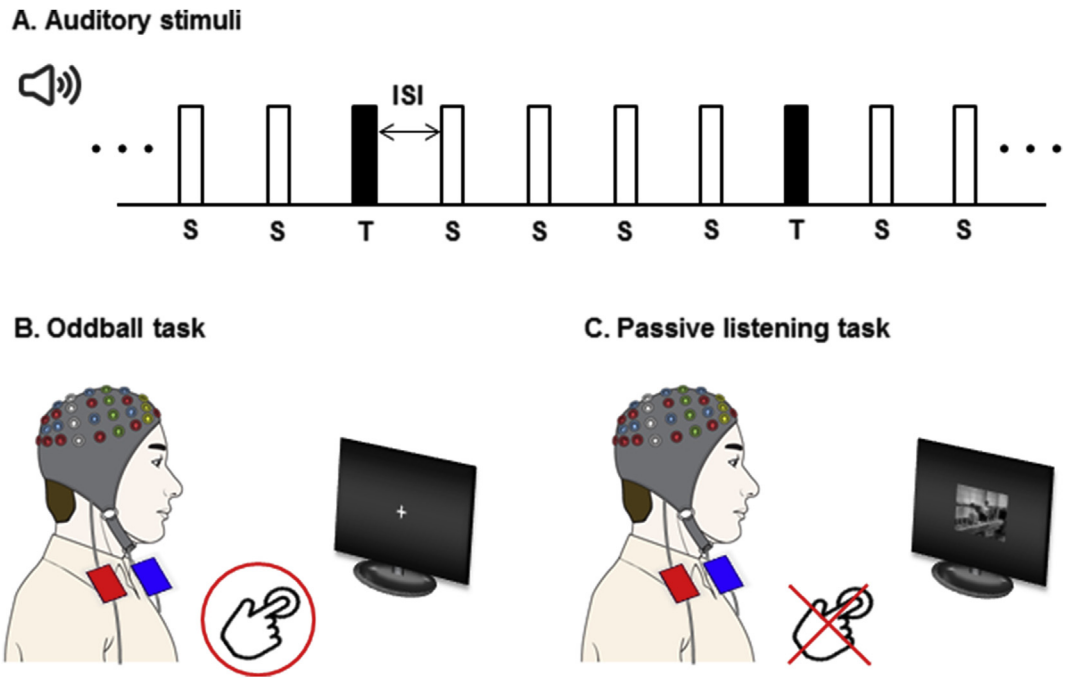


Fig. 1. Experimental design. (A) A task flow diagram with a series of auditory stimuli comprising both rarely presented target sounds (with a 20% occurrence probability) and frequently presented standard sounds (with an 80% occurrence probability). White bars and the letter 'S' indicate standard stimuli, and black bars and the letter 'T' represent target stimuli. The auditory stimuli were presented to participants using binaural insert earphones (depicted as red and blue boxes with connected lines). The frequency of the standard sound is 500 Hz, and that of the target is 8 kHz for healthy participants and an individual tinnitus pitch-matched frequency for patients with tinnitus. Each stimulus was presented for 200 ms with variable inter-stimulus intervals (ISI: 1300–1700 ms). During the oddball task (B: for top-down analyses), participants were instructed to perform a sound-discrimination task by pressing a button. In contrast, during the passive listening task (C: for bottom-up analyses), participants were instructed to watch a silent movie without responding to the presented auditory sounds. In both the oddball and passive listening tasks, the same series of auditory stimuli (with 80 target and 320 standard stimuli) were used.

to 50 dB SPL for both healthy and patient groups. The volumes of auditory stimuli were measured by a sound level meter (Type 2250, Brüel & Kjær Sound & Vibration Measurement, Denmark). During the oddball task, the participants were instructed to fix their eyes on a fixation cross presented on the monitor in front of them to minimize any possible distractive effects due to alterations in visual attention.

On the other hand, since auditory bottom-up attention is a sensory-driven selection mechanism for shifting perception toward a salient auditory subset within an auditory scene (Kaya and Elhilali, 2014), the same stream of auditory stimuli used in the oddball task was also passively heard by the participants; subsequent stimulus-related EEG dynamics were investigated in terms of auditory bottom-up effects using differences in the physical features of the stimulus type (either a frequently presented at 500 Hz or a rarely presented individual tinnitus-pitch-matched sound). As shown in Table 1, the frequencies of the target stimuli in the oddball paradigm for the patient group were their individual tinnitus pitch-matched frequencies. During the passive listening task, in order to distract the participants' attention from the presented auditory stimuli, a black/white and silent movie ('Modern Times': a 1936 comedy film directed by Charlie Chaplin) was shown to the participants, who were instructed to watch the movie and not respond to the simultaneously presented auditory stimuli through the binaural insert earphones. These sounds were the same stream of target and standard stimuli used in the oddball task. The movie was played on a black monitor and the screen window was subtended within the visual angle of 6.5° at a distance of 80 cm (Kaashoek, 2008). The image thus fell onto the focal retinal region (the most sensitive portion of the retina) to minimize possible eye movements.

2.4. EEG acquisition and analytical methods

To measure the EEG signals, we used a BrainAmp DC amplifier (Brain Products, Germany) with an actiCAP consisting of 32 Ag/AgCl electrodes (Brain Products, Germany). The electrode placement was in accordance with the international 10–10 system: a reference electrode was placed on the tip of the nose, and the AFz electrode was used as a ground. Electrode impedances were maintained below 5 kΩ before the recordings. The EEG was recorded at 1000 Hz (analog band-pass filter, 0.5–70 Hz). Eye movement activity was monitored using an electrooculogram (EOG) electrode placed suborbitally onto the left eye, and vertical and horizontal electro-ocular activities were computed using two pairs of electrodes placed vertically and horizontally with respect to both eyes (i.e., Fp1 and EOG for the vertical EOG; F7 and F8 for the horizontal EOG). EOG artifacts were corrected offline using the independent component analysis (ICA) method (Makeig et al., 1997). For further analyses, EEG data were epoched from 500 ms prestimulus to 1000 ms poststimulus. Epochs containing other artifacts (maximum amplitude ± 100 μV and maximal gradient voltage step 50 μV/ms) were rejected from further analyses. One healthy participant and one patient with tinnitus were excluded from further analyses because of poor data quality.

Five dominant ERP components were analyzed: contingent negative variation (CNV), N100, P170, N200, and P300. CNV develops gradually before stimulus onset in a person who is actively predicting the occurrence of some significant stimulus requiring a response. Thus, CNV is thought to reflect the expectation of a subsequent event prior to stimulation (Birbaumer et al., 1990; Rohrbaugh et al., 1976; Walter et al., 1964). Depending on the areas of the brain in which the activity was most pronounced (i.e.,

regions of interest), the following corresponding electrodes were selected for analysis: for CNV (mean amplitude 150–0 ms prestimulus), three centro-parietal electrodes (Pz, CP1, and CP2); for N100 (minimum peak 50–150 ms poststimulus), three frontocentral electrodes (Cz, FC1, and FC2); for P170 (maximum peak 120–220 ms poststimulus), three fronto-central electrodes (Cz, FC1, and FC2); for N200 (minimum peak 150–250 ms poststimulus), five fronto-centro-parietal electrodes (FC1, FC2, Cz, CP1, and CP2); and for P300 (maximum peak 200–400 ms poststimulus), six centro-parietal electrodes (Cz, CP1, CP2, Pz, P3, and P4). As dipole-sources for auditory processing generate the most prominent activity around the vertex of the brain (i.e., the location of the Cz electrode; Näätänen et al., 1992), we consistently observed a central-dominant ERP scalp distribution. All time windows were based on their grand averages while taking individual variations into account. Baseline corrections were performed using the 500–0 ms prestimulus interval. The amplitudes and latencies of each peak were compared for ERP analysis. An offline filter (0.5–30 Hz) was applied to the final results to display the ERP components clearly.

The power of oscillatory activity was investigated by convolving the EEG signals with Morlet wavelets (Herrmann et al., 2005). The wavelet transform was conducted for each individual trial, and the absolute values of the resulting transforms were averaged. This measure of signal amplitude in single trials reflects the *total* activity for a certain frequency range. On the other hand, to compute the *evoked* activity (phase-locked to the stimulus), the wavelet transform was applied to the averaged evoked potential. Because the brain oscillations in the alpha band have been determined to be the most dominant brain activity during relaxed (i.e., mentally inactive) wakefulness, we investigated whether prestimulus total alpha activity reflects possible differences in preparatory mental states for upcoming task performance across the healthy and patient groups. In addition, as EEG theta activity has been considered to be a possible electrophysiological correlate of top-down regulation in memory systems (Sauseng et al., 2008), we also analyzed evoked theta activity. Other frequency bands were not analyzed in the present study, as they did not exhibit observable differences across the experimental conditions in the grand-averaged time-frequency plots. We confined the alpha activity to the frequency range between 8 and 13 Hz, and the theta activity to the frequency range between 3 and 8 Hz. The frequencies used in the wavelet analyses were determined individually for every participant, as the dominant peak frequency within each alpha or theta frequency band varied between participants.

To measure the prestimulus total activity in the alpha band, we measured the maximum power within a time window from 400 to 0 ms prior to stimulus onset. No baseline correction was applied to the total alpha power, as alpha activity in a prestimulus period vanishes after baseline correction. For the evoked theta activity, we assessed the maximum theta power within the time window between 0 and 500 ms after stimulus onset. All of the time windows were selected based on their grand-averages and individual variances. Because there was no stimulus-evoked activity prior to stimulus onset, baseline corrections were performed on the evoked theta activity using the prestimulus interval of 400 to 100 ms prior to stimulus onset.

Based on the areas of the brain where the EEG oscillatory activity was most pronounced, the following corresponding electrodes for each frequency band were selected for spectral analysis: three parietal electrodes (Pz, P3, and P4) for the prestimulus total alpha activity, and four fronto-central electrodes (Fz, Cz, FC1, and FC2) for the evoked theta activity. The averaged amplitudes, latencies, and frequencies across the selected electrodes were analyzed at their dominant peaks within the corresponding time window. All of the measures were analyzed using a repeated measures analysis of variance (ANOVA) with a between-subjects factor [labeled group (healthy and patient)] and two within-subjects factors [labeled task (oddball and passive listening) and stimulus-type (target and standard)]. When necessary, the Greenhouse–Geisser correction was used. In order to further investigate the characteristic neurophysiological behaviors of the patients with tinnitus, post hoc tests were performed on the two subgroups, to which the patients were assigned using a median-split based on their P300 amplitudes (threshold: 7.354 μV) during the processing of target stimuli in the oddball task. The T1 group consisted of patients with higher P300 amplitudes and the T2 group consisted of those with lower P300 amplitudes. The P300 amplitude was used because it is a potent indicator of the cognitive ERP components reflecting fundamental cognitive information processes (Donchin and Coles, 1988; Duncan-Johnson and Donchin, 1982; Johnson, 1988; Picton, 1992; Polich, 1993), and because the degree of top-down involvement in tinnitus pathology was the main question of the present study. The results of the T1 and T2 subgroups were statistically compared with their age/sex-matched normal control subgroups, which were split from the original healthy volunteer group. One-way ANOVAs were used for these post hoc tests and for the analysis of THI (e.g., annoyance). A false discovery rate (FDR) of $q < 0.2$ (Benjamini and Hochberg, 1995) was used to correct for multiple comparisons, as q-values between 0.1 and 0.2 after FDR correction are known to be acceptable for this purpose (Genovese et al., 2002). All analyses were performed using MATLAB (ver. R2015b, MathWorks, Natick, MA) or SPSS Statistics (ver. 22, IBM, Armonk, NY).

2.5. Granger causality analysis

The spatiotemporal distributions of brain activity and network behavior provide significant psychophysiological information. It is thus important to image brain functional connectivity to understand brain function (He et al., 2011; Ioannides, 2007). We conducted Granger causality (Granger, 1969) analysis in the present study. Unlike other model-based connectivity analyses, such as structural equation modeling from fMRI paradigms (Tomarken and Waller, 2005), Granger causality analysis can be used to determine directional causal interactions among electrophysiological signals (He et al., 2011). In particular, the directed transfer function (DTF) has been developed to describe causality among an arbitrary number of signals (Astolfi et al., 2007; Babiloni et al., 2005). Granger causality analysis has the potential to noninvasively delineate brain network connectivity (Astolfi et al., 2004; Babiloni et al., 2005; Ding et al., 2007). Using the eConnectome software (Dai and He, 2011, 2012; He et al., 2011), functional connectivity was mapped for each experimental condition. Granger causality was investigated at the grand-averaged evoked theta activity. The eConnectome software enabled cortical source imaging and the subsequent connectivity analysis of cortical source activity.

In the eConnectome software (He et al., 2011), the cortical current density (CCD) source model (Dale and Sereno, 1993) was used to solve the inverse problem from the scalp EEG to cortical source distribution using minimum norm estimate (MNE) or lead field weighted minimum norm (WMN) algorithm with the aid of the boundary element method (He et al., 1987). A high-resolution cortical surface consisting of 41,136 triangles was segmented and reconstructed for visualization from the MRI images of the Montreal Neurological Institute (MNI) brain using the Curry software package (Compumedics NeuroScan, Charlotte, NC). A down-sampled cortical surface with 7850 dipoles formed the calculated source space. The dipoles were constrained to the gray matter with their orientations perpendicular to the local cortical surface. A scalp

surface, a skull surface, and a brain surface were segmented and reconstructed from the MNI brain. The scalp surface, consisting of 2054 triangles, formed the sensor space. Such generic realistic head models have been suggested to provide improved accuracy in source analysis (Darvas et al., 2006; Valdes-Hernandez et al., 2009). A high-resolution lead field matrix (2054 × 7850) was pre-computed relating all the scalp triangles to the sources. A specific lead field matrix for a user-defined electrode montage can thus be constructed as a subset of the pre-computed lead field matrix to solve the inverse problem. The solution of the inverse problem yielded estimates of continuous time courses for cortical sources. The region of interest (ROI) source can then be computed by averaging estimated cortical sources in the ROI. With the ROI sources, the cortical ROI functional connectivity can be computed using the DTF method in selected frequency components among the selected ROIs.

Based on the most pronounced cortical activity, as estimated by the eConnectome software, 16 bilateral ROIs were selected (i.e., Brodmann area (BA) 24L/R, BA 27L/R, BA 32L/R, BA 39L/R, BA 40L/R, BA 41L/R, BA 42L/R, and BA 46L/R) to map directional connectivity. These cortical areas have significant roles in auditory processing. BA 24 is the ventral ACC and BA 32 is the dorsal ACC. The ACC is associated with top-down attentional inhibitory regulation (Johnston et al., 2007; Silton et al., 2010) and conflict monitoring (Apps et al., 2012; Borsa et al., 2016; Botvinick et al., 2004). BA 27 is the hippocampus/parahippocampal region and is associated with short-term memory function (Vertes, 2005), auditory-verbal memory function (Fletcher et al., 1995; Squire et al., 1992), and navigating the auditory scene (Teki et al., 2012). BA 39 (the angular gyrus) and BA 40 (the supramarginal gyrus) are parts of Wernicke's area involved in the comprehensive processing of the presented auditory stimuli. BA 41 and 42 correspond closely to the primary auditory cortex, which can be linked to the auditory processing induced by the presented auditory stimuli. BA 46 is the part of the dorsolateral prefrontal cortex that is involved in executive cognitive functions (e.g., planning, monitoring, inhibiting, and working memory; Fuster, 2008; Fuster, 2013; Gazzaley and D'Esposito, 2007). Source waveforms were estimated at the 16 ROIs and the DTF analysis showed directional information flow across the sources. Statistical assessment of the connectivity was performed using surrogate approaches (1000 surrogate data sets, $p < 0.05$).

3. Results

3.1. Assessment of tinnitus complaints

Based on responses to the question items in the K-THI and VAS, we observed that the T1 group exhibited significantly enhanced levels of annoyance when experiencing tinnitus compared to the T2 group (T1 group, 7.714 ± 2.059 [standard deviation, SD]; T2 group, 5.143 ± 1.865; $F(1,12) = 6.000$, $p < 0.05$). Compared to the T2 group, more patients in the T1 group reported that they may be distressed by impending susceptibility to a tinnitus sound (T1 group, 83.3% answered 'yes' and one patient did not answer; T2 group, 100% answered 'no' and one patient did not answer; $F(1,10) = 25.000$, $p < 0.005$). All seven patients in the T1 group had unilateral tinnitus, whereas three out of the seven patients in the T2 group had bilateral tinnitus without a clear designation of laterality ($F(1,12) = 7.350$, $p < 0.05$).

3.2. ERPs

3.2.1. CNV

The CNV amplitude of the healthy group was significantly lower than that of the patient group (healthy group, −0.594 μV, patient group, −0.279 μV; $F(1,26) = 7.310$, $p < 0.05$; Fig. 2A). This effect was due to the T2 group, which had a marginally significant difference (−0.184 μV, $F(1,12) = 4.707$, $p = 0.051$), but not the T1 group (−0.373 μV, $F(1,12) = 2.585$, *ns*). In the T2 group, we observed a significant interaction in CNV amplitudes between the group and the stimulus-type factors ($F(1,12) = 10.883$, $p < 0.01$). Subsequent tests indicated that the CNV amplitudes of the T2 group were significantly different from those of the healthy group during the processing of target stimuli (−0.233 μV, $F(1,12) = 10.160$, $p < 0.01$), but not standard stimuli (−0.136 μV, $F(1,12) = 0.254$, *ns*). The T2 group also had significant differences in CNV amplitudes for the target vs. the standard stimuli in the oddball task (target, −0.681 μV; standard, −0.219 μV; $F(1,12) = 19.650$, $p < 0.005$), but not in the passive listening task ($F(1,12) = 3.158$, *ns*). In addition, there was a significant interaction effect between the task and the stimulus-type factors in CNV amplitude ($F(1,26) = 20.802$, $p < 0.001$). Post hoc testing revealed significantly enhanced CNV amplitudes during the processing of target stimuli

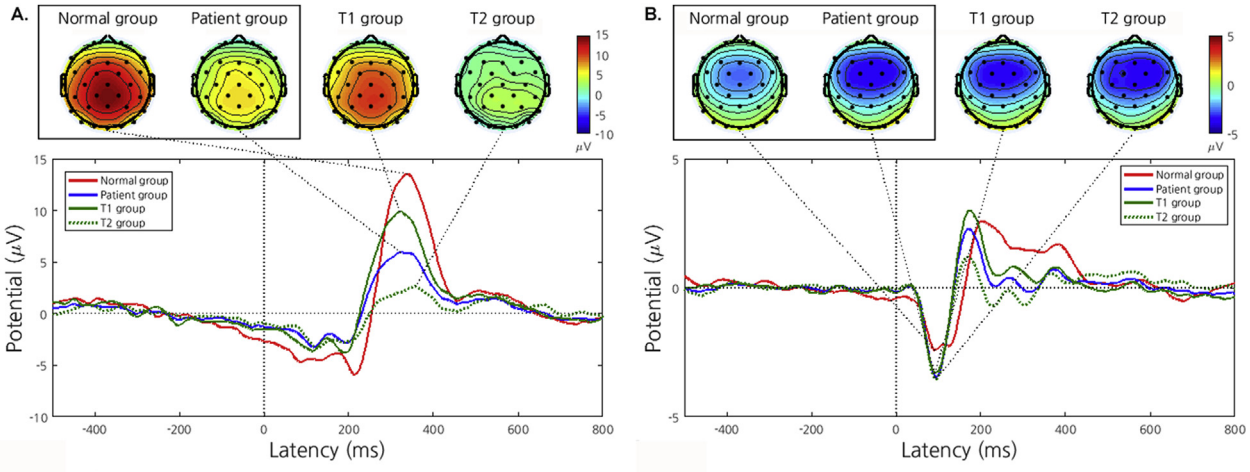


Fig. 2. Grand-averaged ERP time courses for the normal healthy controls (red solid line), patients with tinnitus (blue solid line), T1 (green solid line), and T2 (green dotted line) groups at the Cz electrode and the topographies of their maxima (A) during the processing of target stimuli in the oddball task and (B) the processing of standard stimuli. Note the decreased CNV and systematically reduced P300 amplitudes in the patient groups in (A), and the enhanced N1 amplitudes and shorter latencies of P170 and N200 in the patient groups compared to the healthy group in (B). Time zero indicates stimulus onset. The color bar indicates the amplitude (μV). All topographies are shown from the vertex view, with the nose at the top.

vs. standard stimuli in the oddball task (target, −1.308 μV, standard, −0.392 μV; $F(1,26) = 44.744$, $p < 0.001$), but not in the passive listening task ($F(1,26) = 0.095$, *ns*).

3.2.2. N100

We observed a significant interaction effect for the N100 amplitude across the group, task, and stimulus-type factors ($F(1,26) = 9.908$, $p < 0.005$). Subsequent tests revealed that there was a marginally significant group effect in the N100 amplitude in response to the target stimuli in the oddball task (healthy group, −2.079 μV, patient group, −0.975 μV; $F(1,26) = 4.057$, $p = 0.054$). As shown in Fig. 2B, there were no significant differences in N100 amplitudes between the T1 and T2 groups (T1 group, −1.087 μV, T2 group, −0.863 μV; $F(1,12) = 0.096$, *ns*). The N100 component was detected earlier in response to the target stimuli (85.810 ms) vs. the standard stimuli (112.458 ms; $F(1,26) = 19.541$, $p < 0.001$).

3.2.3. P170

There was a significant interaction effect between the task and stimulus-type factors in both P170 amplitude ($F(1,26) = 28.917$, $p < 0.001$) and latency ($F(1,26) = 18.953$, $p < 0.001$). Post hoc testing demonstrated that processing target stimuli in the oddball task produced significantly lower P170 amplitudes (−1.967 μV) and shorter P170 latencies (165.000 ms) than the passive listening task (1.118 μV, $F(1,26) = 51.329$, $p < 0.001$ for P170 amplitude; and 182.488 ms, $F(1,26) = 12.237$, $p < 0.005$ for P170 latency). There was an additional significant interaction effect between the group and stimulus-type factors in P170 latency ($F(1,26) = 8.611$, $p < 0.01$). Subsequent tests indicated that the patient group exhibited significantly shorter P170 latencies (169.214 ms) than the healthy group (192.786 ms; $F(1,26) = 13.947$, $p < 0.005$) when standard stimuli were presented (Fig. 2B). This effect was due to both T1 and T2 groups (T1 group, 171.667 ms, $F(1,13) = 7.792$, $p < 0.05$; T2 group, 166.762 ms, $F(1,13) = 5.872$, $p < 0.05$).

3.2.4. N200

Interestingly, the same trends observed for P170 latency were continuously detected in the N200 latency, as shown in Fig. 2B. Specifically, there was a significant interaction effect between the group and stimulus-type factors in N200 latency ($F(1,26) = 5.325$, $p < 0.05$). Post hoc tests indicated that the patient group produced significantly shorter N200 latencies (173.264 ms) than the healthy group (201.186 ms; $F(1,26) = 12.415$, $p < 0.005$) when the standard stimuli were presented. This effect was due to both T1 and T2 groups (T1 group, 172.557 ms, $F(1,13) = 7.866$, $p < 0.05$; T2 group, 173.971 ms, $F(1,13) = 4.444$, $p = 0.057$). N200 amplitudes also behaved similarly to P170 amplitudes. There was a significant interaction effect between the task and the stimulus-type factors in the N200 amplitude ($F(1,26) = 6.587$, $p < 0.05$). We found that processing target stimuli produced significantly lower N200 amplitudes (−0.589 μV) during the oddball task compared to the passive listening task (1.197 μV, $F(1,26) = 8.585$, $p < 0.01$).

3.2.5. P300

We observed a significant interaction effect across the group, task, and stimulus-type factors ($F(1,26) = 10.933$, $p < 0.005$) for P300 amplitude. Subsequent tests revealed that the healthy group produced significantly higher P300 amplitudes than the patient group when the oddball task was performed with target stimuli (healthy group, 14.733 μV, patient group, 6.923 μV; $F(1,26) = 15.183$, $p < 0.005$) and standard stimuli (healthy group, 5.658 μV, patient group, 2.713 μV; $F(1,26) = 16.968$, $p < 0.001$), as well as when standard stimuli were presented in the passive listening task (healthy group, 2.105 μV, patient group, 0.593 μV; $F(1,26) = 8.583$, $p < 0.01$). Further investigations revealed that the results observed in the oddball task were due to the T2 group, but not the T1 group, during the processing of target stimuli (T1 group, 9.902 μV, T2 group, 3.944 μV; $F(1,12) = 15.879$, $p < 0.005$) and standard stimuli (T1 group, 3.745 μV, T2 group, 1.680 μV; $F(1,12) = 19.686$, $p < 0.005$). However, the T1 group, but not the T2 group, significantly contributed to the results in the passive listening task when processing standard stimuli (T1 group, 0.437 μV, T2 group, 0.750 μV; $F(1,12) = 6.280$, $p < 0.05$). By definition, the T1 group had significantly higher P300 amplitudes than the T2 group during the processing of target stimuli in the oddball task (T1 group, 9.902 μV, T2 group, 3.944 μV; $F(1,12) = 16.902$, $p < 0.005$; Fig. 2A). No other interactions or latency effects with significant differences were detected in the P300 component.

3.3. EEG alpha and theta oscillations

3.3.1. Prestimulus alpha activity

The total alpha power in the prestimulus period was significantly enhanced under the oddball task (12.198 μV^2) compared to the passive listening task (3.277 μV^2; $F(1,17) = 7.239$, $p < 0.05$; Fig. 3A). However, no significant difference was observed in prestimulus alpha power between the healthy and patient groups ($F(1,17) = 0.018$, *ns*). No other significant effects were detected in prestimulus alpha power, peak latency, or peak frequency.

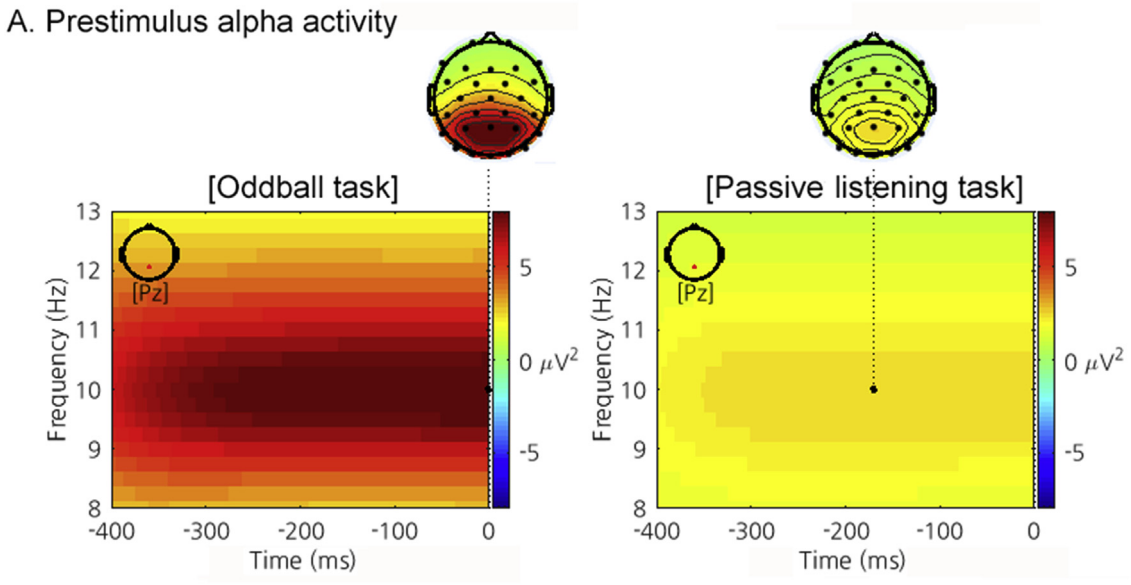
3.3.2. Evoked theta activity

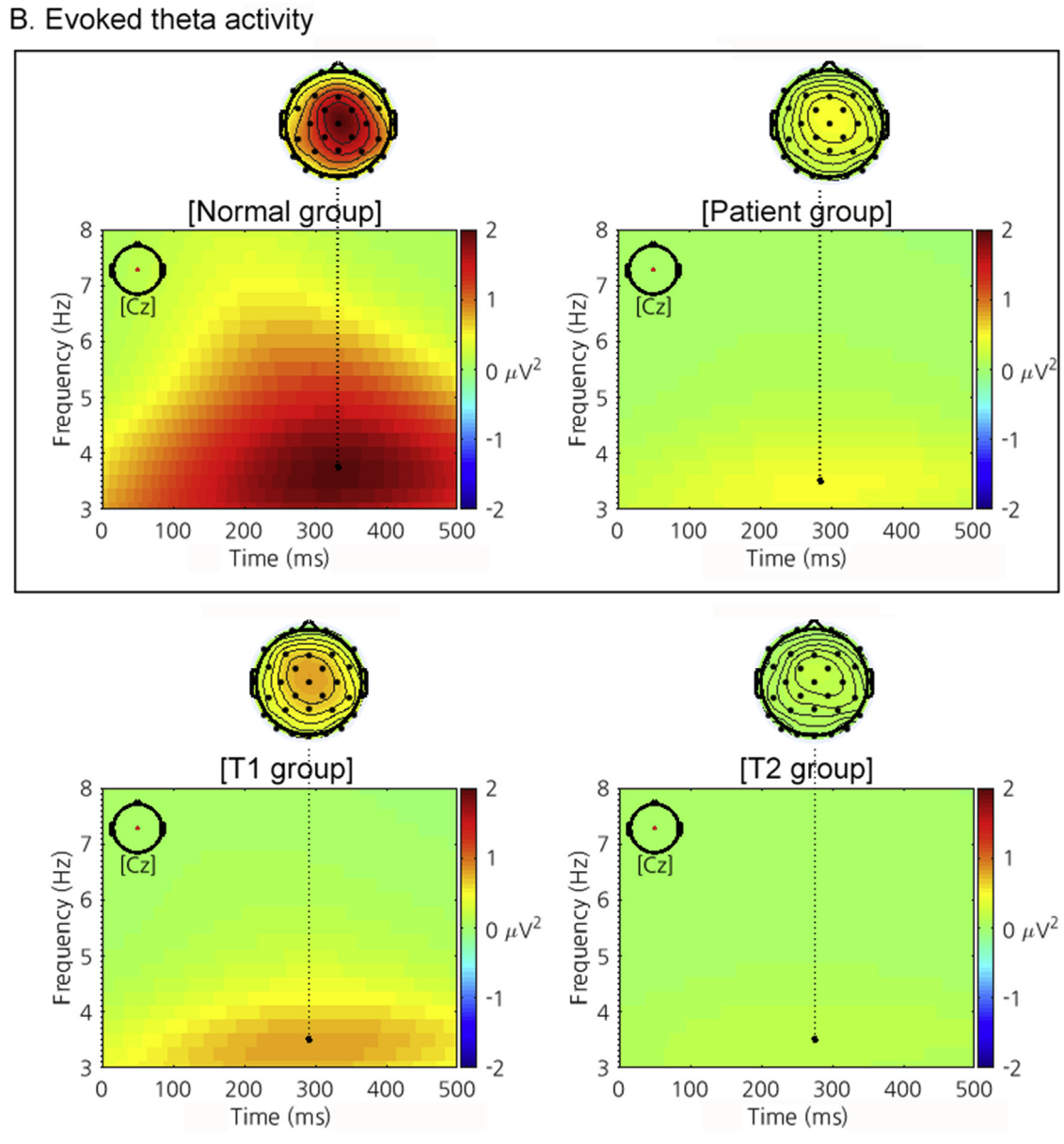
Compared to parieto-occipital alpha activity, the evoked theta activity exhibited a more fronto-central topographical distribution, as shown in Fig. 3B. For evoked theta power, we found a significant interaction effect across the group, task, and stimulus-type factors ($F(1,24) = 6.160$, $p < 0.05$). Subsequent tests revealed that the healthy group yielded significantly higher evoked theta power than the patient group during target processing in the oddball task (healthy group, 3.458 μV^2, patient group, 0.760 μV^2; $F(1,26) = 8.036$, $p < 0.01$). Subsequent tests revealed that this effect was due to the T2 group (0.378 μV^2; $F(1,12) = 15.128$, $p < 0.005$), but not the T1 group (1.141 μV^2; $F(1,12) = 1.634$, *ns*). Similarly, in the passive listening task, the healthy group produced significantly higher evoked theta power than the patient group when the target stimuli were presented (healthy group, 0.262 μV^2, patient group, 0.085 μV^2; $F(1,25) = 6.971$, $p < 0.05$). Post hoc testing indicated that this effect was due to the T1 group (0.0878 μV^2; $F(1,12) = 5.723$, $p < 0.05$), but not the T2 group (0.0831 μV^2; $F(1,12) = 3.274$, *ns*), which is of the opposite of what was observed in the oddball task.

The evoked theta peak latency of the target stimuli (281.345 ms) was significantly longer than that of the standard stimuli (175.862 ms), irrespective of the group or the task type ($F(1,24) = 51.875$, $p < 0.001$). There was also a significant interaction effect between the task and stimulus-type factors in the peak frequency of evoked theta activity ($F(1,24) = 35.880$, $p < 0.001$). Post hoc testing demonstrated that the target stimuli produced significantly lower evoked theta peak frequencies during the oddball task (3.579 Hz) than the passive listening task (5.724 Hz; $F(1,25) = 36.653$, $p < 0.001$). No other significant effects were observed in evoked theta activity.

3.4. Granger causal connectivity

As shown in Fig. 4, the hippocampal/parahippocampal region (BA 27) and the ACC (BA 24 and 32) had prominent overall influences over other brain regions during the processing of auditory information in the healthy group. In contrast, the dominant connectivity centered at BA 39, 40, 41 and 42 were additionally involved in the patient group. When the results of the patient group


A. Prestimulus alpha activity
[Oddball task]
[Passive listening task]
[Pz]
Frequency (Hz)
Time (ms)
0 μV²


B. Evoked theta activity
[Normal group]
[Patient group]
[T1 group]
[T2 group]
[Cz]
Frequency (Hz)
Time (ms)
0 μV²

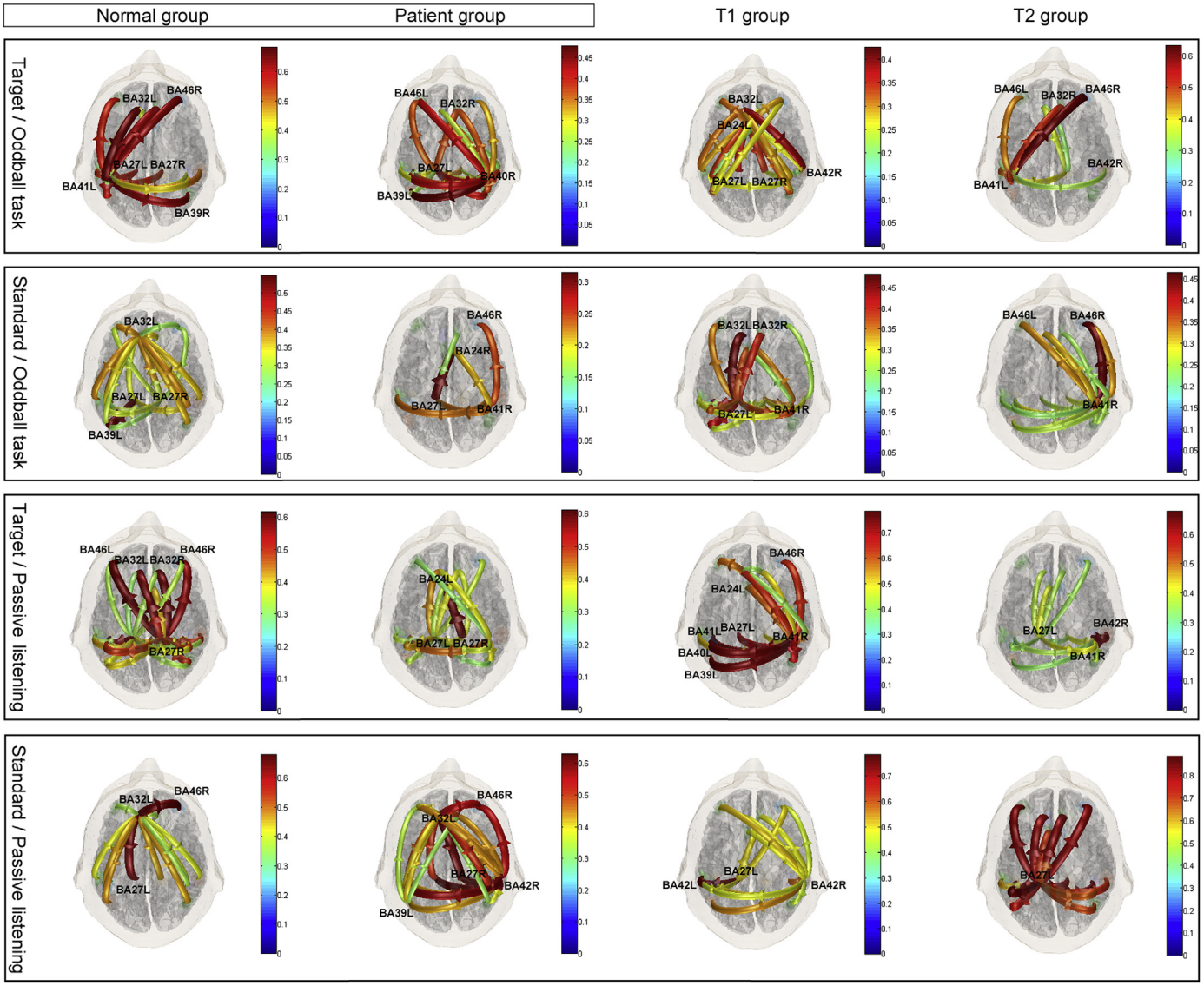


Fig. 4. Granger causal connectivity of grand-averaged evoked theta activity of the normal healthy, patients with tinnitus, T1, and T2 groups (from left to right) for target stimuli in the oddball task (first row), for standard stimuli in the oddball task (second row), for target stimuli in the passive listening task (third row), and for standard stimuli in the passive listening task (fourth row). The color-scaled directional arrows link two causally connected ROIs across 16 ROIs (BA 24L/R, BA 27L/R, BA 32L/R, BA 39L/R, BA 40L/R, BA 41L/R, BA 42L/R, and BA 46L/R) when their Granger causality is statistically significant (i.e., $p < 0.05$). The color-scaled arrows in the cortical connectivity image represent the degree of causal connectivity (ranging from 0 to 1). Note that during the processing of targets in the oddball task, the most prominent outflows of information are observed at BAs 24 and 32 (top-down cognitive processing areas) for both the normal and T1 groups, whereas BAs 41 (primary auditory processing area) and 39 (Wernicke's area) exhibit the most pronounced outflows of information for the T2 group. The topographical view is from the vertex, with the nose at the top of the image.

were further analyzed using the T1 and T2 subgroups, Granger causal connectivity of evoked theta activity consistently confirmed a double dissociation between the T1 and T2 groups in both top-down and bottom-up tasks. That is, the T1 group yielded a similar causal connectivity to that of the healthy group during target processing in the oddball task, which included directional connectivity generated dominantly from the ACC, despite the T1 group having reduced connectivity amplitudes (around 0.395) compared to the healthy group (around 0.683). Furthermore, the T2 group had a causal connectivity dominated not by the ACC but, abnormally, by the auditory cortex and Wernicke's areas during the oddball task. Nonetheless, the T2 group demonstrated dominant hippocampal connectivity during the passive listening task, similar to the healthy group. In contrast, the T1 group had an abnormally

Fig. 3. (A) Time-frequency representations of grand-averaged total alpha (8–13 Hz) activity at the Pz electrode during the oddball (left panel) and passive listening tasks (right panel), and the topographical distributions at the maximum peak from 0 to 400 ms prestimulus. (B) Time-frequency representations of grand-averaged evoked theta (3–8 Hz) activity at the Cz electrode during the processing of target stimuli for healthy individuals (upper-left panel), the patient group with tinnitus (upper-right panel), T1 (lower-left panel), and T2 (lower-right panel) patient groups with tinnitus, along with the topographical distributions at the maximum peak from 0 to 500 ms poststimulus. The color bar indicates the power (μV^2). The topographical view is from the vertex, with the nose at the top of the image. The electrode location is noted in the inset on the upper left corner of the plot.

low dependence on hippocampal areas during the passive listening task.

4. Discussion

Our observations provide neurophysiological evidence that both top-down and bottom-up dysfunctions can cooperatively contribute to tinnitus symptoms, independent of peripheral hearing normality. As shown in Fig. 2, the patient group demonstrated significantly reduced P300 amplitudes than healthy individuals, which is indicative of an impairment in top-down attentional processing in patients with tinnitus but without hearing loss, as the P300 reflects fundamental cognitive processes (Donchin and Coles, 1988; Johnson, 1988; Picton, 1992; Polich, 1993). Consistently, Granger causality analyses revealed a lack of ACC activation during target processing (Fig. 4), which implies abnormal target-detecting processes, as the ACC executes top-down inhibitory control (Johnston et al., 2007; Silton et al., 2010) and conflict monitoring processing (Apps et al., 2012; Borsa et al., 2016; Botvinick et al., 2004). In addition, early ERP components, such as the N100, also had significant differences in the amplitude across the healthy and patient groups. Since the auditory N100 is sensitive to selective attention (Sanders and Astheimer, 2008; Woldorff et al., 1993), patients with tinnitus and without hearing loss seem to have selective attention deficits to external sounds. In addition, as early ERP components are more influenced by physical sensory factors (reflecting bottom-up processes) than the later higher-order cognitive (top-down) ERP components (Kutas et al., 1977; Skrandies, 1984; Zani and Proverbio, 1995), impairment in bottom-up processing is a possible cause of tinnitus (Vanneste and De Ridder, 2016). The latencies of P170 and N200 in non-target stimuli (i.e., those with non-tinnitus frequencies) were significantly shorter than those in healthy individuals.

Interestingly, when the patients were divided into two subgroups depending on the P300 amplitude, P170 and N200 also behaved differently, as shown in Fig. 2B. It is noteworthy that the T1 group reported significantly higher rating scores in annoyance from tinnitus and distress from impending susceptibility to a tinnitus sound than the T2 group. Based on the relationship between ERP dynamics and tinnitus rating scores, the above ERP components can be used as neurophysiological markers for predicting some tinnitus impairments. Three out of the seven patients in the T2 group had bilateral deficits of tinnitus, whereas those in the T1 group all had unilateral tinnitus. Therefore, bilaterally unbalanced impairment of tinnitus seems to evoke more severe psychosomatic complaints. Thus, not only neurophysiologically, but also behaviorally, patients with tinnitus and normal hearing can be categorized into at least two subgroups. As a systematic reduction in P300 amplitude was shown from the healthy group to the T1 group, and from the T1 group to the T2 group (Fig. 2A), the T1 group does not seem to be as seriously deficient in top-down processing as the T2 group. There was no significant difference in N100 amplitude between the T1 and T2 groups. The differences began after the P170 component was observed and were maximized in the P300 amplitude. Presumably, the difference between the T1 and T2 groups begins around the time of the early manifestation of the interactions between top-down and bottom-up processes.

Indeed, the recent theory of “predictive coding” provides a unifying framework for minimizing the error between bottom-up sensations and top-down predictions (Winkler, 2007), with the corresponding mismatch signaling the detection of a deviant. It is probable that the T2 group has more deficits in predictive coding capacity. In line with this notion, the CNV of the T2 group was significantly reduced compared to those of both the healthy and T1 groups during the target response in the oddball task. In the CNV paradigm, a pair of contingent stimuli (S1: a warning stimulus and S2: an imperative stimulus) are presented with a distinct time interval (Birbaumer et al., 1990; Walter et al., 1964). Stimulus contingencies (temporal associations between the two stimuli) allow subjects to predict and prepare for the second stimulus, which requires the execution of a response. Therefore, CNV is indicative of expectancy or prediction. It is plausible that together with the attention deficits in patients with tinnitus, the disparity between the predicted and delivered inputs activates an auditory attention system, facilitating neuroplastic changes that contribute to the generation of tinnitus (Roberts et al., 2013). Together with our ERP observations, both T1 and T2 groups commonly showed deficient neurophysiological behavior in both prestimulus CNV and early poststimulus bottom-up processing stages (i.e., N100). Compared to the T1 group, the T2 group exhibited subsequent abnormal neurodynamics during the interaction stage (i.e., P170 and N200) between bottom-up and top-down processes. Consequently, the T2 group had further reduced P300 amplitudes than the T1 group in the late top-down processing stage.

Since prestimulus alpha activity was significantly modulated only by the task type, but not by the group factor, the preparatory mental states for the upcoming task performance may be intact in patients with tinnitus. Instead, these patients exhibited perceptual or cognitive dysfunction when the acoustic stimulus was presented, which was reflected in evoked theta activity. During the processing of target stimuli, the T1 and T2 groups differentially contributed to the significant differences in evoked theta power from the healthy group, depending on the task type. Specifically, the contribution of the T1 group was observed during the passive listening task (for bottom-up processing), whereas that of the T2 group was found during the active oddball task (for top-down processing). Consistently, the observations of EEG theta-band directional neurodynamics reflect such double dissociations between the T1 and T2 groups across top-down and bottom-up tasks (Fig. 4). During the oddball task, the T1 group yielded similar causal connectivity to the healthy group, which showed directional connectivity dominantly generated from the ACC. In contrast, the T2 group had abnormalities during the oddball task: auditory cortical connectivity was more pronounced than ACC connectivity. Such dysfunction of the ACC in patients with tinnitus has been consistently reported in previous studies (De Ridder et al., 2016; Vanneste et al., 2014). On the other hand, during the passive listening task, both healthy and T2 groups showed dominant parahippocampal connectivity when the target stimuli were presented. It has been consistently reported that the tinnitus network involves the ACC and parahippocampal areas (De Ridder et al., 2006; De Ridder et al., 2014; Landgrebe et al., 2009; Vanneste et al., 2010). However, the T1 group had an abnormally lower dependence on the parahippocampal area. Instead, the T1 group displayed dominant connectivity from the auditory cortex (Fig. 4), which has been reported in relation to perceived tinnitus intensity (van der Loo et al., 2009). However, the T2 group abnormally demonstrated this dominant parahippocampal connectivity even during the processing of standard stimuli in the passive listening task. Since the parahippocampal area has been considered to be a critical hub in the tinnitus network (De Ridder and Vanneste, 2014), as it is involved in tinnitus in general (Maudoux et al., 2012; Song et al., 2012; Vanneste et al., 2011), the T2 group may exhibit unconditional parahippocampal hyper-connectivity, possibly leading to the generation of tinnitus.

The hippocampal/parahippocampal area plays an important role in memory encoding and retrieval (Van Strien et al., 2009). EEG theta activity reflects this function of working memory in the hippocampal area (Raghavachari et al., 2001; Sauseng et al., 2010; Tesche and Karhu, 2000). The patient group had significantly reduced evoked theta power than the healthy group during the

processing of target stimuli. As EEG theta activity has been observed when a person engages in memory retrieval (Jacobs et al., 2006) and takes on cognitive load (Klimesch, 1999), it is likely that patients with tinnitus have cognitive deficits in auditory memory processing. For example, to compare the target auditory stimulus with a series of standard stimuli, one might first retrieve auditory memories regarding the target and the standard stimuli, which are already encoded in a memory system for task performance. It is possible that the patients with tinnitus have impairments in the retrieval of pre-registered auditory memories, which are required to perform the oddball task correctly.

Alternatively, as theta activity is also associated with context updating (Makeig et al., 2004) and cognitive control mechanisms (conflict processing in the ACC; Hanslmayr et al., 2008), the less pronounced theta activity evoked in the patient group might indicate non-efficient context updating when there is a conflict due to intermixed presentations of different stimulus types (target and standard). Since EEG theta activity is considered to be a possible electrophysiological correlate of top-down regulation in memory systems (Sauseng et al., 2008), our observation provides neurophysiological evidence supporting a crucial role of hippocampus-based top-down influence on auditory processing. In parallel, as the ACC is involved in top-down attentional inhibitory regulation (Johnston et al., 2007; Silton et al., 2010), patients with tinnitus may have impairments in top-down attentional inhibitory control. Therefore, abnormal evoked theta and ERP behaviors in patients with tinnitus may account for their dysfunctions in attention and working memory (Mohamad et al., 2016; Rossiter et al., 2006).

As slow oscillations such as theta activity are associated with integrative brain functions in globally distributed neural networks (Sarnthein et al., 1998; von Stein and Sarnthein, 2000) and large-scale neural communicative networks (Başar, 1999), our observations of long-range theta-band directional connectivity, particularly from the top-down brain areas (e.g., hippocampus, ACC, and prefrontal cortex) to the primary sensory cortices, might reflect interregionally integrative and downregulating processes on auditory working memory. Thus, the multi-regional causal connectivity observed in tinnitus patients would imply that the neuropathology of tinnitus is involved in integrated auditory information processing over global brain networks.

However, the present study has some implicational constraints that are worth mentioning. First, in the present study, source localization was conducted based on a limited number of scalp channels. In general, the accuracy of EEG source localization depends on sufficient spatial frequency in the scalp potential field (Song et al., 2015a; Srinivasan et al., 1998), which is limited by the blurring caused by volume conduction effects (Malmivuo and Suihko, 2004; Michel and He, 2011). Although more than 32 channels would yield further confidence in source localization (Lantz et al., 2003; Luu et al., 2001; Song et al., 2015a), measurement noise is a critical limiting factor for the spatial resolution of high-density EEG-systems (Ryynanen et al., 2004, 2006). Therefore, there is a crucial interplay between measurement noise, the number of channels, and conductivity values of the different compartments of the head. Moreover, it remains, for the moment, unclear how much imperfect spatial sampling influences source imaging (Michel and He, 2011). Some data suggest that even with ~32 channels, as used in the present study, one obtains important insight into the underlying brain electrical sources by performing source localization (Ding et al., 2006, 2007; Sperli et al., 2006; Zhang et al., 2003). Although the EEG inverse problem remains a challenge, it is possible to obtain valid estimates of its solutions if reasonable constraints are given on the equivalent source distribution (Pascual-Marqui et al., 1994). For example, if the brain electric sources are assumed to consist of a few moving equivalent current dipoles (He et al., 1987), as used in the present study, solutions to the EEG inverse problem can be estimated yielding results that are consistent with other findings in clinical neurophysiology and neuroscience. Nevertheless, our estimates in causal connectivity should be understood in light of these possible concerns of the EEG source localization. Second, although a larger sample size would result in a higher statistical power, it is not easy to acquire a sufficient number of patients with tinnitus who do not also have hearing loss. Thus, the post-hoc comparison between T1 and T2 should be interpreted carefully, and considering this statistical limitation. Third, the audiograms in the present study were measured up to 8 kHz. Although the inclusion of further high frequencies (i.e., more than 8 kHz) for hidden hearing loss may provide more confidence in evaluating hearing capacity, the clinical significance of such an extended high frequency audiogram is still debatable (Balatsouras et al., 2005; Osterhammel and Osterhammel, 1979; Schmuziger et al., 2007). Moreover, standardizations for acoustics (ISO, 2006) have not been generally established in extended high frequency levels (i.e., more than 8 kHz). Nevertheless, the concern for normal hearing in the present study should be carefully considered with possible hidden hearing loss over 8 kHz in the audiograms. Lastly, since only patients with tinnitus but without hearing loss participated in the present study, further experiments on tinnitus with hearing loss are needed to determine the extent of its pathology. A future study using the same experimental paradigm on patients with tinnitus and hearing loss will provide more informative evidence on the relationship between hearing function and tinnitus pathology from the viewpoint of top-down and bottom-up processing.

5. Conclusions

The results of this study provide neurophysiological and neurodynamic evidence that tinnitus pathology is due to both top-down and bottom-up dysfunctions. Although it is still unclear whether this impairment is induced principally by peripheral cochlear damage or unverifiable hidden hearing loss or abnormality in cognitive circuitry, our observation indicates a differential engagement of top-down impairment combined with deficits of bottom-up processing in patients with tinnitus but without hearing loss. Since top-down processes are involved in a modality-independent complex neural network (Lacey et al., 2009; Sarter et al., 2001), our results reinforce the idea that tinnitus physiopathology can even be associated with non-auditory systems (Henry et al., 2014). Our unpublished results (due to rare observations) using Granger causality analyses reveal abnormally dominant somatosensory or motor cortical connectivity in the patient group. These observations indicate that tinnitus may be modulated by stimulation arising from the somatosensorial system, as well as from the somatomotor and visual-motor systems (Sanchez and Rocha, 2011). Therefore, not only the peripheral auditory system, but also the central non-auditory cognitive system involving top-down processes, should be carefully considered for the clinical management and treatment of tinnitus. In future studies, subsequent exploration of interactive neurodynamics between top-down and bottom-up processes with more elaborated experimental designs will contribute to a better understanding of the top-down involvement in the generation of tinnitus. These studies may then provide further fundamental insights into the neuropathology of tinnitus.

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