Altered top-down cognitive control and auditory processing in tinnitus: evidences from auditory and visual spatial stroop

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Abstract.
Purpose: Tinnitus is the perception of a sound in the absence of external stimulus. Currently, the pathophysiology of tinnitus is not fully understood, but recent studies indicate that alterations in the brain involve non-auditory areas, including the prefrontal cortex. Here, we hypothesize that these brain alterations affect top-down cognitive control mechanisms that play a role in the regulation of sensations, emotions and attention resources.
Methods: The efficiency of the executive control as well as simple reaction speed and processing speed were evaluated in tinnitus participants (TP) and matched control subjects (CS) in both the auditory and the visual modalities using a spatial Stroop paradigm.
Results: TP were slower and less accurate than CS during both the auditory and the visual spatial Stroop tasks, while simple reaction speed and stimulus processing speed were affected in TP in the auditory modality only.
Conclusions: Tinnitus is associated both with modality-specific deficits along the auditory processing system and an impairment of cognitive control mechanisms that are involved both in vision and audition (i.e. that are supra-modal). We postulate that this deficit in the top-down cognitive control is a key-factor in the development and maintenance of tinnitus and may also explain some of the cognitive difficulties reported by tinnitus sufferers.

Keywords: Tinnitus, attention, cognitive control, executive function, hearing impairment, prefrontal cortex, sensory processing, multisensory integration, spatial Stroop

1. Introduction

Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. In industrialized countries, it affects 10–15% of the population and severely impairs quality of life of about 1–2% of all people (Dobie, 2003; Heller, 2003; Langguth, et al., 2013). Despite an increasing interest from the scientific community, the pathophysiology of tinnitus is not fully understood yet. This question is particularly crucial since in spite of the various existing treatments there is no definite cure to tinnitus. Currently, most researchers agree that subjective tinnitus is most often triggered by peripheral mechanisms (e.g. cochlear impairment) and involves the central nervous system when it becomes chronic (Eggermont, & Roberts, 2004; Rauschecker, et al., 2010; Roberts et al., 2010; Tass et al., 2012; Langguth et al., 2013; De Ridder et al., 2013; Yang & Bao, 2013). Accumulating evidences indicate that structural and functional alterations in the brain involve

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not only auditory regions, but also non-auditory areas, including the limbic system and prefrontal regions such as the ventromedial prefrontal cortex (vmPFC) (Mirz, et al., 2000; Lanting, et al., 2009; Schneider et al., 2009; Schlee et al., 2009a, b; Leaver et al., 2011). The abnormalities found in brain regions known as being part of emotion and/or attention networks (MacDonald, et al., 2000; Fan, et al., 2005; Rauschecker et al., 2010; Wang, et al., 2010), probably explain why concentration difficulties are frequently reported by tinnitus sufferers (Langguth, 2011). Altough studies on attention (e.g. divided or selective attention) in tinnitus patients are scarce, most of them indicate impaired performances in these patients (Hallam, et al., 2004; Rossiter, et al., 2006; Stevens, et al., 2007; Heeren et al., 2014). According to recent neuropsychological models of tinnitus, dysfunctions in attention mechanisms should not be regarded as accompanying symptoms or as a consequence of tinnitus, but should rather be considered as contributing components to tinnitus itself (e.g. Roberts, et al., 2013). Attention deficits would affect the habituation process that normally prevents "phantom" auditory perception from reaching awareness (Jastreboff & Jastreboff, 2000; Anderson, et al., 2000). In the prefrontal cortex, the anterior cingulate cortex and the dorsolateral prefrontal cortex have been associated with auditory attention (Alain, et al., 1998; Lewis, et al., 2000; Voisin, et al., 2006) and described as exerting both an early inhibitory modulation of input to the primary auditory cortex (Knight, et al., 1989) and a top-down modulation of auditory processing in humans (Mitchell, et al., 2005). These structures are connected to the vmPFC (Grimm et al., 2006) that is affected in tinnitus and would play a predominant role in the noise canceling pathway (Mühlau et al., 2006; Rauschecker et al. 2010; Leaver et al., 2011; De Ridder, et al., 2011; Seydell-Greenwald et al., 2012; De Ridder et al., 2013).

Although deficiency performances in attention tests have been observed in tinnitus patients, it is not clear which attention network or cognitive sub-component of attention is specifically altered and whether attention impairment primarily depends on tinnitus itself or on some associated disorders (e.g. depression, stress or anxiety). While some researchers considered the observed deficits in attention tests as resulting from a general decrease of the processing speed (Das, et al., 2012) or a global depletion of attentional resources (Andersson et al., 2000; Hallam et al., 2004; Rossister et al., 2006; Stevens et al., 2007), others pointed out

that the observed cognitive difficulties would rather depend on the selective impairment of specific subcomponents of attention (Roberts et al., 2013; Heeren et al., 2014). This question is important since understanding the exact nature of the cognitive deficit in tinnitus is crucial to develop adapted forms of treatments, e.g. determining which cognitive aspect and/or brain region should be targeted by such revalidation procedures as cognitive training, transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS). It is also a prerequisite to promote a better identification of the different types of tinnitus.

In the present study, the efficiency of the top-down executive control, as well as simple reaction speed and processing speed were evaluated in tinnitus participants and control subjects matched for age, gender, educational level and hearing acuity. A particular attention was paid to the inclusion criteria to homogenize the tinnitus sample and limit potential confounding factors (e.g. depression, anxiety, hearing loss). The same tests, including a spatial Stroop, were adapted and used in both the auditory and the visual modality. The purpose was to identify which cognitive aspects were altered in tinnitus. We postulated that slowed down processing speed or a global decrease in attention resources in tinnitus patients would affect similarly their performances in vision and audition, whereas more specific alterations of the executive control mechanisms would impair their performances mostly in the two (visual and auditory) spatial Stroop tasks only, with no or few effect in the other conditions. Finally, any processing impairment specific to the auditory modality would selectively affect performances in the auditory modality while keeping those in the visual one preserved.

2. Ethics statement

All participants provided their written informed consent prior to the study according to the Declaration of Helsinki (BMJ 1991; 302:1194). The experimental protocol of the study was approved by the Biomedical Ethics Committee of the school of Medicine of the Université catholique de Louvain.

3. Participants

Tinnitus participants (TP) were recruited among patients who consulted the ear, nose and throat (ENT)

Table 1
Characteristics of Tinnitus participants

Subjects	Age [years]	Gender	Hearing Loss Right/Left [dB]	Tinnitus Frequency [Hz]	Tinnitus Duration [months]	THI [Score: 0–100]	Tinnitus Annoyance [Score: 0–10]
1	65	F	27/29	4000	72	24	7
2	54	F	10/12	8000	60	82	8
3	23	F	12/12	1500	33	46	2
4	62	F	20/18	4000	74	82	6
5	68	M	20/20	4000	24	56	4
6	29	F	1/6	1500	10	22	0
7	36	F	16/14	6000	15	76	5
8	44	F	11/10	6000	12	44	8
9	67	M	15/18	8000	24	48	5
10	60	M	8/6	8000	8	44	3
11	36	M	10/14	6000	11	34	0
12	56	F	11/10	6000	240	28	2
13	54	M	2/2	6000	13	24	1
14	20	F	8/11	6000	24	40	10
15	48	M	11/14	4000	9	32	4
16	58	F	15/8	6000	164	24	2
17	53	F	17/14	8000	7	30	7

THI: Tinnitus Handicap Inventory. VAS: Visual Analogue Scale. Hearing loss: Average between 250–4000 Hz.

department of the St. Luc academic hospital in reason of tinnitus. To select the patients, we used strict inclusion criteria in order both to homogenize the best possible the group of tinnitus patients, since there are different kinds of tinnitus, baring different characteristics and involving slightly different pathophysiological mechanisms (Jastreboff, 1990; Roberts et al., 2010; Landgrebe et al., 2010, Langguth et al., 2013), and to isolate tinnitus from potential confounding factors that are frequently associated, such as hearing loss, depression, anxiety or hyperacusis (Langguth et al., 2007, 2013). Accordingly, we only included patients who suffered from a subjective (1) and non-pulsatile tinnitus (2), that was present permanently (not by intermittence) (3), for at least 6 months (chronic) (4), in both ears (bilateral) (5), who had either a normal hearing acuity or a slight hearing loss (i.e. average hearing loss inferior to 35 dB in each ear) (6), without hyperacusis (7), with no record of neurological or diagnosed psychiatric disorder (including major depression) at the time of the testing (8), and without psychotropic medication consumption (9). In total, 17 TP accepted to participate and were included in the study (6 men, 11 women, mean age: 49, SD: 15.2, ranging from 20 to 67 years, see Table 1 for detailed characteristics). Control subjects (CS) were recruited via flyers posted on the university campus and hospital. All of them were healthy, without any recorded history of neurological or psychiatric problems or major hearing impairment. All TP and CS were French speakers and underwent a brief audiometric evaluation of each separate ear (for 250, 500, 1000, 2000 and 4000 Hz frequencies). Then, seventeen CS were selected and individually matched to a TP for gender, age (CS: 48.76 years ± 14.63), educational level, as well as hearing acuity (each subject being categorized as having either (1) a normal hearing: hearing loss (hl)<20 dB, or (2) slight hearing loss: hl between 21 and 35 dB (see Table 1). Fourteen subjects were right-handed in each group (3 left-handed).

4. Questionnaires

All the TP filled out five questionnaires or scales recommended by the Tinnitus Research Initiative (TRI) (http://www.tinnitusresearch.org/index.php) or commonly used by clinicians and researchers in the field: the Tinnitus Sample Case History Questionnaire (TSCHQ), the Tinnitus Handicap Inventory (THI), the Beck Depression Inventory (BDI), the Self-Rating Depression Scale (SDS) and the Beck Anxiety Inventory (BAI). The TSCHQ allows identifying the history and characteristics of tinnitus (Langguth et al., 2007) while the THI provides an evaluation (between 0 and 100) of its impact on daily living (Newman, et al., 1998). The depression and anxiety scales were used to control the potential effect of emotional state on performance to our tests. In addition, the annoyance caused by tinnitus was assessed on the day of testing using a visual analogue scale (VAS) in which each

Table 2
Clinical evaluation and questionnaires scores

	Tinnitus (n = 17) Mean (SD)	Control (n = 17) Mean (SD)	unpaired t-test
Age [years] [ns]	49.00 (15.22)	48.76 (14.63)	p = 0.4818
Bilateral Hearing Loss [db] [ns]	13.55 (7.26)	11.39 (6.86)	p = 0.1895
Educational level [years] [ns]	14.41 (3.04)	15.24 (2.05)	p = 0.1807
Beck Depression Inventory [13 items] [ns]	2.94 (2.75)	2.41 (2.96)	p = 0.5404
Zung Self-Rating Depression Scale [ns]	0.47 (0.09)	0.44 (0.10)	p = 0.1966
Beck Anxiety Inventory [ns]	6.82 (2.19)	5.47 (2.62)	p = 0.0761

Bilateral Hearing Loss: according to the International bureau for Audiophonology (BIAP).

participant had to rate the level of subjective discomfort by marking a 10 centimetres line whose left extremity represented the lowest degree of discomfort (no discomfort linked to tinnitus). Table 2 shows the scores to the audiometry, questionnaires and scales in TP and CS.

5. Experimental conditions

The experiment comprised three parts, each thought to evaluate a different aspect or level of attention or perceptual (cognitive) processing in both the auditory and the visual modality: (1) stimulus detection (simple reaction speed), (2) stimulus processing (processing speed to recognize or to localize the stimulus) and (3) spatial Stroop (top-down executive control).

(1) Stimulus detection aimed at measuring the reaction speed in response to auditory or visual stimulation when processing of stimuli was kept to a minimum and little attentional resources were required. In our design, these conditions represented the lowest level of sensory processing and intended to serve as baseline for each subject's reaction speed.

(2) Stimulus processing aimed at evaluating the processing speed of auditory and visual stimuli when no interference between stimulus attributes was present, i.e. stimulus localization did not require its recognition and vice versa (see below).

(3) The spatial Stroop conditions specifically aimed at evaluating the efficiency of the top-down executive control (or central executive component) which is a cognitive module (or an executive function) dedicated to the resolution of conflicts between stimulus attributes, in this case stimulus location and stimulus meaning.

6. Materials and stimuli

Stimulus detection: Visual stimuli consisted in a grey circle appearing on a black background at the centre of a computer screen. Between the stimuli, a grey fixation cross was displayed at the centre of the screen. Each stimulus was presented for 250 ms with a variable inter-stimulus interval (ISI) ranging from 450 to 850 ms. The auditory stimuli consisted in a pure tone of 440 Hz (duration: 250 ms, rise and fall times: 10 ms) binaurally presented via headphones (HD 280 Sennheiser Pro) with a variable ISI (450-850 ms). In both modalities there were 72 trials.

Stimulus processing: (1) Visual localization: Two French words, "botte" (boot) and "manche" (sleeve) were successively displayed either at the left or the right middle part of a computer screen (Fig. 1). (2) Auditory localization: The same two words were audio recorded and provided monaurally through headphones, either in the left or the right ear. In both localization conditions, each stimulus (word) was presented 50 times (25 times on the left and 25 times on the right) for a total of 100 trials. (3) Visual recognition: Two French words, "gauche" (left) and "droite" (right) were successively displayed at the center of the computer screen. (4) Auditory recognition: The same two words were provided binaurally through headphones. In the recognition conditions, each stimulus (word) was presented 50 times for a total of 100 trials.

Spatial Stroop: Visual conditions: The French words, "gauche" (left) and "droite" (right) were successively displayed either at the left or the right middle part of the computer screen (Fig. 1). Auditory conditions: The same two words were provided monaurally through headphones, either in the left or the right ear. In each condition of the spatial Stroop, each stimulus (word) was presented 50 times (25 times on the right and 25 times on the left) for a total of 100 trials.
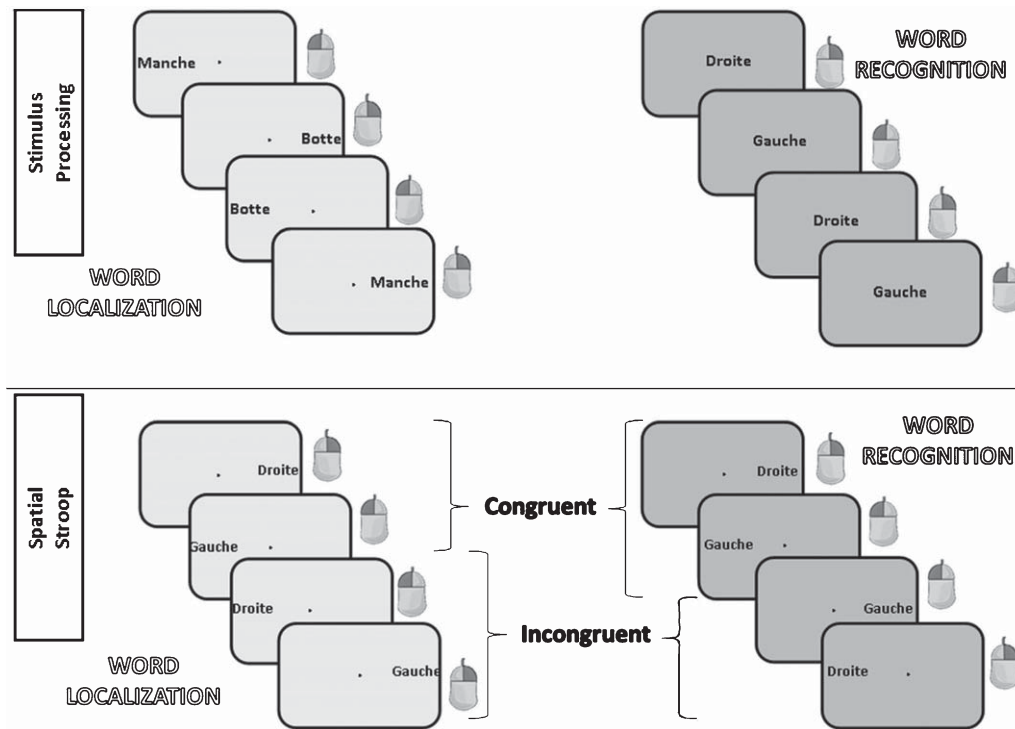
Fig. 1. Illustration of a sequence of stimulation in the visual modality during the stimulus processing conditions (processing speed, upper part) and the spatial Stroop conditions (lower part) for the word localization tasks (left) and the word recognition tasks (right). Word localization task during stimulus processing: the words "manche" (sleeve) and "botte" (boot) appeared in the left or the right part of a computer screen and the subjects had to press the left or the right button of a computer mouse according to where the word appeared (e.g. left button when it was left-sided). Word recognition task during stimulus processing: the words "gauche" (left) and "droite" (right) appeared at the center of a computer screen and the subjects had to press the left or the right button of a computer mouse according to the meaning of the word (e.g. left button when the word "gauche" appeared). Word localization task during spatial Stroop condition: the words "gauche" (left) and "droite" (right) appeared in the left or the right part of a computer screen and the subjects had to press the left or the right button of a computer mouse according to where the word appeared (e.g. left button when the word appeared on the left). Word recognition task during spatial Stroop condition: the words "gauche" (left) and "droite" (right) appeared in the left or the right part of a computer screen and the subjects had to press the left or the right button of a computer mouse according to the meaning of the word (e.g. left button when the word "gauche" appeared).

Noteworthy, in only 50% of the trials there was a conflict between the stimulus location and its meaning (i.e. incongruent trials, e.g. the word "gauche" presented on the right side), as in the other 50% the stimulus features were congruent. Therefore, the congruent trials could serve as controls to isolate the specific effect of interference on the task performance. During both visual and auditory conditions, subjects had to gaze at a fixation cross at the center of the computer screen.

In the stimulus processing and spatial Stroop conditions, the order of stimulus presentation was randomized. Each new trial started after the subject had responded to the previous one or maximum 2000 ms after the presentation of the previous trial. Participants delivered their responses by pressing the right or left button of a two buttons mouse of high temporal accu-

racy (Razer, model number: RZ01-0015) held in the right hand. Stimulations and recording of responses were controlled using E-Prime 2 Professional® (Psychology Software Tools, Pittsburgh, PA, USA).

7. Tasks and procedures

The testing took place in quiet and dimly lit room. Subjects were seated in front of a computer screen (placed at about 60 centimeters from subjects' head) with headphones covering the ears. After a brief familiarization session to the tasks, the different tests were administered in pseudo-random orders that were counterbalanced between subjects and groups. For stimulus detection, subjects were instructed to press as quickly

as possible on the left mouse button at stimulus (i.e. circle or sound) presentation. For stimulus localization (stimulus processing and spatial Stroop), subjects had to localize each stimulus and to press as quickly as possible on the left mouse button when the stimulus was left-sided and on the right button otherwise. For stimulus recognition (stimulus processing and spatial Stroop), subjects were instructed to press as quickly as possible on the left mouse button when the word "gauche" (left) was presented and on the right button otherwise. During the spatial Stroop conditions, the meaning of the words interfered with their location in 50% of the trials. Subject responses and response times were recorded.

8. Data analysis

Data reduction was first applied to deal with errors and outliers in the response time data: (1) trials with incorrect responses (1.57% of the trials) were excluded from the response time analyses and (2) response times beyond 2 standard deviations below or above each participant's mean for each experimental condition were discarded as outliers (0.59% of the trials).

According to our initial hypotheses, we were mostly interested in the effect of tinnitus on the efficiency of the top-down executive control, the reaction speed and processing speed in the auditory and visual modalities. Therefore, tasks (i.e. word localization and word recognition) and conditions (i.e. stimulus detection, processing and spatial Stroop) were not used as relevant factors in the analyses; rather, separate analyses were performed within each processing level and task. This allowed reducing the number of (irrelevant) comparisons and simplifying the statistical models. In addition, to better circumscribe our components of interest (i.e. the processing speed and the top-down executive control), "variables differences" were calculated (see here-below).

(1) Response times to stimulus detection (reaction speed): Analyses were performed on the mean response times for stimulus detection in the auditory and the visual modality, separately.
(2) Processing speed: We subtracted the individual mean response times in the auditory and visual detection tasks from the individual mean response times in the "word localization" and "word recognition" conditions: i.e. {auditory

word localization *minus* auditory detection}, {auditory word recognition *minus* auditory detection}, {visual word localization *minus* visual detection} and {visual word recognition *minus*} visual detection}. This allowed us controlling for potential group differences in reaction speed that would affect the response times in the stimulus processing conditions (i.e. word localization and word recognition).
(3) Top-down executive control: We subtracted the individual mean response times for the congruent trials from those for the incongruent ones in the spatial Stroop. This method ensured that any group difference observed in the spatial Stroop would be independent from any difference in processing speed and lower level sensory processing.

In addition, we performed a correlation analysis in the tinnitus group to test the potential relationship between the degree of annoyance of tinnitus (VAS scores), its impact on quality of life (THI scores) and the performance in the auditory and visual spatial Stroop conditions (i.e. response speed for the incongruent trials). Additional correlation analyses were performed in the whole group (TP and CS) to test the relationship between the visual and the auditory spatial Stroop. Statistical analyses were performed using STATA/SE 12.0 for Windows® (StataCorp, Texas, USA).

9. Results

9.1. Clinical scores (subjects characteristics, questionnaires and scales)

There was no group difference for age [t(32) = 0.04, p = 0.48], education level [t(32) = 0.92, p = 0.81], depression (BDI and SDS) [t(32) = 0.54, p = 0.29] and [t(32) = 0.86, p = 0.19], anxiety (BAI) [t(32) = 1.63, p = 0.06] and hearing acuity (hearing loss) [t(32) = 0.96, p = 0.17] (see Table 2 for scores)).

9.2. Psychophysical measurements

Shapiro-Wilk tests showed that the response times (RTs) were normally distributed in the sample in all conditions (all $p's$>0.05).
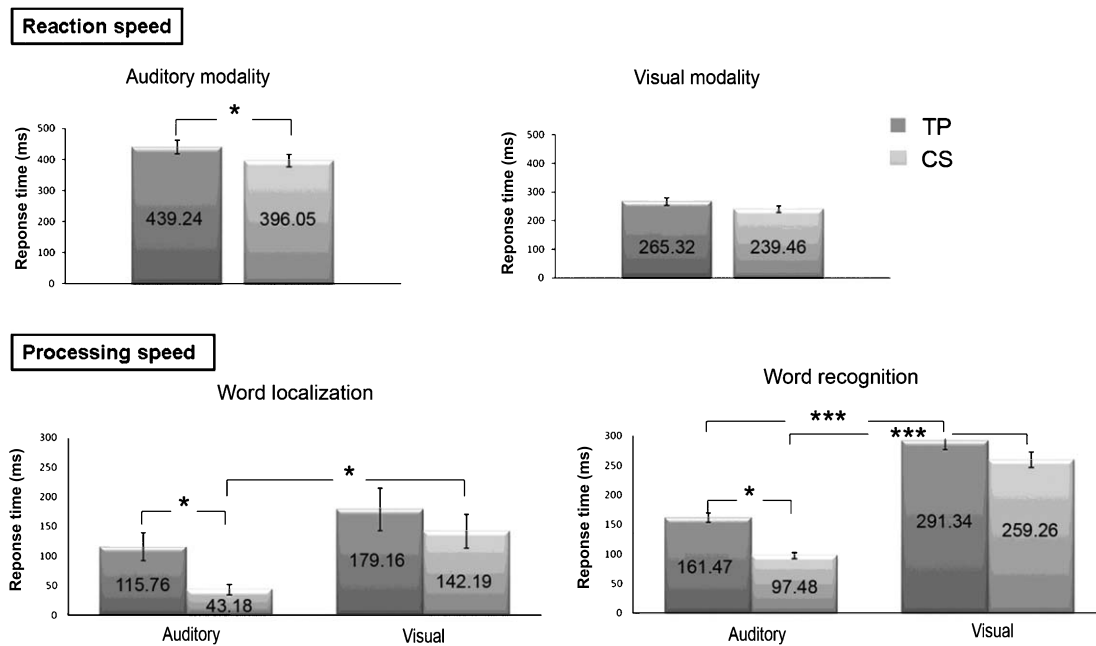
Fig. 2. Response times during the stimulus detection and processing conditions in tinnitus patients and control subjects. The upper part of the Figure shows the response times for the stimulus detection conditions (simple reaction speed) as a function of the group in the auditory modality (left) and the visual modality (right). The lower part of the Figure shows the response times for stimulus processing after subtraction of the individual response times to stimulus detection (see methods). The obtained "corrected" response times are presented as a function of the group and the sensory modality during the word localization condition (left) and the word recognition condition (right). Error bars represent standard errors of the mean (sem). TP: tinnitus patients; CS: control subjects. $*p < 0.05$; $**p < 0.005$; $***p < 0.001$.

Stimulus detection (reaction speed): One-way analyses of variance (ANOVA) performed on the response times in each modality separately, revealed a group effect in the auditory modality [F(1.32) = 4.48, $p < 0.05$], with slightly longer response times in tinnitus patients (TP) than control subjects (CS), but no group effect in the visual modality [F(1.32) = 2.36, $p = 0.1344$] (see Fig. 2).

Stimulus processing (processing speed for word localization and word recognition): A 2 (group: TP vs CS) × 2 (sensory modality: auditory vs visual) ANOVA was performed on "variables differences" (i.e. stimulus processing times *minus* stimulus detection times) in each task separately (i.e. in word localization and in word recognition) (Fig. 2). In the word localization conditions, the ANOVA revealed an effect of the group, TP being slower than CS [F(3.64) = 5.49, $p < 0.05$], an effect of the modality [F(3.64) = 12.06, $p < 0.001$] and no interaction [F(3.64) = 0.58, $p = 0.449$]. *Post-hoc* comparisons using Wald's test with Bonferroni correction showed an effect of the group in the auditory modality

($p < 0.05$) but not in the visual modality ($p = 0.2677$). An effect of the modality was also found in CS ($p < 0.05$), while only a trend was observed in TP ($p = 0.06$). In the word recognition conditions, there was an effect of the group [F(3.64) = 4.01, $p < 0.05$], an effect of the modality [F(3.64) = 36.31, $p < 0.001$] and no interaction [F(3.64) = 0.43, $p < 0.5120$]. *Post-hoc* comparisons showed an effect of the group in the auditory modality ($p < 0.05$) only, and an effect of the modality in both CS ($p < 0.001$) and TP ($p < 0.001$).

Spatial Stroop (top-down executive control): In each group and condition, the response times to incongruent trials were longer than the response times to congruent trials (all p's<0.05, Student *t*-tests) (Fig. 3).

A 2 (group: TP vs CS) × 2 (sensory modality: auditory vs visual) ANOVA was performed on "variables differences" (i.e. response times for the incongruent trials *minus* response times for the congruent trials in spatial Stroop conditions) in each task separately (i.e. in word localization and in word recognition) (Fig. 4, see also Fig. 3 for the raw response times in spatial Stroop). In the word local-
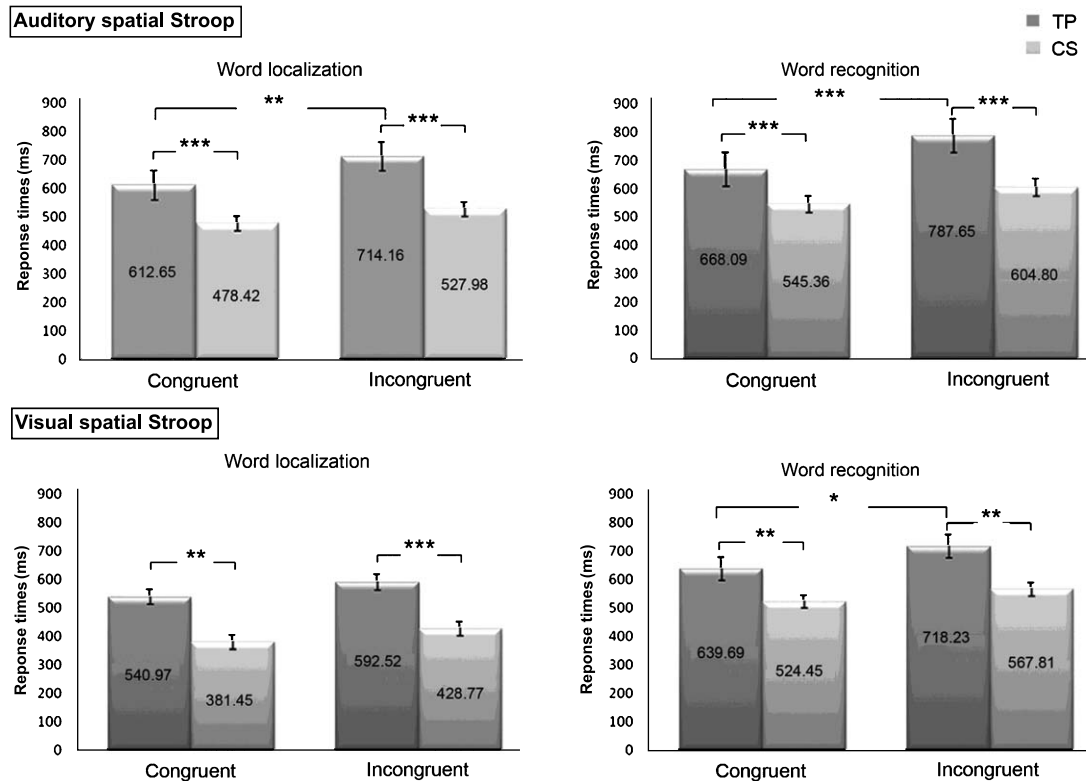
Fig. 3. Response times during the spatial Stroop conditions in tinnitus patients and control subjects. Response times are displayed as a function of the group and the trial type (congruency of the stimulus attributes: congruent vs incongruent) during the word localization conditions (left part) and the word recognition conditions (right part). The upper part of the Figure shows the results in the auditory modality and the lower part of the Figure shows the results in the visual modality. Error bars represent standard errors of the mean (sem). *$p < 0.05$; **$p < 0.005$; ***$p < 0.001$.

ization conditions, we observed an effect of the group [$F(3.64) = 6.47$, $p < 0.05$], an effect of the modality [$F(3.64) = 5.58$, $p < 0.05$] and an interaction between group and modality [$F(3.64) = 4.67$, $p < 0.05$]. *Post-hoc* comparisons using Wald's test with Bonferroni correction showed an effect of the group in the auditory modality ($p < 0.005$) only. There was also an effect of the modality in TP ($p < 0.005$) only. In the word recognition conditions there was an effect of the group [$F(3.64) = 13.94$, $p < 0.001$], an effect of the modality [$F(3.64) = 5.00$, $p < 0.05$] and no interaction [$F(3.64) = 0.95$, $p = 0.3326$]. *Post-hoc* comparisons showed an effect of the group in both the auditory ($p < 0.005$) and the visual modalities ($p < 0.05$) and an effect of the modality in TP only ($p < 0.05$).

Too few errors were made during the stimulus detection and processing conditions to allow analyses (percentage of errors <1%). Therefore, statistical

analyses on response accuracy were only performed for the spatial Stroop conditions. A 2 (group: TP vs CS) x 2 (sensory modality: auditory vs visual) ANOVA was performed on the response accuracy rate in each task separately (i.e. in word localization and in word recognition) (Fig. 5). In the word localization conditions, there was an effect of the group [$F(3.64) = 28.61$, $p < 0.001$], an effect of the modality [$F(3.64) = 13.87$, $p < 0.001$] and a trend for an interaction [$F(3.64) = 3.34$, $p = 0.0722$]. *Post-hoc* comparisons revealed an effect of the group, with more errors in TP than CS, both in the auditory ($p < 0.001$) and in the visual modalities ($p < 0.05$) and an effect of the modality in TP only ($p < 0.001$). In the word recognition conditions, there was an effect of the group [$F(3.64) = 19.74$, $p < 0.001$], no effect of modality [$F(3.64) = 1.47$, $p = 0.23$] and no interaction [$F(3.64) = 1.16, p = 0.2854$]. *Post-hoc* comparisons showed an effect of the group in both
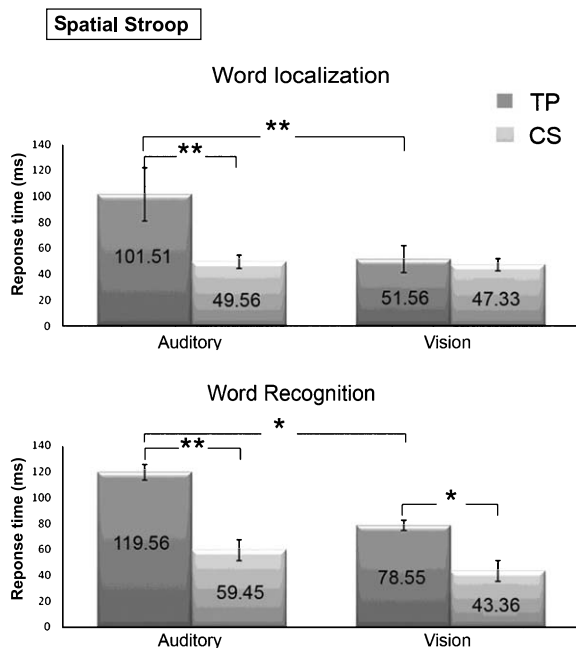
Fig. 4. Response times during the spatial Stroop conditions in tinnitus patients and control subjects. This Figure shows the response times for the incongruent trials minus the response times for the congruent trials. The obtained "corrected" response times are presented as a function of the group and the sensory modality during the word localization condition (upper part) and the word recognition condition (lower part). Error bars represent standard errors of the mean (sem). TP: tinnitus patients; CS: control subjects. $^*p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.001$.
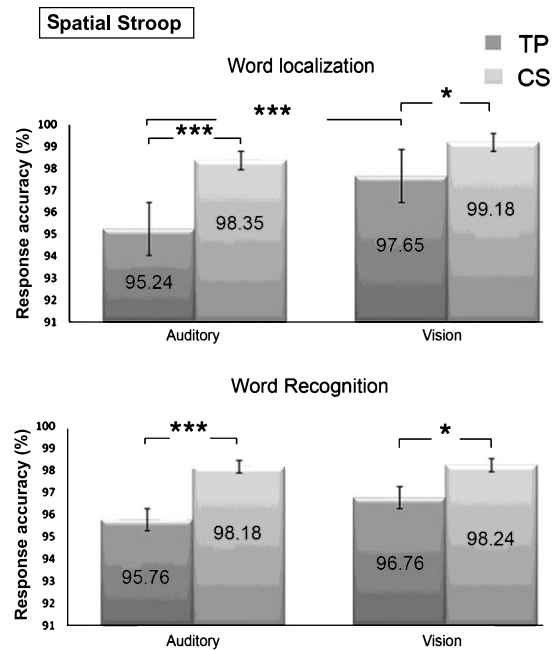

Fig. 5. Response accuracy (percentage of correct responses) during the spatial Stroop conditions in tinnitus patients and control subjects. This Figure shows the percentage of correct responses as a function of the group and the sensory modality during the word localization condition (upper part) and the word recognition condition (lower part). Error bars represent standard errors of the mean (sem). TP: tinnitus patients; CS: control subjects. $^*p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.001$.

the auditory $(p < 0.001)$ and the visual modalities $(p < 0.05)$.

Correlation analyses: The TP group showed a link between the response times in the spatial Stroop conditions (incongruent trials) and tinnitus annoyance (VAS) in all the conditions except for the visual word localization: auditory word localization $(r = 0.7410, p < 0.001)$, visual word localization $(r = 0.4536, p = 0.0674)$, auditory word recognition $(r = 0.7440, p < 0.001)$ and visual word localization $(r = 0.6829, p < 0.005)$. The performance in the spatial Stroop tasks was not correlated with any other clinical scores (e.g. THI; all p's>0.05). Correlation analyses performed in the whole group (TP and CS) between the auditory and visual spatial Stroop tasks showed a link between sensory modalities for response accuracy, both in (auditory and visual) word localization $(r = 0.7208, p < 0.001)$ and in (auditory and visual) word recognition $(r = 0.8335, p < 0.001)$. Correlation analyses performed within each group separately were also significant (all p's<0.05).

10. Discussion

Very few studies have investigated the tinnitus-related cognitive impairments so far, hence very little is known about the importance and nature of the cognitive deficits in tinnitus sufferers. The purpose of the present study was to test to what extent top-down executive control and stimulus processing speed were affected in tinnitus subjects and whether deficits were restricted to the auditory modality or could also be observed in vision. Here we observed that tinnitus patients (TP) were slower and less accurate than control subjects (CS) during both the auditory and the visual spatial Stroop tasks (i.e. they were slower and made more errors in incongruent or interference trials), in particular during the word recognition conditions (Figs. 4 and 5). In addition, TP showed longer response times to stimulus detection (simple reaction speed) and stimulus processing (word localization and word recognition) in the auditory modality only (Fig. 2).

10.1. Slowed down processing speed in tinnitus

The longer response times observed in TP during the auditory word processing conditions were independent from any slowed down reaction speed since individual response times to stimulus detection were subtracted from the stimulus processing response times. However, the deficit was restricted to the auditory modality (with normal response times in the visual modality). Therefore, a global slowed down in the processing speed (Das et al., 2012) or a global depletion of attention resources (Stevens et al., 2007) in TP seems excluded.

Although we cannot exclude that the slow down in the auditory word processing in TP was due to a deficit in speech discrimination undetected during the audiometry with pure tones, such effect should be minor given the nature of experimental conditions in the present study. Previous studies showed that speech discrimination was mostly affected in TP in noisy environment which was not the case in the present study (Spitzer et al., 1983; Huang et al., 2007; Ryu et al., 2012). In addition, the two French words "gauche" (left) and "droite" (right) that were used in the word recognition condition sounded clearly differently, which should have facilitated their discrimination. Therefore, the longer response times to stimulus processing in the auditory modality could rather result either from the alteration of cognitive modules dedicated to the processing of auditory information (e.g. spectral analysis, phonemes recognition), that would be less efficient in TP, or from interferences occurring during the processing of auditory stimuli. In the latter perspective, one may hypothesize that auditory stimulations would automatically triggered emotional responses in TP that would slow down the processing of (auditory) stimuli. Noteworthy, a similar phenomenon has been described in chronic pain patients (Wiech, Ploner, Tracey, 2008). Such interference would not occur in non-auditory modalities given the auditory-specific nature of tinnitus. This hypothesis is consistent with recent models that postulate a role of limbic structures and aversive memory networks in tinnitus (Rauschecker et al., 2010; De Ridder et al., 2011). In accordance with this view, hyperactivity in limbic structures (e.g. the nucleus accumbens) has been reported in response to auditory stimulations in TP, especially when using tinnitus-matched frequencies as the stimulus (Leaver et al., 2011). Auditory stimulations in TP also elicit brain activity in the distress network, i.e. the anterior cingulate cortex,

anterior insula, and amygdala (De Ridder et al., 2011). In the present study, longer response times were also observed in TP during the auditory stimulus detection condition (i.e. simple reaction times). This could reflect a latency effect in response to the presentation of (auditory) stimuli that have an emotional valence in TP.

10.2. Altered top-down cognitive control in tinnitus

TP were slower and less accurate than CS during the spatial Stroop conditions in both the auditory and visual modalities. The longer response times observed in TP during the interference conditions (incongruent trials) were independent from any slowed down in the stimulus detection and processing speed since the group difference was still present after subtraction of the individual response times for the congruent trials (requiring detection and processing, i.e. reaction speed and processing speed without interference). The observation of longer response times and lower accuracy rates in TP than CS during the spatial Stroop conditions in both the visual and auditory modalities indicates that top-down executive control mechanisms are impaired in TP. Although performance appeared slightly worse in the auditory modality, a deficit was present in both modalities, which is consistent with the idea according to which these cognitive processes are supra-modal, i.e. exert a control in all the sensory modalities (Roberts and Hall, 2008; Donohue, et al., 2012). This greater deficit in TP was more pronounced in the auditory modality; this is probably due to an additional decrease in the efficiency of the executive control resulting from the interactions between impaired cognitive modules: executive control and auditory stimulus processing. The strong correlations between response times in the visual and auditory spatial Stroop tasks confirm that a similar process is at work during the Stroop conditions in the two modalities. Moreover, the observation of a deficit in the top-down executive control in the present study is consistent with previously reported deficits in TP in studies that used Stroop tasks or the attention network test (ANT) (Andersson et al., 2000; Stevens et al., 2007; Heeren et al., 2014). Here, the use of strict inclusion criteria to limit confounding factors allows us to provide clear demonstration that this top-down cognitive control deficit is primarily related to tinnitus and not to any of the disorders that are frequently associated to this condition (Langguth et al., 2007, 2013; Knipper, et al., 2013). In particular we paid a particular

attention to exclude comorbidity conditions that are known to affect the cognitive functioning and performances to psychological tests: depression and anxiety (Pessoa, 2009; Kanske & Kotz, 2012), aging or hearing acuity (Lindenberger & Baltes, 1994; Salthouse, et al., 1996; Baltes & Lindenberger, 1997; Baldwin & Ash, 2011). The top-down executive control is known to play a role in the resolution of conflicts between stimulus attributes, as in the present spatial Stroop tasks, but also in the distribution of attention resources and the regulation of emotion and sensations (Alain et al., 1998; Lewis et al., 2000; Mitchell et al., 2005; Voisin et al., 2006; Boggio, et al., 2008; Boggio, et al., 2009; Ochsner, et al., 2012). Given the prominent role of the executive control in the cognitive functioning and its involvement in many attention tasks, one may hypothesize that a deficit in the executive control impacts performance in various cognitive tasks (e.g. divided attention, working memory). Therefore, it is tempting to suggest that this specific deficit may primarily cause the concentration difficulties frequently reported by tinnitus sufferers. It may also explain the altered performances in cognitive and attention tasks (Cuny, et al., 2004; Hallam et al., 2004; Rossiter et al., 2006; Das et al., 2012). Here we postulate that the top-down cognitive control is a major component of the process that prevents phantom sensations to reach consciousness, i.e. the top-down inhibitory processes (Norena, et al., 1999). A dysfunction of the top-down executive control, along with alterations of the auditory system, would be a necessary condition for the generation and maintenance of tinnitus. In this perspective, the efficiency of top-down executive control can potentially be considered as a (cognitive) marker of tinnitus that could be used as an indicator of its severity (correlated to tinnitus annoyance) as well as a major target in a treatment and an indicator of the efficiency of a revalidation procedure.

From a neural point of view, Stroop tasks usually recruit the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC) (Botvinick, et al., 2001; Egner & Hirsch, 2005 a, b). The dlPFC is also known to exert early inhibitory modulation of input to primary auditory cortex in humans (Knight et al., 1989), which is thought to be compromised in TP (Vanneste, et al., 2013). Noteworthy, the stimulation of the dlPFC using transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) affects both tinnitus intensity and distress (Kleinjung et al., 2008; Vanneste et al., 2010a; Vanneste et al.,

2013). Since the dlPFC is involved in the regulation of emotions (Fregni et al., 2006; Ochsner et al., 2012), it is also probably influenced by emotional states. On the one hand, the dlPFC, with the ACC, the anterior insula and the amygdala, is part of the distress network activated during auditory stimulation in tinnitus patients (Vanneste et al., 2010b; Vanneste, et al., 2012; De Ridder et al., 2013). On the other hand, the dlPFC is connected to parts of the limbic system, such as the ventromedial prefrontal cortex (vmPFC), which are altered in tinnitus (Mülhau et al., 2006; Leaver et al., 2011; Seydell-Greenwald et al., 2012). In the present study, the performance in the spatial Stroop tasks was correlated with the degree of tinnitus annoyance; the more the executive control was impaired the worst the perception of tinnitus was. This leads to the idea that the dlPFC may interact with the limbic corticostriatal circuit that constitutes the noise cancelling pathway (Mühlau et al., 2006; Rauschecker et al., 2010, see also De Ridder et al., 2011). In tinnitus, the cognitive and emotional aspects are probably intimately interconnected and influencing each other, so that the alteration of one component affects the functioning of the other one, resulting in tinnitus perception.

In conclusion, here we showed that tinnitus is associated with both modality-specific deficits along the auditory processing system, though their exact nature is still unclear, as well as an impairment of the top-down executive control. We postulate that alterations in these cognitive control mechanisms would play a key-role in tinnitus generation and maintenance. Therefore, the effect of cognitive training methods targeting specifically the top-down executive control should be evaluated. In addition, future functional brain imaging studies should further establish a direct link between a deficit of the top-down executive control and alterations of the dorsolateral prefrontal cortex in tinnitus patients.

Acknowledgments

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