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Research Report

The neural correlates of cognitive dysfunction in phantom sounds

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ABSTRACT

Tinnitus is an auditory phantom percept with a tone, hissing or buzzing sound in the absence of an objective physical sound source. It has been shown that tinnitus can lead to emotional and cognitive impairment and people with tinnitus perform worse than a control group on different cognitive tasks. The hippocampus is known to play an important role in cognitive performance, and also in the pathophysiology of tinnitus. Hippocampal deficits have been described in animal models of tinnitus and in tinnitus patients a decrease in grey matter in the hippocampus has been demonstrated. Nineteen patients with tinnitus and fifteen healthy controls performed different cognitive processing tasks and underwent an EEG with source analysis to investigate the relationship between tinnitus loudness, tinnitus distress and tinnitus duration, cognitive impairment and neurophysiological changes in the hippocampus. Results show that both tinnitus loudness, tinnitus distress and tinnitus duration correlated positively with different cognitive measures (trail making test, Montreal cognitive assessment, mini mental state examination). It was also shown that these cognitive measures correlate with beta activity in the hippocampus, the pregenual and subgenual anterior cingulate cortex extending into the right insula. A region of interest analysis further confirms that beta activity in the left and right hippocampal area correlated with the trail making performance. In conclusion, these results support for the first time the notion that cognitive changes in tinnitus patients are associated with changes in hippocampal activity as well as the anterior cingulate and insula.

1. Introduction

Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source (Jastreboff, 1990). The American Tinnitus Association estimates that 50 million Americans perceive tinnitus, and that 12 million of these people have chronic tinnitus that prompts them to seek medical attention. Since tinnitus prevalence increases with age (Hoffman and Reed, 2004), these numbers are expected to increase due to the demographic development. The constant awareness of this phantom sound often causes a considerable amount of distress. Between 6 and 25% of the affected people report symptoms that are severely debilitating (Baguley, 2002; Eggermont and Roberts, 2004) and 2 to 4% of the whole population suffers from the worst severity degree. In this group the condition leads to a noticeable decrease in the quality of life (Axelsson and Ringdahl, 1989). Psychological complications such as lifestyle detriment, emotional difficulties, sleep deprivation, work hindrance, interference with social interaction and decreased overall health have been attributed to tinnitus (Folmer et al., 1999; Folmer and Griest, 2000; Scott and Lindberg, 2000; Tyler and Baker, 1983).

But apart from social and emotional problems, studies have also documented cognitive impairments in persons with tinnitus (Hallam et al., 2004; Jacobson et al., 1996; McKenna et al., 1996; Wilson et al., 1991). Tinnitus patients performed more poorly than a control group on arithmetic, letter cancelation, verbal fluency, and trail making tasks (McKenna et al., 1996). As such, tinnitus might be associated with a reduced cognitive functioning on working and long-term memory as well as on aspects of selective and divided attention (Andersson et al., 2000, 2002; Hallam et al., 2004; Rossiter et al., 2006).

Rats exposed to blast waves showed cognitive deficits in behavioral testing (Cernak et al., 2001; Saljo et al., 2009; Saljo et al., 2010; Saljo et al., 2011). Recent data from combat personnel

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exposed to excessive noise levels, explosions and blast waves show not only severe hearing loss and tinnitus but also severe cognitive and memory impairment (Cave et al., 2007). Although cognitive complaints are common among tinnitus patients, only a few studies have adopted an objective approach to examine the nature of these cognitive deficits. That is, the cognitive performance deficits may be associated with neurophysiological changes in people with tinnitus.

The hippocampus is known to play an important role in learning, memory, mood, spatial navigation and also in cognitive performance (Becker and Wojtowicz, 2007; Lafenetre et al., 2011; Moscovitch et al., 2005). The involvement of the hippocampal area in tinnitus has been documented by transient tinnitus diminution after suppression of the amydalo-hippocampal complex by supraselective amobarbital injections in the anterior choroidal artery (De Ridder et al., 2006). Further support for involvement of the hippocampus in the pathophysiology of tinnitus comes from an imaging study which has demonstrated in tinnitus patients a decrease in grey matter in the hippocampus (Landgrebe et al., 2009). It has been suggested that the involvement of the hippocampal area might reflect a paradoxical memory (Shulman, 1995), or an aversive auditory memory trace (De Ridder et al., 2011). In animal models of noise trauma and auditory overstimulation, both of which are known to generate tinnitus, hippocampal changes have been described, interfering with hippocampal neurogenesis (Kraus et al., 2010) and impairing place cell function (Goble et al., 2009). Thus the question remains whether cognitive deficits described in humans in tinnitus might be related to hippocampal involvement.

The present study focused on objective measures of cognition (i.e. TMT-A, TMT-B MoCA and MMSE) which are associated with hippocampal activity (Leirer et al., 2010), and especially medial temporal lobe atrophy (Oosterman et al., 2010). These measures have been used across a variety of studies and clinical populations, and are a cognitive processing. The primary goal of this study is to determine whether tinnitus influences cognitive function in humans, in view of hippocampal place cell function changes described in animals (Goble et al., 2009), and whether these changes are associated with activity changes in the hippocampus. Hence, we use source localized EEG recordings of tinnitus patients and analyzed the spectral components related to the trail making cognitive measure, as well as the Montreal cognitive assessment and the mini mental state examination.

2. Results

2.1. Behavioral outcomes

Correlation between the different questionnaires revealed a significant relationship between TMT-A, TMT-B, MMSE and MoCA (see Table 1 for overview). A very strong correlation could be obtained between TMT-A and TMT-B ($r=.80$, $p<.001$) and between MMSE and MoCA ($r=.76$, $p<.001$). Correlations between the trail making task (TMT-A and TMT-B) and MSSE and MoCA are negative. However, for the trail making test a higher score indicates that more time is needed for a person to complete the task, while for the MMSE and the MoCA the lower the score the worse a person was performing cognitively.

2.1.1. Trail Making Test Part A and B

Tinnitus patients had a mean score of 29.05 s ($Sd=10.10$ s) on TMT-A and 66.89 s ($Sd=36.88$ s) on TMT-B and thus do not deviate from a norm population. Nevertheless, standard deviations indicate a high interindividual variability particularly for the TMT-B. Seven (36.84%) patients had a higher score than the norm for TMT-A and four (21.05%) had a higher score then the norm for TMT-B.

A significant positive correlation was found between tinnitus distress, VAS loudness and tinnitus duration and respectively TMT-A as well as for TMT-B (see Table 1). No significant correlation could be demonstrated between respectively age, hearing loss, and TMT-A and TMT-B.

For healthy controls a mean score was obtained of 29.67 s ($Sd=9.47$) on TMT-A and 59.87 ($Sd=20.18$) and thus do not deviate from the norm population. A comparison between healthy controls and tinnitus patients revealed no significant result for TMT-A ($t=.18$, $p=.86$) and TMT-B ($t=.32$, $p=.52$). Albeit, compared to the tinnitus patients the standard deviations for TMT-B is less pronounced for the healthy controls (38.88 vs. 20.18). Compared to the norm score 7 (46.67%) healthy subjects had a higher score for the TMT-A and 2 (13.33%) for the TMT-B. However, the average deviation is 9 seconds for the norm score for TMT-A and 15 s for TMT-B. No significant correlation was obtained between respectively age, hearing loss, and the TMLT-A and TMT-B respectively for healthy subjects.

Table 1
Correlations between the different cognitive assessments including tinnitus patients and healthy controls.

Tinnitus patients and Healthy controls	TMT-B	MMSE		MoCA
TMT-A	.80***	−.44**		−.46**
TMT-B	–	−.41**		−.41**
MMSE	–	–		.76***
Tinnitus patients	**Distress**	**Loudness**	**Hearing loss**	**Duration**
TMT-A	.40*	.57**	.21	.48*
TMT-B	.45*	.47*	.22	.50*
MMSE	−.64***	−.73***	.25	−.37†
MoCA	−.39*	−.48*	.19	−.37†

† $p<.10$,
* $p<.05$,
** $p<.01$,
*** $p<.001$

2.1.2. Montreal cognitive assessment

A mean score on the MoCA was 24.68 ($Sd=3.16$) for the tinnitus group. Compared to the norm 10 (52.63%) patients had a score lower than 27. A negative correlation was obtained between the MoCA and respectively distress ($r=-.39$, $p<.05$), loudness ($r=-.48$, $p<.05$) and a marginal significant effect with duration ($r=-.37$, $p=.06$) (see Table 1). No significant correlation could be demonstrated between age and the MoCA.

For the healthy controls the mean score was 27.8 ($Sd=1.33$). No healthy subjects had a score lower than the norm score. No significant correlation was obtained between respectively age, hearing loss, and the MoCA for healthy subjects.

A comparison between tinnitus patients and healthy subjects yielded a significant effect indicating that tinnitus patients score lower than healthy subjects on the MoCA ($t=3.55$, $p=.001$) (see Fig. 1).

2.1.3. Mini-mental state examination

The mean score on the MMSE for tinnitus patients was 27.26 ($Sd=27.26$). Nine (47.37%) patients had a score under the norm score. A negative correlation was obtained between the MMSE and respectively distress ($r=-.64$, $p<.001$), loudness ($r=-.73$, $p<.001$) and a marginal significant effect with duration ($r=-.37$, $p=.06$) (see Table 1). No significant correlation could be demonstrated between age and the MMSE.

For the healthy subjects the mean score on the MMSE was 29 ($Sd=1.03$). None of the healthy subjects had a score below the norm score. In addition, no correlation could be obtained between age and the MMSE.

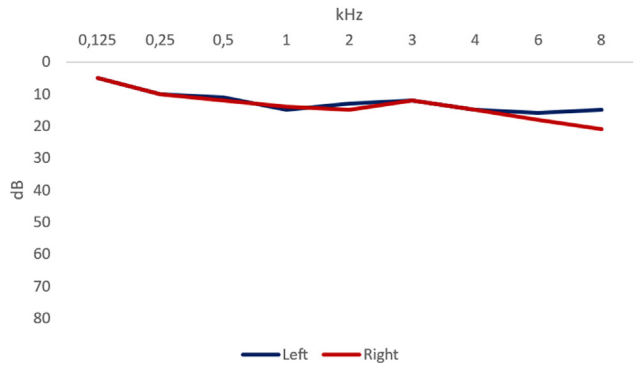

Fig. 1. Audiogram averaged overall tinnitus patients.

A comparison between the tinnitus groups and the healthy subjects demonstrated a significant effect A ($t=2.62$, $p<.05$), revealing that the tinnitus group had a significant lower score on the MMSE in comparison to the health control group (see Fig. 1).

2.2. Source localization

2.2.1. Tinnitus patients versus Healthy controls

A comparison between tinnitus patients versus healthy controls indicates a significant decreased activity in the right auditory cortex for the alpha2 frequency band and a significant increase in the right auditory cortex for the gamma frequency band (Fig. 2). No significant effect was obtained between patients that perceive their tinnitus unilateral or bilateral Fig. 3.

2.2.2. Trail making Test Part A and B

For the tinnitus patients a significant positive correlations were obtained between TMT-A and respectively subgenual anterior cingulate cortex and hippocampus for beta1 frequency ($r=.88$, $p<.05$), the hippocampus, pregenual anterior cingulate cortex and subgenual anterior cingulate cortex extending to the right insula for beta2 frequency ($r=.83$, $p<.05$), and the pregenual anterior cingulate cortex for beta3 frequency ($r=.77$, $p<.05$) (see Fig. 4). No significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band. Similar results were obtained for TMT-B for the tinnitus patients. Significant positive correlations were demonstrated with the hippocampus and the subgenual anterior cingulate cortex extending to the right insula for beta1 frequency ($r=.67$, $p<.05$), the hippocampus and subgenual anterior cingulate cortex as well as the right insula for beta2 frequency ($r=.70$, $p<.05$), and the pregenual anterior cingulate cortex for beta3 frequency ($r=.62$, $p<.05$) (see Fig. 4). No significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band.

For the healthy controls no significant correlations could be obtained for TMT-A and TMT-B respectively and brain activity for the delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency band.

2.2.3. Montreal Cognitive Assessment

A negative correlation was obtained between the MoCA and the insula, the hippocampus, the subgenual anterior cingulate cortex and pregenual anterior cingulate cortex for the beta1 frequency band ($r=-.61$, $p<.05$). For the beta2 frequency band a significant negative correlation was demonstrated between the insula, the

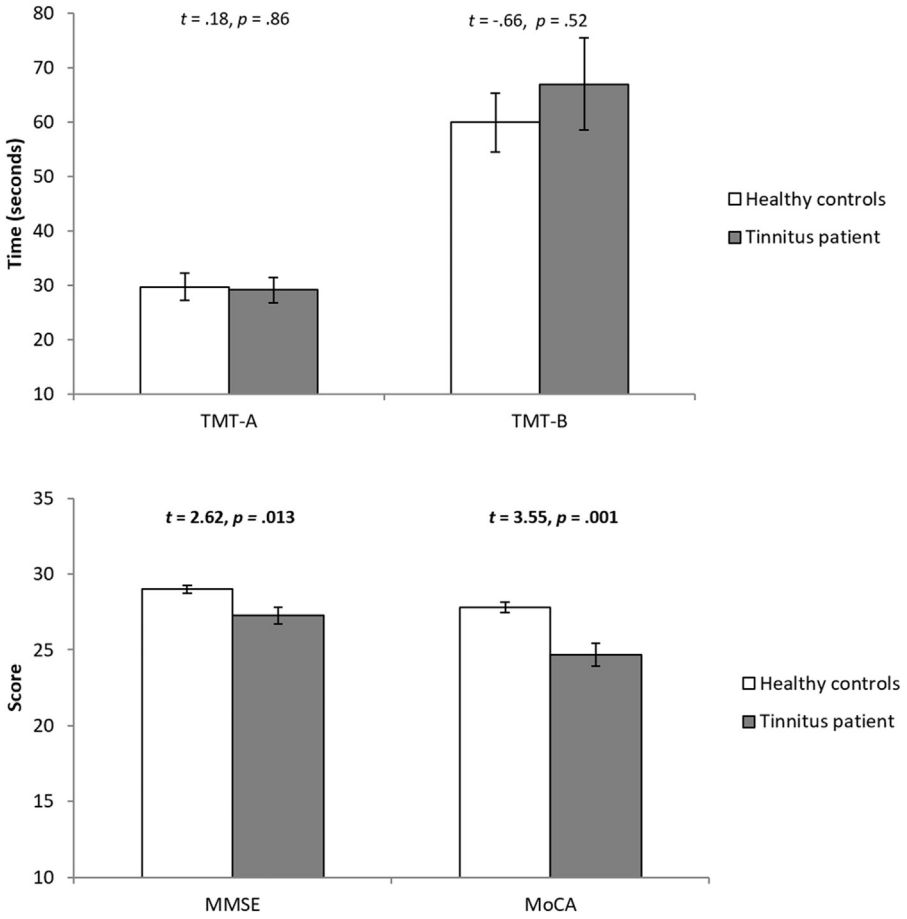

Fig. 2. A comparison between healthy controls and tinnitus patients for the different cognitive assessments.

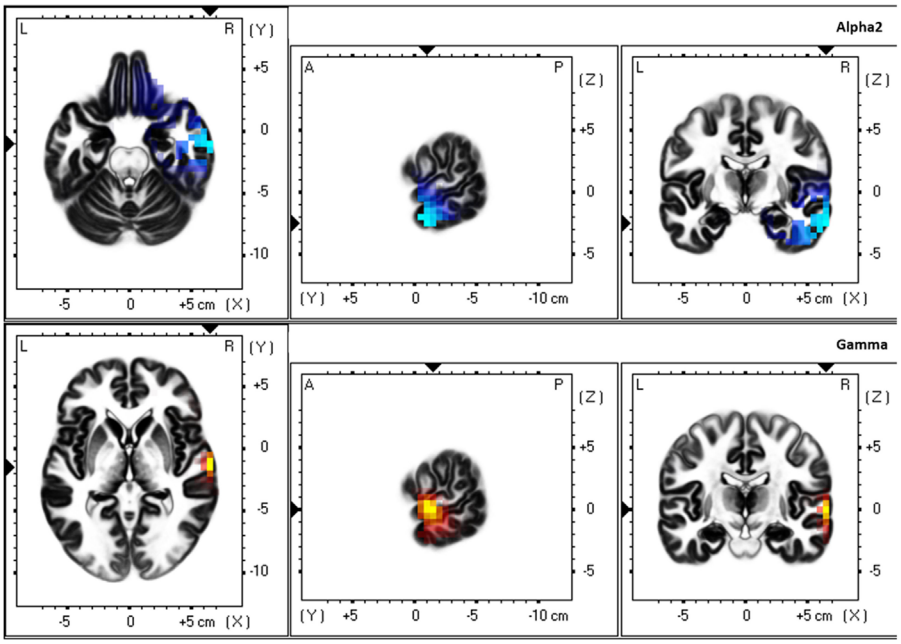

Fig. 3. A comparison between healthy controls and tinnitus patients in resting state source localized (sLORETA) EEG demonstrated significant differences. Tinnitus patients had a decrease in the auditory cortex for alpha2 frequency band and an increase in the auditory cortex for the gamma frequency band in comparison to healthy controls.

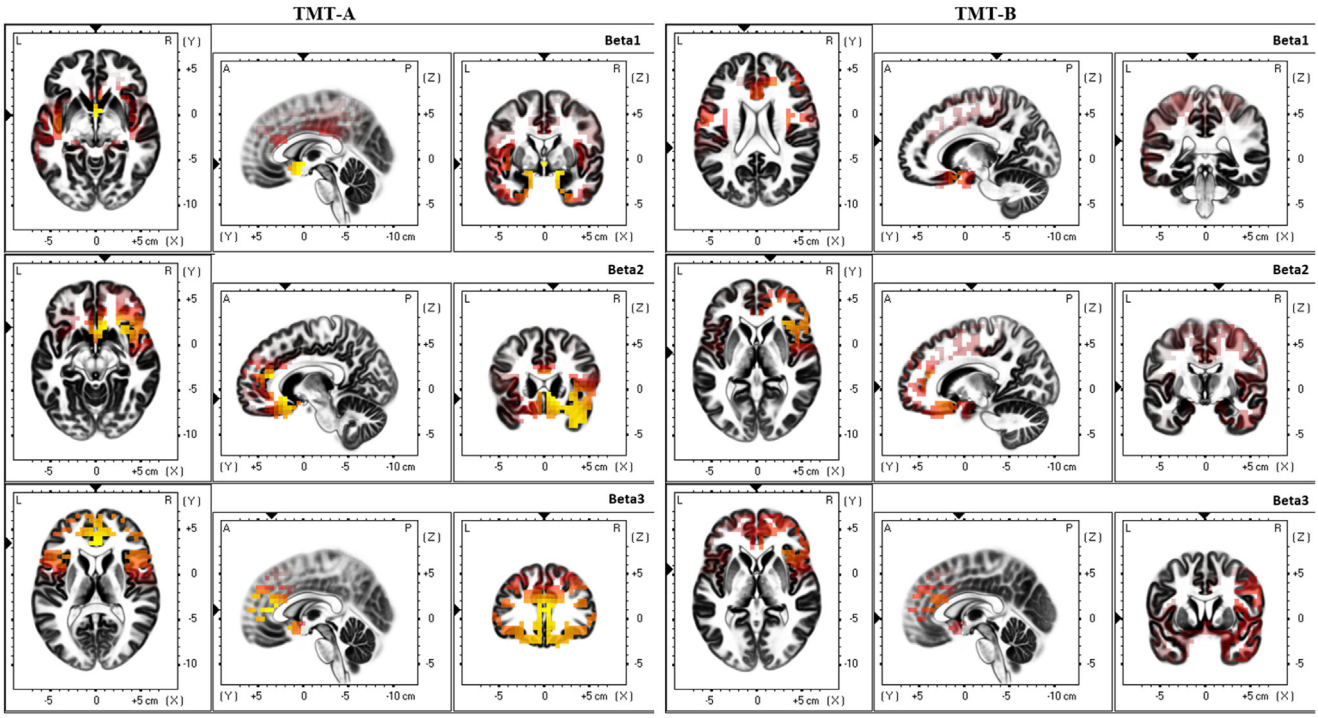

Fig. 4. Correlation between the TMT-A and TMT-B, respectively and resting state source localized (sLORETA) EEG revealed a significant correlation for the beta1, beta2 and beta3 frequency band.

hippocampus, the subgenual anterior cingulate cortex and pregenual anterior cingulate cortex ($r=-.64$, $p<.05$). Between the insula, the hippocampus, the subgenual anterior cingulate cortex and pregenual anterior cingulate cortex and the MoCA was a significant negative correlation obtained for beta3 frequency band. See Fig. 5 for an overview. No significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band.

A comparison between tinnitus patients who score lower than the norm score and the tinnitus patients who had a score similar or higher than the norm yielded an increased activity in the insula, the hippocampus, the subgenual anterior cingulate cortex and pregenual anterior cingulate cortex for the beta1 ($t=7.31$, $p<.05$), beta2 ($r=9.85$, $p<.01$) and beta 3 ($r=10.2$, $p<.001$) frequency band for tinnitus patients who score lower than the norm (see Fig. 6). No significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band.

For MoCA and brain activity for the delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency band for the healthy controls no significant correlations were obtained.

2.2.4. *Mini-mental state examination*

For the tinnitus patients, significant negative correlations were

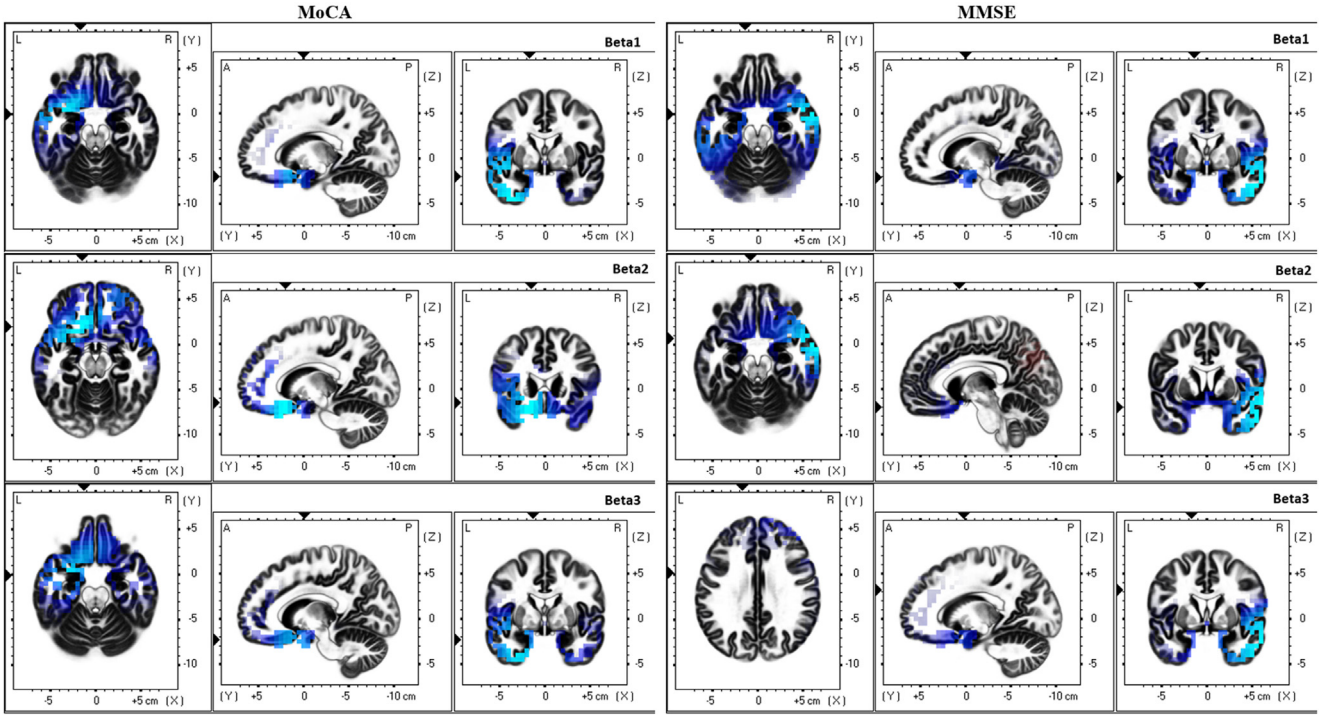

Fig. 5. Correlation between the MoCA and MMSE, respectively and resting state source localized (sLORETA) EEG revealed a significant correlation for the beta1, beta2 and beta3 frequency band.

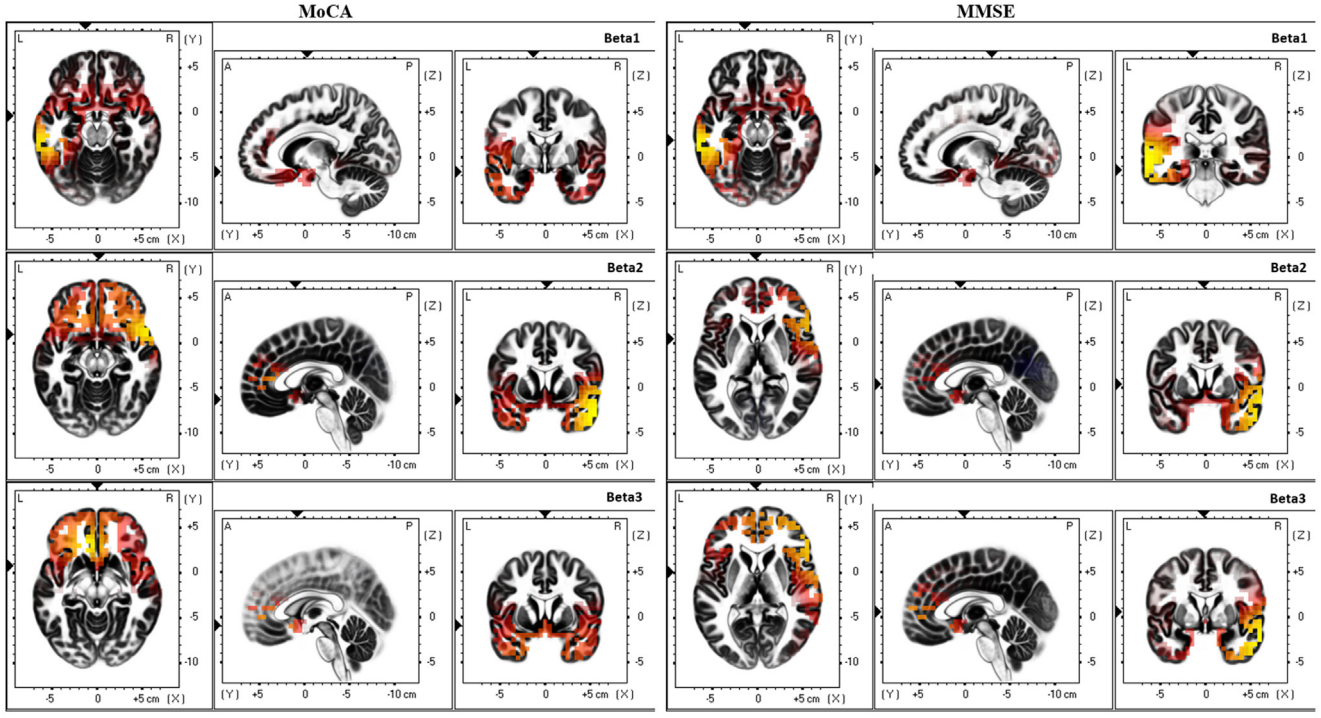

Fig. 6. Comparing tinnitus patients scoring lower than the norm score in comparison to tinnitus patients have a scoring similar or higher than the norm on the MoCA and MMSE respectively demonstrate increased activity for beta1 beta2 and beta 3 frequency band. For the MoCA, the differences are located in the inferior temporal and hippocampal area (beta1), pregenual ACC, hippocampal area and orbitofrontal area (beta2 and beta3). For the MMSE, the differences are located in the inferior temporal and hippocampal area (beta1), pregenual ACC, hippocampal area and right insular area (beta2 and beta3) as well as the frontal area (beta 3).

obtained between MMSE and respectively insula, pregenual anterior cingulate cortex and hippocampus for beta1 ($r=.62$, $p<.05$), beta2 ($r=.65$, $p<.05$) and beta 3 ($r=.67$, $p<.05$) frequency band (see Fig. 5). No significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band.

When comparing tinnitus patients scoring lower than the norm score in comparison to tinnitus patients scoring similar or higher than the norm demonstrated increased activity in the insula, the hippocampus, the subgenual anterior cingulate cortex and pregenual anterior cingulate cortex beta1 ($t=2.87$, $p<.05$), beta2 ($r=7.98$, $p<.01$) and beta 3 ($r=10.4$, $p<.001$) frequency band for tinnitus patients scoring lower than the norm (see Fig. 6). No

Table 2
Pearson correlations between the left and right hippocampus and the different cognitive assessments as well as partial correlations between the left and right hippocampus and the different cognitive assessments controlling for distress, loudness, and duration respectively.

	Beta1		Beta2		Beta3	
	Left	Right	Left	Right	Left	Right
TMT-A	.54**	.54**	.54**	.51**	.59**	.55**
TMT-B	.46*	.50**	.47*	.47*	.51*	.49*
MMSE	−.37†	−.33†	−.34†	−.29	−.42*	−.40*
MoCA	−.40*	−.33†	−.40*	−.33†	−.53**	−.43*
Controlling for Distress						
TMT-A	.55**	.55**	.57**	.54**	.57**	.54**
TMT-B	.44*	.49*	.47*	.48*	.46*	.45*
MMSE	−.37†	−.31	−.31	−.30	−.40*	−.40*
MoCA	−.37†	−.29	−.38†	−.32	−.49*	−.40*
Controlling for Loudness						
TMT-A	.55**	.55**	.57**	.54*	.61**	.57**
TMT-B	.45*	.49*	.48*	.48*	.51*	.49*
MMSE	−.41*	−.36†	−.38†	−.35†	−.47*	−.47*
MoCA	−.40*	−.32	−.41*	−.35	−.54*	−.44*
Controlling for Duration						
TMT-A	.55**	.55**	.57**	.54**	.57**	.54*
TMT-B	.44*	.49*	.47*	.48*	.46*	.45*
MMSE	−.37†	−.32	−.31	−.30	−.40*	−.42*
MoCA	−.37†	−.29	−.38†	−.32	−.49*	−.40*

*** $p < .001$
† $p < .10$,
* $p < .05$,
** $p < .01$,

significant results were obtained for the delta, theta, alpha1, alpha2 and gamma frequency band.

For the healthy controls no significant correlations could be obtained for MMSE and brain activity for the delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency band.

2.3. Region of interest analysis

2.3.1. Trail making Test Part A and B

Pearson correlations were calculated between the left and right hippocampal area for all frequency bands with respectively TMT-A and TMT-B. For TMT-A significant positive correlations were obtained for beta1, beta2, beta3 for the left and right hippocampal area (see Table 2). A similar result was obtained for TMT-B. Also significant positive correlations were obtained for beta1, beta2, beta3 for the left and right hippocampal area (see Table 2). No significant results were obtained for respectively delta, theta, alpha1, alpha2 and gamma and the left and right hippocampal area for the TMT-A and TMT-B.

After controlling for distress, loudness and duration, respectively our analysis revealed a similar correlation between TMT-A, TMT-B respectively and the left and right hippocampus for beta1, beta2 and beta3 frequency band (see Table 2).

2.3.2. Montreal Cognitive Assessment

Using a Pearson correlation between the left and right hippocampal area for all frequency bands with respectively MoCA indicates a significant correlation between the MoCA and the left hippocampus for the beta1, beta2 and beta3 frequency band (see Table 2). For the right hippocampus the effect with the MoCA was only marginally significant for the beta1, beta2 and significant for the beta3 frequency band (see Table 2). No significant results were obtained for respectively delta, theta, alpha1, alpha2 and gamma frequency band and the left and right hippocampal area for the MoCA.

After controlling for distress, loudness and duration, respectively our analysis revealed an effect similar between MoCA respectively and the left and right hippocampus for beta3 frequency band.

2.3.3. Mini-mental state examination

Using a Pearson correlation between the MMSE and respectively the left and right hippocampal area for all frequency bands demonstrates a significant association between the MMSE and the left hippocampus for the beta3 frequency band (see Table 2). Both beta1 and beta3 frequency were only marginally significant. For the right hippocampus the effect with the MoCA was only marginally significant for the beta1, beta2 and significant for the beta3 frequency band (see Table 2). No significant results were obtained for respectively delta, theta, alpha1, alpha2 and gamma frequency band and the left and right hippocampal area for the MoCA.

After controlling for distress, loudness and duration, respectively our analysis shows an effect similar between MMSE respectively and the left and right hippocampus for beta3 frequency band. For the beta2 frequency band these effects were not present.

2.3.4. Loudness, distress, hearing loss and duration

Using a Pearson correlation between the loudness, distress, hearing loss and duration, respectively and the left and right hippocampal area for all frequency bands respectively no significant effect for delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency band was obtained (see Table 3).

3. Discussion

This study examined the relationship between tinnitus characteristics, cognitive function and hippocampal function. In detail we assessed the performance on different cognitive measures and investigated correlations of the results with tinnitus loudness, tinnitus distress, tinnitus duration and activity changes in the brain and particularly in the hippocampus. This study yielded several significant findings. First, it was shown that tinnitus distress, tinnitus loudness and tinnitus duration correlated with the processing speed measured by the trail making cognitive measure (i.e. TMT-A and TMT-B), the MOCA and MMSE which are an objective measure for cognitive performance. In addition, it was shown that these measures do not correlate with age. Secondly, tinnitus patients have a decreased alpha power and increased gamma power within the auditory cortex in comparison to healthy controls. Thirdly, it was shown that the cognitive measures correlate with activity changes in the subgenual and pregenual anterior cingulate cortex extending to the right insula as well as the hippocampus for beta frequencies. These correlations indicate that increased high frequency activity during resting state correlates with more time required completing the TMT or less performing on the MoCA and MMSE. Fourthly, a region of interest analysis further confirms that the left and right hippocampal area

Table 3
Pearson correlations between the left and right hippocampus and distress, loudness, hearing loss and duration respectively.

	Beta1		Beta2		Beta3	
	Left	Right	Left	Right	Left	Right
Loudness	.10	.09	.04	.02	.09	.07
Distress	.17	.16	.13	.11	.24	.21
Hearing loss	.06	.07	.05	.03	.07	.05
Duration	.17	.16	.13	.11	.24	.21

† $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

indeed correlated with the cognitive measure.

Our study shows a decrease in alpha power together with an increase gamma power within the auditory cortex in tinnitus patients. This finding corroborates with previous studies that indicate that the amount of gamma band activity is correlated to the subjectively perceived tinnitus loudness (van der Loo et al., 2009; Vanneste et al., 2012) and a decrease in alpha power is associated with an increase in gamma power in tinnitus (Adamchic et al., 2012; Adamchic et al., 2014; Lorenz et al., 2009; Ramirez et al., 2009). To a certain extent this fits with the concept of thalamocortical dysrhythmia (Llinas et al., 2005; Llinas et al., 1999). This model states that in the deafferented state, the dominant resting state alpha rhythm (8-12 Hz) decreases to theta (4–7 Hz) (Llinas et al., 1999) band activity. As a result, lateral inhibition is reduced (Llinas et al., 2005), inducing gamma (> 30 Hz) band activity (Llinas et al., 1999) surrounding the deafferented theta area, also known as the edge effect (Llinas et al., 2005). Interestingly, the increase in theta power within the auditory cortex was not found in this study.

This study however shows that poor cognitive performance is related to the tinnitus distress, tinnitus loudness and tinnitus duration, suggesting that distress, sound intensity as well as the duration influences the cognitive performance of a tinnitus patient. This is in accordance with a previous report that suggests that tinnitus related distress is related to the cognitive functioning of the patient (Andersson and McKenna, 2006) and that tinnitus impairs cognitive functioning (Hallam et al., 2004).

Our findings confirm recent research that has shown that the different cognitive measures were associated with hippocampal activity (Leirer et al., 2010). Tinnitus is strongly correlated with noise-induced hearing loss, stress and depression (Folmer et al., 1999; Holgers, 2003; Nicolas-Puel et al., 2002). Emotions and memories evoked by severe tinnitus have been postulated to involve the hippocampus and the limbic system, as suggested by brain-imaging studies, which show changes in hippocampal and parahippocampal activity in tinnitus or evoked by tinnitus-like acoustic stimuli (Lockwood et al., 1998; Mirz et al., 2000; Vanneste et al., 2010a; Vanneste et al., 2010b; Vanneste et al., 2010c). Moreover, a decrease in hippocampal grey matter has been observed in tinnitus patients (Landgrebe et al., 2009). A recent study demonstrated that tinnitus duration correlates with metabolic resting activity in the hippocampal area (Schecklmann et al., 2013), paralleling our findings of correlations between tinnitus duration, poorer cognitive performance and hippocampal beta activity. We are well aware, that our study similarly to all mentioned imaging studies follows a correlative approach and therefore does not allow any firm conclusions about the direction of causality. Theoretically all assessed aspects (tinnitus loudness/distress/duration, cognitive performance, high beta-activity in the hippocampus) could be the proximate cause for the others, but also an independent other cause (such as hearing) could explain the obtained correlations (Andersson, 2003; Sereda et al., 2013). Our results do not show an effect for hearing loss, however this could mainly be related to low variance (> 20 dB on all frequencies). We only tested hearing acuity in tinnitus patients by means of a standard pure tone audiometry limited to 8 kHz. However, recent research has shown that tinnitus can occur in relationship with hearing loss at supra-clinical frequencies (above 8 kHz) (Melcher et al., 2013) or profound auditory brainstem response (Chambers et al., 2016).

Recently, a parallel between the pathophysiology of depression and tinnitus has been proposed, based also on imaging, neurotransmission, neuroendocrinological and genetic commonalities, and also involving, among other brain areas, hippocampal and anterior cingulate involvement (Langguth et al., 2011). In this light it is of interest that the network related to worsening cognitive performance is the same as the network involved in tinnitus distress (Vanneste et al., 2010a), but that oscillatory frequencies differ. Whereas the amount of distress is related to alpha oscillatory changes, the worsening of the spatial cognitive functioning is related to the amount of beta oscillatory activity, extending the idea that tinnitus is an emergent property of multiple overlapping dynamical networks with each network related to a specific tinnitus characteristic (De Ridder et al., 2011).

A possible associated explanation for our findings relates to hippocampal neurogenesis. Impaired hippocampal neurogenesis has been documented in animals after noise trauma (Kraus et al., 2010), as in animal models of depression (Langguth et al., 2011), diabetes (Korczak et al., 2011a; Korczak et al., 2011b) and stress (Samuels and Hen, 2011). It is known that the hippocampus plays a major role in learning, memory, mood and spatial navigation (Becker et al., 2007; Leirer et al., 2010). Recent studies have shown a link between hippocampal neurogenesis and memory (Ehninger and Kempermann, 2008; Kempermann and Gage, 2000). It was also shown that sound exposure in a separate, contextually unrelated environment can cause cell death of granule and pyramidal cells and affect location-specific firing of hippocampal neurons during normal spatial exploration (Goble et al., 2009; Kraus et al., 2010). That is, exposure to noise trauma which can produce tinnitus, also affects location-specific firing in the hippocampal neurons and can significantly and persistently decrease hippocampal neurogenesis suggesting that hippocampal plasticity plays a significant role in the pathophysiology of tinnitus (Goble et al., 2009; Kraus et al., 2010). As such, one could speculate that the observed alterations of hippocampal activity, which are related to lower performance may also be related to impaired hippocampal neurogenesis. The decrease in hippocampal grey matter in tinnitus patients (Landgrebe et al., 2009) is suggestive of this hypothesis. Since we found that tinnitus patients with longer tinnitus duration performed poorer on the trail making test, one could further speculate that over time tinnitus continues to affect location-specific firing in the hippocampal neurons and decreases hippocampal neurogenesis. However, further research is needed to confirm this latter hypothesis.

An alternative or associated explanation might be that tinnitus is the result of a memory trace involving the hippocampal area (De Ridder et al., 2011; Shulman, 1995). In a recent paper a pathophysiological analogy between phantom pain and tinnitus as a phantom sound is proposed (De Ridder et al., 2011), and adds to earlier suggestions of a similar pathophysiology for both symptoms (Llinas et al., 1999) as well as to the well-known clinical analogy between pain and tinnitus (De Ridder et al., 2007; De Ridder and Van de Heyning, 2007; De Ridder et al., 2011; Moller, 1997; Moller, 2000; Moller, 2007; Tonndorf, 1987). Pain can induce single-event learning, the memory of which can last for the rest of life. Many people with amputations report phantom limb pain that is similar in both quality and location to pain experienced before the amputation. Moreover, pain experiences before the amputation are powerful predictors and elicitors of phantom pain (Flor et al., 2006). The continuous experience of pain can produce continuous aversive emotional association and does not provide an opportunity for extinction of the memory of pain (Apkarian et al., 2009). Based on these findings it was stipulated that bothersome or distress for the tinnitus might also be the result of an (aversive) memory trace (De Ridder et al., 2011). As the hippocampus is likely to be involved in the generation of tinnitus (De Ridder et al., 2006; De Ridder et al., 2012), the performance in additional tasks that require hippocampal involvement is worse in comparison to a control group due to capacity limitations (Rossiter et al., 2006).

A limitation of this study is the low sample size as small numbers of patients lead to low degrees of freedom in variance

estimation (Adjamian et al., 2009). Therefore, the results have to be interpreted carefully. Another drawback of the study is that except for pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders we did not control for the etiology of the tinnitus. However, the current study paves way for further research to explore the relationship between cognitive impairment and tinnitus.

4. Conclusion

To our knowledge this study is the first to examine the correlation between tinnitus and cognitive impairment proposing neurophysiological changes to explain it in humans. Our results support the notion that the hippocampal area are related to cognitive dysfunction in tinnitus. Because tinnitus is exceedingly prevalent in societies, it is important to further explore on how tinnitus may impair hippocampal activity and cognition. Further research is needed to investigate what the mechanistic basis of this observed association is and whether rehabilitative interventions could affect cognitive decline.

4.1. Methods and materials

4.1.1. Tinnitus subjects

Nineteen tinnitus patients ($N=19$; 7 females and 12 males) with a mean age of 47.37 ($Sd=12.99$ years) were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the University Hospital of Antwerp, Belgium. Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were not included in the study in order to obtain a homogeneous sample.

All patients were investigated for the extent of hearing loss using audiograms. Tinnitus pitch (frequency) and tinnitus loudness were assessed by matching procedures. Additionally, tinnitus loudness and distress were evaluated by a Visual Analogue Scale ranging from 1 to 10. Participants were requested to refrain from alcohol consumption 24 h prior to recording and from caffeinated beverages on the day of recording. Nine patients had unilateral tinnitus and 10 patients had bilateral tinnitus. Eight patients had a pure tone tinnitus and eleven patients had narrow band noise tinnitus. The mean tinnitus loudness on a VAS scale was 6.05 ($Sd=2.22$) ('How loud is your tinnitus?') and the tinnitus distress on a VAS scale was 5.79 ($Sd=2.42$) ('How stressful is your tinnitus?'). The tinnitus duration was 3.95 years ($Sd=4.33$) In addition, all patients were screened for the extent of hearing loss (dB HL) using a pure tone audiometry using the British Society of Audiology procedures at .125 kHz,.25 kHz,.5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz (Audiology, 2008). Based on this audiogram we calculated both the mean hearing loss by taking the average of the hearing loss over all frequencies measured. Patients had little to no hearing loss (see Fig. 1) (Farrior, 1956).

This study was approved by the local ethical committee (Antwerp University Hospital) and was in accordance with the declaration of Helsinki. Subjects signed an informed consent before the procedure.

4.2. Control subjects

Fifteen healthy controls ($N=15$, 7 females and 8 males) with a mean age of 48.47 years ($Sd=9.53$ years) were invited. Individuals had no hearing loss and no tinnitus.

4.3. Trail making Test Part A and B

The Trail Making Test Part (TMT) A and B were administered. Trail making tests required participants to connect a series of either numbers or numbers and letters in ascending order (Reitan, 1958). TMT-A involved only connecting a series of ascending numbers with a continuous series of lines and was designed to assess the psychomotor speed and visual scanning ability of the participant. TMT-B requires the participant to connect a series of numbers and letters in alternating and ascending order. The tests were scored on the time to finish the task. These examinations have a large number of normative studies many of which can be found in Mitrushina and Satz (2005). The norm score for TMT-A is 29 s and TMT-B is 75 s (Fernandez and Marcopulos, 2008; Gaudino et al., 1995).

4.4. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) was administrated (Nasreddine et al., 2005). The MoCA assesses several cognitive domains and include as short-term memory recall task, visuospatial abilities, clock-drawing, a three-dimensional cube copy, adaptation of trail-making B task, a phonemic fluency task, and a two-item verbal abstraction task, sustained attention task, a serial subtraction task, and digits forward and backward, a three-item confrontation naming task with low-familiarity animals, repetition of two syntactically complex sentences, and the aforementioned fluency task. As well as orientation to time and place is evaluated. The norm score for the MoCA in a healthy control group is 26 or higher.

4.5. Mini-mental state examination

The mini–mental state examination (MMSE) is a questionnaire that is used to screen for cognitive impairment (Folstein et al., 1975). It is used to estimate the severity of cognitive impairment and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. It examines functions including arithmetic, memory and orientation. A score of 27 of higher indicates normal cognition.

4.6. Statistical analyses

Pearson correlations were calculated between the TMT-A, TMT-B, MoCA and the MMSE to verify how related the measures are. In addition, we calculated the correlations between TMT-A, TMT-B, MoCA and the MMSE, respectively and distress, loudness, hearing loss and tinnitus duration for the tinnitus group. We combined for this analysis both tinnitus patients and healthy controls. In addition, we analyzed the difference between tinnitus patients and healthy controls for the TMT-A, TMT-B, MoCA and the MMSE using an independent t-test.

4.7. EEG data collection

EEGs (Mitsar, Nova Tech EEG, Inc, Mesa) were obtained at rest in a fully lighted room with each participants sitting upright in a comfortable chair. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10–20 International placements average referenced and impedances were checked to remain below 5 kΩ. Data were collected for 100 2-s epochs with eyes closed, at a sampling rate=1024 Hz, and band pass filtered 0.15–200 Hz. Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz. These data were transposed into Eureka! Software

(Congedo, 2002), plotted and carefully inspected for manual for artifact. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifacts were removed from the stream of the EEG. In addition, an independent component analysis (ICA) was conducted to further verify if all artifacts were excluded. To investigate the effect possible ICA component rejection, we compared the power spectra in two approaches: (1) after visual artifact rejection only (before ICA) and (2) after additional ICA component rejection (after ICA). To test for significant differences between the two approaches we performed a repeated-measure ANOVA, considering mean band power as within-subject variables. The mean power in delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz) did not show a statistically significant difference between the two approaches. Therefore, we continue by reporting the results of ICA corrected data.

4.8. Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands (Pascual-Marqui, 2002). sLORETA computes electrical neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The sLORETA solution space consists of 6,239 voxels (voxel size: $5 \times 5x5$ mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template (Fuchs et al., 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5% system (Jurcak et al., 2007).

4.9. Region of interest analysis

The log-transformed electric current density was averaged across all voxels belonging to the region of interest, respectively left and right hippocampus separately for each frequency band.

4.10. EEG statistical analyses

The methodology used is non-parametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis. This methodology corrects for multiple testing (i.e., for the collection of tests performed for all voxels, and for all frequency bands). As explained by Nichols and Holmes, the SnPM methodology does not require any assumption of Gaussianity and corrects for all multiple comparisons (Nichols and Holmes, 2002). We performed one voxel-by-voxel test (comprising 6,239 voxels each) for the different frequency bands.

A comparison was made between healthy controls and tinnitus patients, between tinnitus patients and tinnitus patients who scored lower than the norm and then tinnitus patients who had a score similar or higher than the norm. In addition, the correlations between the different cognitive measures and source localized current density were calculated.

For the region of interest, we computed the Pearson correlations between the left and right hippocampus and the different cognitive measures. Furthermore, we calculated the partial correlations between the left and right hippocampus and the different cognitive measures, controlling for distress, loudness and tinnitus duration respectively.

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