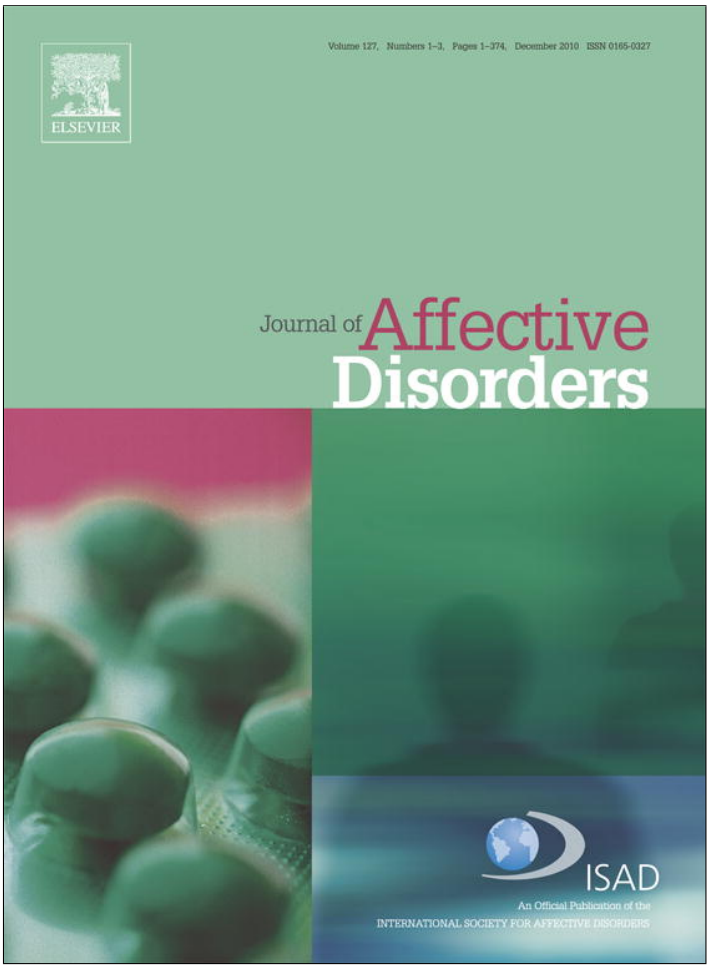

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Research report

Pure-tone auditory thresholds are decreased in depressed people with post-traumatic stress disorder

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ABSTRACT

Background: Depression has been related to sensory modulation and notably to auditory modifications such as alterations in auditory event-related potentials, abnormal patterns of auditory habituation, increased activation of primary and secondary auditory cortex, and higher bilateral auditory thresholds. However, few experiments have considered the exploration of the auditory system in depression. The aim of the experiment is to further explore auditory thresholds across a higher number of frequencies than has previously been undertaken in depressed subjects, to determine whether thresholds are modified as compared to controls, and if so, at which frequencies.
Methods: 25 pure-tones covering a large range of frequencies from 125 Hz to 8 kHz were used to measure both air and bone conduction (AC and BC respectively) hearing thresholds. 13 patients with depression and post-traumatic disorder matched for age, sex and education level with 13 healthy subjects, were tested.
Results: Hearing thresholds were found to be significantly poorer in depressed participants than in controls for frequencies from 2.75 Hz to 8 kHz in BC, and for 0.5, 0.75, 0.875 and 2.0–8.0 kHz pure-tone frequencies in AC.
Limitations: Given that the depressed patients also had comorbid post-traumatic disorder, it should be verified whether their modified pure-tone audiometry is only related to depression.
Conclusions: The AC and BC pure-tone auditory threshold measurement may provide new and different insights into the aetiology and evolution of depression.

1. Introduction

A very recent review on mood and depression (Canbeyli, 2010) underlines that depression is related to the sensori-motor system. The link is bidirectional since depression can be modulated by this system and can, in turn, modify it. The motor system is in fact known to be generally slowed down (Szabadi et al., 1976). Although only a small number of experiments have been designed to explore the sensory systems of depressed subjects, these experiments still managed to put forward some evidence that olfactory, visual and auditory processing may be altered by depression (Millot and Brand, 2001; Rosenthal and Wehr, 1992; Schiffman et al., 1995). For Canbeyli (2010), the hyper- or hypo-activation of a sensory modality, audition in particular, may influence mood and, consequently, depression. For example, a reduction in the recurrence of subjective pleasure associated with a given sound has been observed in depressed subjects (Collet and Duclaux, 1986). Other studies have explored auditory event-related potentials and demonstrated alterations in subgroups

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of depressed patients (Hegerl et al., 2001). More precisely, a repeated auditory stimulation paradigm was used in a magnetoencephalography study to explore habituation patterns in depressed patients (Tollkötter et al., 2006). A subset of these patients was found to present disturbed auditory processing to vowels and tones, i.e., missing N1m and subsequent habituation. Depression thus seems to be accompanied by dysfunctions of the cortical auditory system. This finding was further confirmed by studies using functional magnetic resonance imaging (fMRI). Similarly, Michael et al. (2004) pointed out an abnormal pattern of auditory habituation. Also using fMRI, Christ et al. (2008) found cortical dysfunction in depression including impaired auditory processing of non-speech stimuli. An increased activation of the primary and secondary auditory cortices was indeed demonstrated as the severity of the depression increased. Furthermore, a study exploring the intensity (loudness) dependent amplitude change of the auditory event-related potential has evidenced a positive correlation between the intensity dependent N1 amplitude slope and the degree of some somatic symptoms of depression (Linka et al., 2009). Early auditory processing of tones is also impaired in major depressive disorder since P1 and P1m latencies are decreased in depressed patients (Kähkönen et al., 2007). On an auditory signal detection task, auditory sensitivity was found to be lowered during depression (Malone and Hemsley, 1977).

Finally, auditory thresholds have been explored among subjects diagnosed with major depression. Depressed patients appeared to present higher bilateral thresholds than normal controls with marked hearing loss for the highest pure-tone frequency (Yovell et al., 1995). At lower frequencies, patients displayed significant asymmetry, with poorer hearing in the left ear. This result has not been replicated by Gopal et al. (2004).

Despite the promising aforementioned studies, their results have neither been confirmed by other studies nor extended to a wider range of pure-tone frequencies. The aim of the current experiment is thus to further explore the auditory thresholds in depressed subjects so to determine whether they are modified when compared to control subjects.

In order to precisely study auditory thresholds in depression, we chose to use 25 pure-tones covering a large range of frequencies from 125 Hz to 8 kHz. In addition, both air and bone conduction (AC and BC respectively) hearing thresholds were examined since these two measures do not involve the same peripheral auditory mechanisms. AC results from a sound pressure in the ear canal that is transmitted to sound pressure in the vestibule of the cochlea by the tympanic membrane and middle ear ossicles (Stenfelt, 2006). BC stimulation involves sound radiation into the ear canal, inertial motion of the middle ear ossicles, fluid in the cochlea, as well as compression and expansion of the bone encapsulating the cochlea (Stenfelt and Goode, 2005). Auditory thresholds were obtained from both right and left ears since depressed patients appear to display poorer hearing in the left ear (Yovell et al., 1995).

Based on the above-mentioned studies, we hypothesized that depressed subjects would display higher AC and BC auditory thresholds than control subjects for the highest frequencies, especially in the left ear.

2. Materials and methods

2.1. Participants

Thirteen depressed patients (10 males, 3 females) with a mean age of 38.9 ± 11.1 years and a mean education level of 7.7 ± 3.2 years (after grade 7) were recruited at the Psychiatry Pole of the Conception Hospital in Marseille, France. They all met the DSM-IV criteria for depression and post-traumatic stress disorder (PTSD). They had no previous history of neurologic, psychiatric or hearing disorders. There is a frequent co-occurrence of depression and anxiety disorders, addictive disorders…(Kessler et al., 1997). It was consequently hard to find "pure" depressed patients. In order to avoid confounding factors by including too many comorbid psychiatric disorders, only depressed patients with only PTSD were considered. Subjects' self-reports on the French version of the Beck Depression Inventory (Cottraux, 1985) confirmed that they were experiencing depression (scores higher than 17). The mean Beck score was 19.6 ± 3.8. Five patients had mild depression, and eight patients had moderate depression. Only three patients were on medication. One patient took an antidepressant (selective serotonin reuptake inhibitor) and sleeping pills, one took an anxiolytic (benzodiazepine), and the third took both an antidepressant (selective serotonin reuptake inhibitor) and an anxiolytic (benzodiazepine).

Thirty healthy adult volunteers (10 males, 3 females) with a mean age of 34.9 ± 7.7 years and a mean education level of 10.7 ± 1.9 years (after grade 7) were recruited via screening lists at the clinical investigation unit at the Timone Hospital in Marseille, France. They had no history of psychiatric, neurological illnesses or hearing disorders. Subjects' self-reports on the French version of the Beck Depression inventory (Cottraux, 1985) confirmed that they were not currently depressed (scores below 8). The mean Beck score was 2.5 ± 2.5. Healthy volunteers were matched with patients for age, sex and education level. None of the control subjects was on medication.

For all participants, the absence of psychosis was assessed by a psychiatrist with the French version of the structured Mini-Internal Neuropsychiatric Interview for DSM-IV (Lecrubier, 1998).

The experimentation has been approved by the Institutional Review Board of the University where the study was performed (CPP committee South Mediterranean 2). Participants provided informed consent in accordance with the guidelines set forth by this CPP committee South Mediterranean 2.

2.2. Audiometry

Sounds were delivered monaurally by the Diagnostic Audiometer AD 229b (Interacoustics laboratory) through TDH 39 earphones (Telephonics). The left ear AC and BC auditory thresholds were first assessed in the left ear followed by the right ear. For both ears, AC was assessed prior to BC. Tonal audiometry was performed to measure pure-tone thresholds, i.e., minimum detectable level of sounds in the absence of any external sounds (Goldstein and Shulman, 1996; Khalfa et al., 2004). Sound levels were expressed in dB HL at 25 frequencies from the highest to the

lowest frequencies in the following decreasing gradient of pitch order: 8, 6, 5, 4.5, 4, 3.5, 3, 2.75, 2.5, 2.25, 2, 1.87, 1.75, 1.625, 1.5, 1.375, 1.25, 1.125, 1, 0.875, 0.75, 0.625, 0.5, 0.25 and 0.125 kHz. All pure-tones were of 500 ms duration with onset/offset ramps of 50 ms. All stimuli presentation were performed in one session in a soundproof room, and were initiated by the experimenter.

First, the AC auditory thresholds were measured by decreasing pure-tone intensity until the subjects could no longer detect it. Subjects were instructed to raise their hand as soon as they were certain to perceive a sound: right hand if the sound was perceived on the right ear, and left hand if the sound was perceived on the left ear. The tone level was initially set at 30 dB HL and decreased in 5-dB steps until the participants stopped raising their hand indicating that the tone was no longer audible. It was then increased in 5-dB steps until the subjects started to hear the tone again, following the standard up-and-down-staircase procedures. The lowest intensity, at which the tone was perceived, corresponded to the absolute threshold. The procedure was repeated a second time to verify the validity of the measurement. If the second threshold differed from the first, the procedure was repeated until identical auditory thresholds were obtained on two consecutive trials. In this experiment, it was never necessary to repeat the procedure more than twice. Subjects whose pure-tone thresholds mean was greater than 30 dB HL (Hearing Level) (across all frequencies per ear) were excluded from the study, as well as those with a known auditory disorder.

Second, the BC hearing thresholds were measured for the same frequencies as AC auditory thresholds except for the 0.125 kHz tone which used a bone conduction vibrator headphone, model B 71 (Radioear) placed on the mastoid (American National Standards Institute, 2004). The same up-and-down-staircase procedure was used, with the participant raising his/her hand on the side of the perceived tone. Subjects were asked to sit quietly and avoid movement and to signal whenever the bone vibrator moved.

2.3. Statistical analyses

Statistical analyses were conducted using SPSS 15.0. Three-way repeated measures ANOVAs, with Frequencies (25 or 24 levels; respectively for AC and BC audiometric measures) and Ear (2 levels; right and left) as within factors, and Population (2 levels; controls and patients with depression and PTSD) as a between factor, were performed on AC and BC pure-tone auditory thresholds (at 8, 6, 5, 4.5, 4, 3.5, 3, 2.75, 2.5, 2.25, 2, 1.87, 1.75, 1.625, 1.5, 1.375, 1.25, 1.125, 1, 0.875, 0.75, 0.625, 0.5, 0.25 and 0.125 kHz pure-tones). Significant effects allowed for subsequent *post hoc* comparison tests with Bonferroni correction.

3. Results

3.1. Air conduction (AC) auditory thresholds

As illustrated by Fig. 1A and B, pure-tone thresholds were lower than 25 dB HL and therefore comparable to clinical norms, showing that the participants had neither hearing loss nor auditory suprathresholds. More precisely, average audiometric thresholds were in the range of 5 to 22 dB HL with standard errors of 0.16 to 0.6, reflecting clinically acceptable intersubject response variability (Sherlock and Formby, 2005).

The auditory threshold significantly varied according to the Frequency X Population interaction ($F(24,576)=4.70$, $p<0.0001$) with hearing thresholds being higher in depressed subjects than in controls for the 0.5, 0.75, 0.875, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, and 8 kHz pure-tones ($p<0.05$) (see Fig. 1A and B). The auditory thresholds were also significantly greater in the left than in the right ear ($F(1,24)=7.12$, $p<0.05$), but this difference was neither related to the Frequency nor to the Population.

3.2. Bone conduction (BC) auditory thresholds

Fig. 2A and B display BC auditory thresholds and show that the hearing thresholds were in the normal range of hearing from 7 to 27 dB HL. Standard errors of average hearing thresholds ranged between 0.17 and 0.55.

As for AC auditory thresholds, the BC auditory thresholds depended on the Frequency × Population interaction ($F(23,460)=1$ .94, $p<0.01$). However, unlike AC, the only significant between group difference for BC was observed for middle to high frequencies ($p<0.05$), and not for low frequencies. Indeed, depressed participants exhibited poorer thresholds for the 2.75, 3, 3.5, 4, 4.5, 5, 6, and 8 kHz pure-tones.

A between ear difference was also observed, but it varied according to the pure-tone frequencies ($F(23,460)=1.86$, $p<0.05$), with lower thresholds in the left than in the right ear for the two following frequencies: 0.75 and 1.125 kHz ($p<0.05$).

4. Discussion

4.1. Population effect on auditory thresholds

In accordance with our hypothesis, depressed patients exhibited higher AC and BC hearing thresholds than healthy subjects. This difference was restricted to middle and high frequencies (from 2.75 to 8.0 kHz) for BC thresholds. For AC thresholds, both low (0.5, 0.75, 0.875 kHz) and middle-high (from 2.0 to 8.0 kHz) frequencies tones were less well perceived by the patients than by the controls. These results confirmed the previous findings of Yovell et al. (1995) demonstrating higher bilateral thresholds in patients with a major depressive disorder, especially for the 8.0 kHz pure-tone. Our study extends this result to larger and more precise middle and high frequency ranges of pure-tone thresholds, to low frequencies on one hand, and to mild and moderate depression on the other. Discrepancies that therefore arise with the previously experiment must be explained first and foremost by the poorer auditory thresholds observed in the latter (Yovell et al., 1995), which may in turn minimize the differences between depressed and control subjects. These lower thresholds are most likely due to a difference in the mean age of the groups included in the two protocols since the subjects in our experiment were on average 20 years younger than those in Yovell's. In the present experiment, the average threshold was 25 dB HL whereas the average

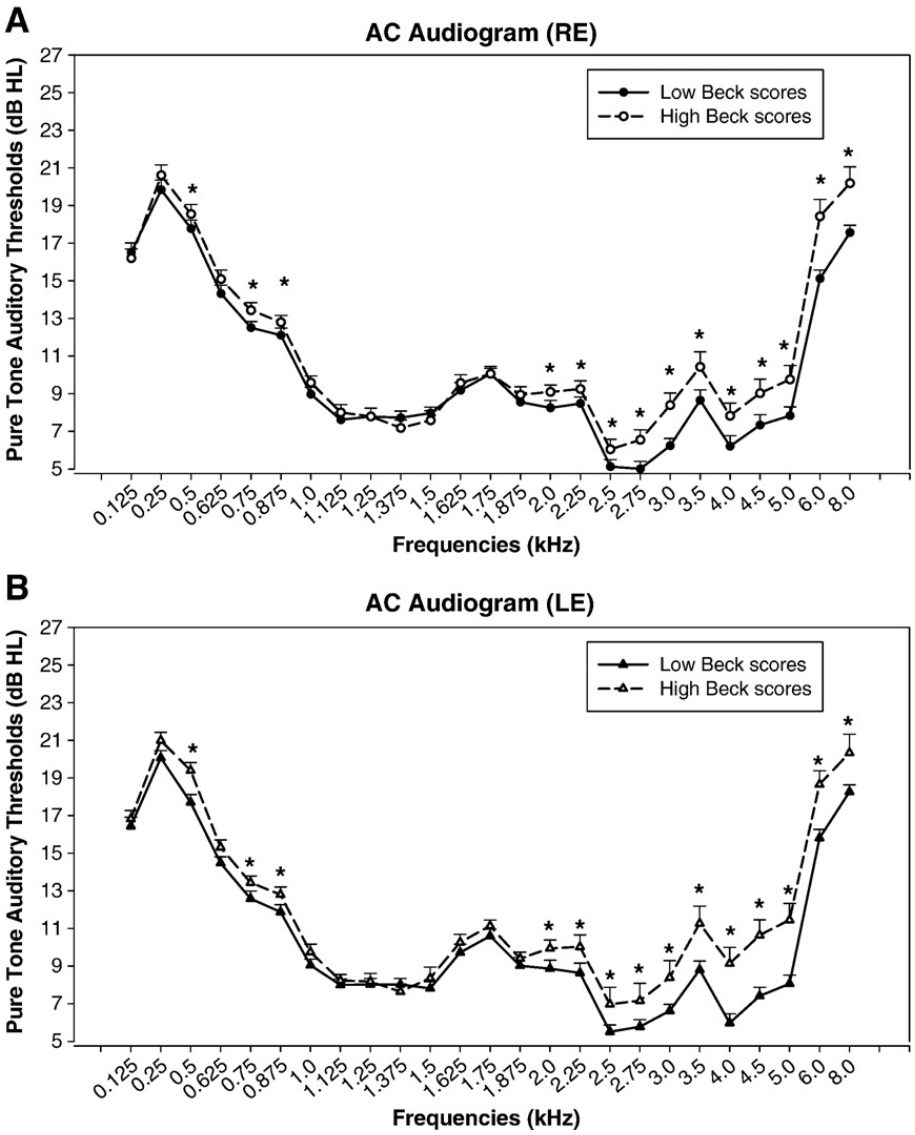

Fig. 1. Air conduction (AC) audiogram. Means and error bars of AC pure-tone auditory thresholds, in both depressed (with post-traumatic stress disorder) and non-depressed subjects, in the right (1A) and the left ear (1B), for the following frequencies: 8, 6, 5, 4.5, 4, 3.5, 3, 2.75, 2.5, 2.25, 2, 1.87, 1.75, 1.625, 1.5, 1.375, 1.25, 1.125, 1, 0.875, 0.75, 0.625, 0.5, 0.25 and 0.125 kHz. * indicates statistically significant differences between the two groups of subjects, results for ears being confounded.

threshold was 35 dB HL in Yovell et al.'s study. Second, our study was more precise and refined since we tested 19 more pure-tone frequencies than the previous experiment. The additional tones allowed us further highlighting of greater hearing thresholds in patients with depression at low, middle and high frequencies regardless of the ear laterality. This result has not been observed by Gopal et al. (2004), but Gopal et al. (2005) have nevertheless noticed that pure-tone thresholds are slightly higher in a depressed group as compared to controls. The difference between our results and those of Gopal may be explained by the fact that the statistical analyses they performed were on pure-tone averages regardless of frequency. Given that we observed hearing thresholds differences between groups according to the frequency, averaging the auditory thresholds may have attenuated the group differences we obtained.

We did not find group differences for pure-tone thresholds from 1000 to 1875 Hz, as if depression had selectively spared those middle range frequencies. This frequency effect is difficult to explain. It may involve specific hearing mechanisms as well as modulation by variables such as attention, motivation and emotion. This should be further explored to better understand the mechanisms underlying depression's effect on pure-tone auditory thresholds as well as its frequency selectivity.

It is interesting to note that in BC, depression effect on thresholds was also frequency specific. Nevertheless, contrary to results in AC, the effect was only observed for the 2.75, 3, 3.5, 4, 4.5, 5, 6, 8 kHz pure-tones. Only the high frequencies auditory thresholds were greater in patients with depression than in controls. The lack of effect at low frequencies could be because the level was sufficient (around 20 dB HL) to activate tactile mechanisms rather than auditory mechanisms. This is the first time that such a result is obtained using BC. In order to understand this result, it should be reminded that five factors seem to contribute to bone conduction hearing (see

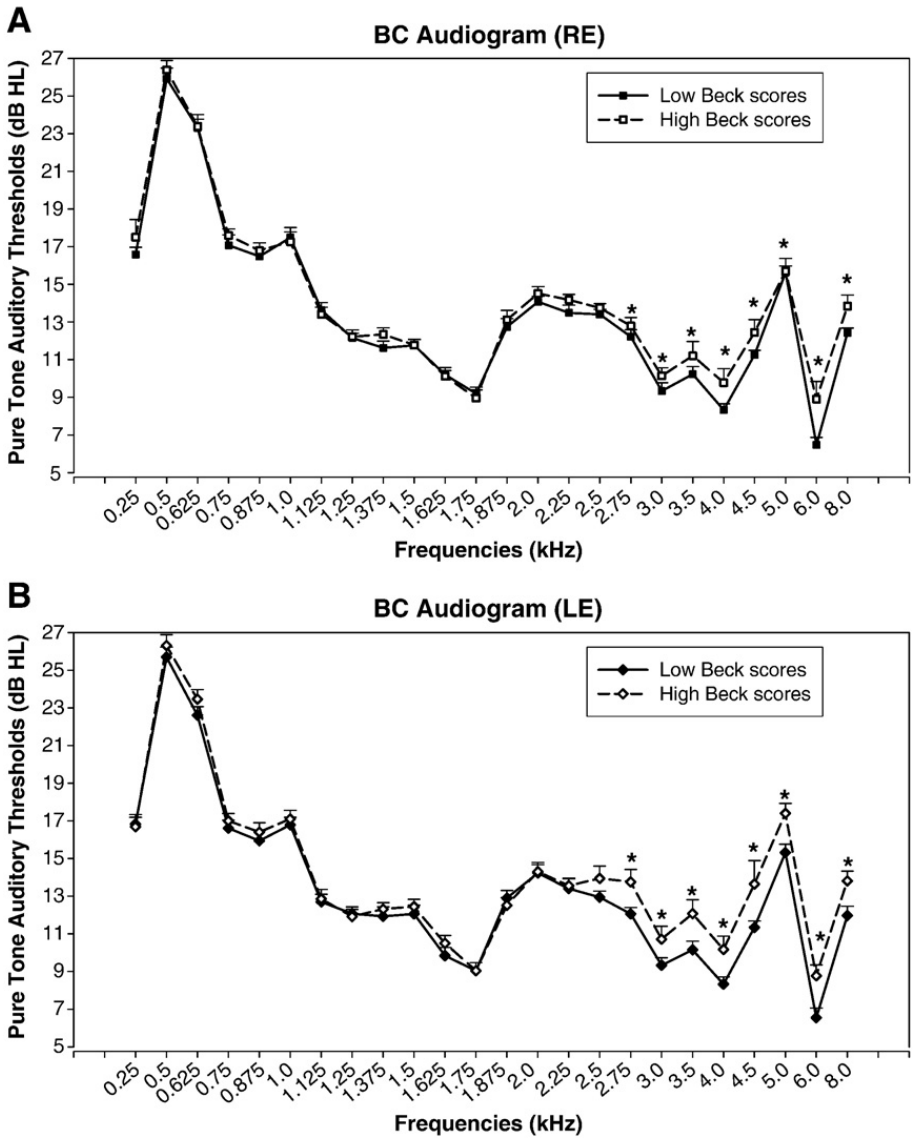

Fig. 2. Bone conduction (BC) audiogram. Means and error bars of BC pure-tone auditory thresholds, in both depressed (with post-traumatic stress disorder) and non-depressed subjects, in the right (2A) and the left ear (2A), for the following frequencies: 8, 6, 5, 4.5, 4, 3.5, 3, 2.75, 2.5, 2.25, 2, 1.87, 1.75, 1.625, 1.5, 1.375, 1.25, 1.125, 1, 0.875, 0.75, 0.625, 0.5, and 0.25 kHz. * indicates statistically significant differences between the two groups of subjects, results for ears being confounded.

Stenfelt and Goode for review; Stenfelt, 2006; Stenfelt et al., 2003). In fact, bone conduction seems to rely upon sound radiation into the external ear canal, middle ear ossicle inertia, compression of the cochlear walls, and pressure transmission from the cerebrospinal fluid, but the most important appears to be the inertia of the cochlear fluids. The depression effect on BC hearing thresholds would then exclude the possibility that outer ear mechanisms are involved in depression-related thresholds changes.

In addition, it remains to be better understood why are auditory thresholds, either AC or BC, greater in patients with depression than in healthy subjects. Are these modifications a subsequent cause of depression or are they rather involved in the aetiology of depression?

A first element of response is brought by the central serotoninergic system itself, as it has received particular attention in depression research because selective serotonin reuptake inhibitors exhibit antidepressant effects (Drevets et al., 2008). The monoamine hypothesis of depression postulates a deficiency in serotonin or norepinephrine neurotransmission in the brain (Belmaker and Agam, 2008) even though this hypothesis does not take into account the multitude of interconnected systems (genetic, stress,…) involved in the pathophysiology of major depressive disorder (Rot et al., 2009). However, an indicator of cortical serotoninergic function, the intensity dependent amplitude change of the auditory event-related potentials (N1/P2) has been frequently used in patients with major depression (review from Hegerl et al., 2001). A significant relationship between a strong intensity dependence of the N1/P2-components (indicating low serotoninergic function) and a favourable response to selective serotonin reuptake inhibitors has been demonstrated (Hegerl et al., 2001). This intensity dependence has also been associated with clinical symptoms of major depression (Linka et al., 2009).

Second, the serotoninergic system is not only involved in depression but also intervenes in the auditory system functioning. The primary sensory cortex is known to be the

target of dense serotoninergic projections (Lewis et al., 1986; Berger et al., 1988; Azmitia and Gannon, 1986; Campbell et al., 1987). Serotonin neurons have also been shown to terminate on brainstem motoneurons innervating the middle ear muscles (Thompson et al., 1998), and on cochlea, eight nerve, cochlear nucleus, superior olivary nuclei, lateral lemniscus, and inferior colliculus (Gil-Loyzaga et al., 1997, 2000; Thompson et al., 1994). Consequently, a modified serotoninergic brain system in depressed patients may in turn modulate the auditory system, the auditory evoked potentials, as well as the AC and BC pure-tone thresholds, as illustrated in our experiment. The depression might thus be responsible for these auditory perception modifications.

Moreover, the PTSD has also been associated with alterations in 5-HT activity in brain regions involved in this pathology (Krystal and Neumeister, 2009). The auditory thresholds differences observed in the patients with depression might also be reinforced or be due to their comorbidity (PTSD). Further studies should determine the respective roles of these two pathologies and their brain mechanisms involved in such auditory perception modification.

4.2. Ear effect on auditory thresholds

Contrary to previous results (Yovell et al., 1995), we demonstrated higher AC hearing thresholds in the right than in the left ear regardless of Frequency and Group. Indeed, the between ears difference was not related to depression. Again, it is difficult to compare our results with those of Yovell et al. (1995) since their clinical population was older on average and more depressed (major depressive disorder) than ours. Nevertheless, our AC thresholds result are in accordance with the lateralization of the peripheral auditory system evidenced by larger oto-acoustic emissions, and more effective olivo-cochlear system in the right than in the left ear (Khalfa et al., 1998; Khalfa and Collet, 1996; Philibert et al., 1998).

The BC hearing thresholds ear asymmetry was only consistent for the 0.75 and 1.125 kHz pure-tones, and thresholds were higher on the right than on the left ear. This discrepancy between previous experiments cited above concerning AC thresholds and our AC auditory thresholds results may underlie the difference between AC and BC hearing mechanisms, and, consequently, highlights the interest in exploring both AC and BC auditory thresholds measures. However, given that the ear asymmetry was only found for two frequencies out of twenty-four, it should be further replicated for more reliability and subsequent significant interpretation.

In addition, the PTSD involvement in this absence of auditory asymmetry should be further verified even more since individuals with PTSD were not found to differ from controls on resting electroencephalogram asymmetry (Shankman et al., 2008).

4.3. Limitations

One of the limitations of this study is that three patients out of thirteen were on antidepressant or anxiolytic medication. Yet, SSRI medication would have rather improved the auditory perception according to the results obtained from Tollkötter et al. (2006) and Gopal et al. (2005) leading to the inverse result than that which we obtained. In addition, the between groups differences for pure-tone auditory thresholds are still significant whether the three medicated patients are removed.

The second limitation is that the depressed patients also had comorbid PTSD. It was shown that the incidence of a new-onset major depression is around 13.4% in PTSD (Maes et al., 2000). As such, depression may be a disorder occurring after a traumatic event, or comorbidity with PTSD (Ducrocq et al., 2001). To the best of our knowledge, the AC and BC pure-tone audiometry has never been so far specifically studied in PTSD. However, as in depression, this disorder has been associated with modified intensity dependence of the P2 auditory event-related potentials. This dependence in PTSD was either in the direction of an increase (Metzger et al., 2008; Metzger et al., 2002) or of a decrease (Paige et al., 1990; Lewine et al., 2002). According to Metzger et al. (2008), the increased intensity dependence may be related to the PTSD symptomatology rather than to depression or anxiety. Depression and PTSD would thus share alterations of the serotoninergic system. In addition, these central modifications of the 5-HT system in depression may be related to the poorer pure-tone audiometry observed in the patients of the present study. It remains necessary to exclude the possibility that the AC and BC pure-tone audiometry may be sensitive to PTSD per se. Further experiments may arbitrate on that issue by comparing the auditory thresholds in PTSD patients with and without depression, and/or by testing depressed people without associated psychiatric pathologies.

Moreover, Shalev et al. (1988), has also explored the auditory system of patients with PTSD, via audiological evaluation of non-alcoholic, drug-free post-traumatic disorder patients. Tolerance of intense auditory stimuli by patients was similar to that of controls. The only significant differences observed were not between patients and controls as expected, but between right and left ear central auditory functions, and only in a subgroup of patients with PTSD. The results of this experiment may indicate that depression rather than PTSD may be related to the AC and BC pure-tone threshold modifications evidenced in the patients of the present study.

The third limitation could be that decision and motor responses are slower in depressed patients, as compared to normal groups, in response to visual, auditory, and tactile stimuli in both simple and choice paradigm (see review from Sobin and Sackeim, 1997). One may wonder whether motor retardation is involved in the auditory thresholds differences observed between patients and controls. If it was the case, all thresholds at each frequency should be modified in the depressed group which is not the case. Considering the literature, it is also unlikely that motor retardation could influence our results since patients have no problem with motor response and decision, but rather need longer time to respond (Sobin and Sackeim, 1997).

Finally, we always measured AC thresholds before BC thresholds as it is usually done in clinical settings, but it might have introduced a bias in our study. For example, subjects may be less attentive for BC than AC thresholds or be more trained for BC thresholds. Even though, both AC and BC thresholds are very close, future experiments should randomize AC and BC threshold measurements.

To conclude, our major result lays in greater pure-tone hearing thresholds in patients with depression than healthy controls at high and low frequencies in AC, and at high frequencies in BC. The auditory threshold modification may be explained by a deficiency in cortical serotonin that modulates the central and peripheral auditory system. The AC and BC pure-tone auditory threshold measurement may provide new and different insights into the aetiology and evolution of depression. This should be further explored in experimental paradigms including patients before and after treatment and symptom removal, since the AC and BC pure-tone audiometry could serve as a treatment predictor as loudness dependence of the auditory evoked N1/P2 response (Hegerl et al., 2001). Such an experiment would allow determining whether the modified AC and BC pure-tone audiometry should be considered a state or trait marker of depression.

Furthermore, the combination of a thorough exploration of the auditory system at both the cerebral (using functional magnetic resonance imaging) and peripheral levels (evoked oto-acoustic emissions recording, medial olivo-cochlear system exploration, tympanometry), in addition to a study of AC and BC pure-tone thresholds, would allow a greater understanding of the origin of the higher auditory thresholds evidenced in patients with mild and moderate depression.

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Funding for this research was provided by CNRS and TDSA which had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no conflict of interest.

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