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Selective serotonin reuptake inhibitors treatment effects on auditory measures in depressed female subjects

Kamakshi V. Gopal *, Kelly A. Briley, Elizabeth S. Goodale, Oana M. Hendea

Department of Speech and Hearing Sciences, University of North Texas, P.O. Box 305010, Denton, TX 76203, Texas, USA

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Abstract

The purpose of this study was to evaluate the auditory effects of selective serotonin reuptake inhibitors (SSRI), known to enhance serotonin (5-HT) transmission in the brain. The experimental group consisted of 14 clinically depressed female subjects, and the control group consisted of 11 non-depressed females. A battery of tests was administered to the experimental group while on and off of SSRI medication. The control group was also administered the test battery twice. Results indicated no significant differences in the control group between sessions. The experimental group showed significantly smaller transient evoked emissions, higher SCAN-A (auditory processing test) composite scores, and smaller amplitude growth functions for Auditory brainstem response peak V and Auditory late response peak N_1P_2 while on SSRI medication. The increased 5-HT levels in the presence of SSRI (due to reduced reuptake of 5-HT) may be contributing to the significant changes seen in auditory measures with the experimental group.

Keywords: Serotonin; Selective serotonin reuptake inhibitor; Auditory measure; Transient evoked emission; Auditory evoked potential; SCAN-A

1. Introduction

Prior research has shown serotonergic pathways to interface with the auditory system, although the exact role of serotonin (5-hydroxytryptamine; 5-HT) in the auditory system is not well characterized. Serotonergic fibers originating in midline raphe regions of the brain have been found to terminate in several auditory structures including the cochlea, eighth nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus (Gil-Loyzaga et al., 1997, 2000; Thompson et al., 1994). Densest cortical serotonergic innervation has been reported in the superior temporal gyrus (Azmitia and Gannon, 1986; Campbell et al., 1987; Lewis et al., 1986). Electrophysiological studies in both animals and humans have shown that intensity dependent auditory evoked potentials reflect the involvement of serotonin in the auditory cortex (Gallinat et al., 2000; Hegerl and Juckel, 1993; Juckel et al., 1999; Linka et al., 2004).

Abnormal functioning of the serotonergic system results in a wide range of neurological and psychological disorders such as depression, schizophrenia, anxiety disorders and obsessive–compulsive disorder. Pharmacological intervention as a means of balancing the actions of serotonergic neurotransmission is central to many therapeutic approaches. Selective serotonin re-uptake inhibitors (SSRI) are antidepressants, known for their effectiveness in the enhancement of serotonin available in the synaptic cleft by blocking the re-uptake mechanism. This allows for increased amounts of the neurotransmitter available for transmission to the next neuron, thereby enhancing serotonergic transmission in the brain (Pinel, 1997; Vandermalen, 1985). Individuals suffering from clinically diagnosed depression are often prescribed an SSRI, since there is strong support for the notion that depressed individuals exhibit a compromised balance of the brain neurotransmitter serotonin (Perez et al., 1998).

While lumbar punctures and assessment of neurotransmitter function in cerebrospinal fluid provide a reflection of

* Corresponding author. Tel.: +1 940 369 7432; fax: +1 940 565 4058.
E-mail address: gopal@unt.edu (K.V. Gopal).

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the cortical activity of 5-HT, more peripheral models are now preferred (Sarrias et al., 1990). Ninety five percent of whole blood 5-HT is derived from the platelets, which are thought to reveal important aspects of central 5-HT transmission (Murphy, 1990). Blood platelets are found to bear strong similarities to 5-HT-containing neurons in the central nervous system (CNS). The primary structures of the human platelet serotonin uptake site and the brain serotonin transporter (where reuptake takes place) are identical, so changes in neuronal reuptake of 5-HT are reflected in blood serotonin levels (Lesch et al., 1993). Hence, blood 5-HT can be used as a reliable indicator or model for the biochemical and pharmacological activity of 5-HT containing neurons (Da Prada et al., 1988; Sarrias et al., 1990; Evers and Suhr, 2000). Further, a decrease in intracellular 5-HT reflects increased 5-HT release with activated serotonergic transmission (Evers and Suhr, 2000). Intake of SSRI leads to reduced neuronal reuptake of serotonin molecules in the brain, and reduced serotonin reuptake in blood platelets resulting in a decrease in platelet and whole blood 5-HT levels (Bourdeaux et al., 1998; Hughes et al., 1996; Narayan et al., 1998). This change in 5-HT levels in blood between pre- and post-treatment with SSRIs has been used as an indicator of the actions of serotonergic antidepressant on the human serotonin system.

The Beck Depression Inventory-II is a scale that is widely used in clinical settings to assess the degree of depression. It follows the criteria set by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental disorders IV, 1994, (DSM IV). The Beck Depression Inventory-II consists of a 21- item questionnaire addressing two different areas: the cognitive-affective and the somatic (Beck et al., 1996, 1999).

Another important issue in the field of depression is the high incidence of clinical depression in women. In fact, one of the risk factors in the DSM-IV for depression is being female. Depression is the most critical mental disorder facing women today, with approximately seven million American women implicated (Bruder et al., 2001). Furthermore, it has been shown consistently that women exhibit increased risk for depression than men by a ratio of 2:1. Potential biological, genetic, psychological, personality and social factors have been put forth as possible explanation for the higher incidence of depression in women (Goodwin and Gotlib, 2004; Veijola et al., 1998). Marriage and motherhood seem to be associated with greater risk for depression in females (Hirschfeld and Cross, 1982; Paykel, 1991).

The purpose of the current study was to evaluate the auditory effects of SSRIs, which are known to enhance serotonin (5-HT) transmission in the brain. This was done by assessing auditory skills in a group of clinically depressed female individuals while on and off of SSRI medication. Since SSRIs are known to enhance serotonin levels in the synaptic cleft, evaluating clinically depressed individuals while on and off SSRI medication would enable us to delineate the role of serotonin in auditory function. A control group consisting of non-depressed females, also tested twice, was used for comparison. In addition to auditory behavioral and physiologic measures, the study also compared Beck Depression Inventory-II scores and 5-HT blood levels among subjects. Although our earlier case study (Gopal et al., 2000) showed altered auditory measures while the subject was undergoing SSRI treatment, the present investigation was designed to evaluate the auditory effects in a larger group of patients undergoing SSRI treatment.

2. Materials and methods

2.1. Subjects

A total of 25 adult female subjects took part in this study. Subjects were questioned and eliminated from the study if they had a positive history of head injury, mental illness (other than depression), intake of ototoxic drugs or hearing loss. The control group consisted of 11 adult female subjects who had no history of clinical depression, and had never been on SSRI medication at any time. The experimental group consisted of 14 adult female subjects with clinical depression. Inclusion criteria for the experimental group were: 1) diagnosis of unipolar depression, by a physician, based on DSM IV criteria; 2) physician's prescription for one of the following SSRI medications: fluoxetine hydrochloride (Prozac), sertraline hydrochloride (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), or paroxetine (Paxil); and 3) willingness to take the test battery twice. Of the 14 female subjects in the experimental group, 6 subjects were prescribed Prozac (20–40 mg), 7 subjects were prescribed Zoloft (50–150 mg) and 1 subject was prescribed Paxil (20 mg).

All subjects were evaluated twice. The experimental subjects were tested once during their medicated period and once in their unmedicated period. For SSRIs to reach steady-state levels, 2–4 weeks of constant medication is necessary (DeVane, 1992; Hiemke and Hartter, 2000). Elimination half-life for Prozac is 2–3 days and for other SSRIs, including Zoloft and Paxil, is one day (DeVane, 1992). Hence, subjects were tested only if they were on an SSRI for at least a month for their medicated session, and off of their SSRI for at least a month for their unmedicated session. In the experimental group, seven subjects were tested first (round/session one) during their unmedicated condition and tested next (round/session two) during their medicated condition. The remaining seven were tested first (round/session one) during their medicated condition and tested next (round/session two) during their unmedicated condition, however, all seven reported of a relapse of their depressive symptoms following termination of SSRI medication a month ago. These symptoms were not considered to be transient symptoms as seen in SSRI discontinuation syndrome (Lejoyeux and Ades, 1997; Rosenbaum and Zajecka, 1998), but were true depressive symptoms similar to what they had experienced prior to initiation of SSRI medication. There was no reason to believe that residual SSRIs effects would be present, since we

had waited for at least a month after cessation of SSRI medication for the unmedicated round of testing given the information that elimination half-life for SSRIs is 2–3 days or less. To identify if duration of SSRI medication correlated with any of the test results, Pearson product moment correlation coefficients were obtained. The control group was also tested twice within a span of 4–5 months in order to determine if there were any session effects. All subjects were paid to take part in the study. Approval for this study was obtained from the University of North Texas Institutional Review Board prior to the initiation of the investigation.

2.2. Procedures

The test battery consisted of the following procedures: Case history, Beck Depression Inventory-II questionnaire, whole blood-5HT level (administered only to experimental subjects), otoscopy, pure-tone audiometry, tympanometry, acoustic reflex thresholds, uncomfortable loudness level testing, transient evoked otoacoustic emissions, auditory evoked potentials, and the SCAN-A test (a screening test for auditory processing). The tests were administered in a random order to minimize the order effect. Total test time was approximately four hours. All subjects were awake and alert throughout the testing process. Uniform instructions, protocols, monitoring and analysis techniques were adopted throughout the study.

After obtaining detailed case history information, the Beck Depression Inventory-II (Form A1) was administered to all subjects. The Beck Depression Inventory-II uses the following classification based on the score obtained on the Inventory; minimal depression: 0 to 13, mild depression: 14 to 19, moderate depression: 20 to 28, and severe depression: 29 to 63 (Beck et al., 1996).

Prior to audiological testing the subjects provided a small sample of blood for the whole blood 5-HT test. Previous studies have indicated that meals, smoking and phase of menstrual cycle have no significant effects on 5-HT concentration (Kremer et al., 1990). Hence, the only requirement placed on our subjects was to provide a small sample of blood prior to round one and round two of audiological testing at the University Health Center, which was then processed for whole blood-5HT level at a local Medical Pathology Laboratory. Otoscopic examinations were conducted to ensure that there were no contraindications for audiological testing. Pure-tone testing was performed in a double-walled sound treated booth using the Auricle audiometer (Madsen Orbiter 922 Clinical Audiometer, Copenhagen, Denmark), calibrated according to American National Standards Institute (1989) standards. Using the modified Hughson-Westlake procedure, the octave frequencies from 250 Hz – 8000 Hz were tested. Tympanograms and acoustic reflex thresholds were obtained from each ear using a calibrated Middle Ear Analyzer (Grason-Stadler GSI-33, Littleton, MA), and the intensity level for acoustic reflex threshold testing did not exceed 105-dB HL. Uncomfortable loudness level testing was done using recorded speech stimuli from a CD recording via the Auricle audiometer using the Hawkins procedure (Hawkins, 1984). The uncomfortable loudness level, basically aimed at identifying the intensity at which the subject repeatedly indicated intolerance, was recorded using the ascending method, and repeated twice to ensure accuracy.

Transient evoked otoacoustic emissions were measured using an Otodynamic Analyzer (ILO-96, Otodynamics, Ltd., Hatfield, United Kingdom). A linear click train consisting of 80 microsecond clicks of 70 dB peSPL was presented separately to right and left ears (Berlin et al., 1995). Two hundred sixty presentations were averaged to determine the transient evoked otoacoustic emissions results for frequencies of 1, 1.5, 2, 3 and 4 kHz. The test was repeated twice in each ear for reliability.

Auditory evoked potentials were obtained on the Bio-Logic Navigator System (Bio-Logic Systems, Corp. model Navigator Pro, Mundelein, IL) using disposable eartips (ER3, Indianapolis, IN). All auditory evoked potential recordings were obtained using bilateral stimulation. The following electrode arrangement was adopted: FPz for the non-inverting electrode, nape of the neck for the inverting electrode, and nasion for the ground electrode. Electrode impedance was maintained below 1000 Ohms. Stimuli were delivered binaurally, and responses were obtained twice at each intensity level to ensure repeatability of responses. Auditory brainstem responses and auditory late responses were measured. Auditory brainstem responses were obtained for alternating clicks with a duration of 0.1 ms presented at a repetition rate of 21.1/s. Responses were averaged for a minimum of 1024 runs. Following establishment of auditory brainstem response threshold, response were recorded at intensity levels presented randomly at 15, 25, 35, 45 and 55 dB above the patient's auditory brainstem response threshold (dB nSL). Auditory late responses were obtained for rarefaction 1 k Hz tone bursts with a rise decay time of 10 ms and duration of 30 ms, presented at a repetition rate of 1.1/s. Responses were averaged for a minimum of 300 runs, and repeated at each intensity level. Auditory late responses were also obtained for 15, 25, 35, 45 and 55 dB nSL levels. Two judges knowledgeable in auditory evoked potential measurements independently evaluated the recordings on all subjects.

With the auditory evoked potentials, only amplitude growth functions were analyzed for this study. This decision was based on previous research that had indicated no significant differences in absolute or inter-peak latencies, but significant differences in amplitude growth function between non-depressed individuals and unmedicated clinically depressed individuals (Gopal et al., 2004b). Amplitude growth refers to the difference in amplitude for auditory brainstem response peak V and auditory late response peak N_1P_2 between 55 and 15 dB nSL stimuli. In order to account for individual differences between subjects' threshold and amplitude growth functions, measurements were obtained

relative to the person's threshold rather than to fixed physical levels.

The SCAN-A test was administered using the Auricle audiometer. Although it is a screening test, the subtests assess different aspects of auditory processing (Keith, 1994, 1995), hence the test was used in the battery. The test was administered in accordance with the standardized procedure outlined by Keith, 1995, at the subject's most comfortable loudness level. Raw scores were obtained for each condition and converted to a standard score.

2.3. Data analysis

Statistics Program for Social Sciences (SPSS) software was used to analyze the data. A number of statistical tests were carried out in this study. Appropriate data screening including outlier analysis was done. Pearson product moment correlations were used to examine the association between (1) degree of depression (as measured from Beck Depression Inventory-II scores) and various auditory measures, and (2) duration of SSRI medication and various auditory measures obtained during the medicated round of testing. Paired samples *t*-test was used to compare the blood 5-HT levels of experimental subjects between their medicated and unmedicated conditions. For the remaining comparisons, 2×2 mixed effects analysis of variance (ANOVA) with one grouping and one repeated measures factor followed by simple effects analyses (based on pairwise comparisons) for significant interactions were used. Statistical level of $\alpha=0.05$ was adopted as the level of significance.

3. Results

The study was conducted on eleven control subjects with a mean age of 24.36 years (S.D. 3.61 yrs) and fourteen experimental subjects with a mean age of 24.42 yrs (S.D. 6.50). The test battery was administered to the experimental group once when the subjects were on SSRI medication and once when they were off of SSRI medication. The rounds/sessions were referred to as medicated and unmedicated for round 1 and round 2 respectively. The medication period among the experimental subjects ranged from 1 – 36 months. To identify if length of medication correlated with the test results, Pearson product moment correlation coefficients were obtained. No significant correlation was found between duration of SSRI medication and any of the test measures, which led us to conclude that even when subjects were on

Table 1
Number of people exhibiting difficulty understanding speech and difficulty tolerating environmental sounds

Group	Number of people complaining of difficulty understanding speech in noise/groups	Number of people complaining of environmental/ conversation sound levels being too loud
Control round 1	0/11	1/11
Control round 2	0/11	1/11
Medicated	10/14	4/14
Unmedicated	11/14	5/14

Table 2
Results of otoscopy, tympanometry, pure tone averages (PTA), acoustic reflex thresholds (ART) and uncomfortable loudness levels (UCL)

Measure	Control round 1	Control round 2	Experimental medicated	Experimental unmedicated
Otoscopy	Normal	Normal	Normal	Normal
Tympanometry	Type A	Type A	Type A	Type A
PTA-right (dBHL)	Mean: 3.33 S.D.: 1.87	Mean: 2.89 S.D.: 2.21	Mean: 8.00 S.D.: 6.09	Mean: 7.40 S.D.: 6.59
PTA-left (dBHL)	Mean: 4.78 S.D.: 2.44	Mean: 3.11 S.D.: 1.96	Mean: 7.00 S.D.: 6.63	Mean: 6.70 S.D.: 6.80
ART-right ipsi (dBHL)	Mean: 93.9 S.D.: 8.14	Mean: 95.61 S.D.: 11.67	Mean: 94.86 S.D.: 8.89	Mean: 92.64 S.D.: 8.12
ART-right contra (dBHL)	Mean: 100.3 S.D.: 10.27	Mean: 101.4 S.D.: 10.40	Mean: 101.7 S.D.: 7.42	Mean: 99.21 S.D.: 7.50
ART-left ipsi (dBHL)	Mean: 96.21 S.D.: 12.74	Mean: 92.88 S.D.: 12.67	Mean: 93.89 S.D.: 8.36	Mean: 90.14 S.D.: 6.21
ART-left contra (dBHL)	Mean: 102.9 S.D.: 9.83	Mean: 102.0 S.D.: 11.13	Mean: 101.3 S.D.: 8.32	Mean: 97.50 S.D.: 8.09
UCL-right (dBHL)	Mean: 89.55 S.D.: 9.34	Mean: 89.18 S.D.: 6.43	Mean: 88.57 S.D.: 7.45	Mean: 85.71 S.D.: 5.50
UCL-left (dBHL)	Mean: 87.72 S.D.: 8.47	Mean: 87.27 S.D.: 7.54	Mean: 88.21 S.D.: 8.68	Mean: 85.71 S.D.: 6.16

Mixed effects ANOVA results indicated no significant differences between groups or within groups across rounds for PTA, ART or UCL data.

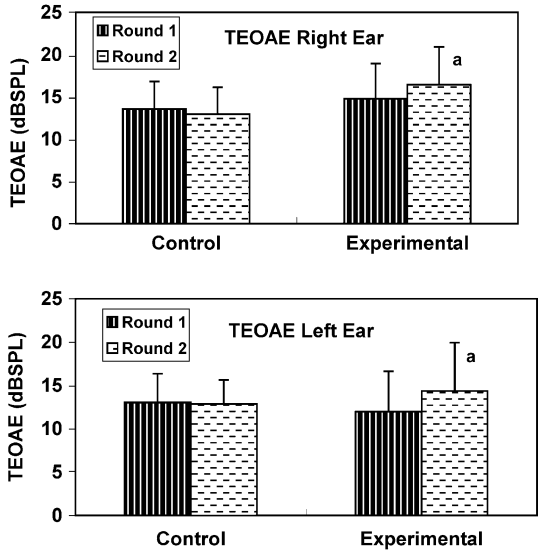

Fig. 1. Transient Evoked Otoacoustic Emissions (TEOAE) in the control group (round 1 and round 2), and in the experimental group (round 1=medicated, and round 2=unmedicated). Shown are means and S.D. scores. Mixed effects ANOVA followed by simple effects analysis indicated significant differences between unmedicated and medicated conditions within the experimental group ($p<0.05$) for both right and left ears. Note: [a] indicates significant difference.

SSRIs for more than the required one-month medication period, the duration of medication did not have any significant effect on the grade of test scores obtained in the medicated session. The same test battery was also administered twice to the subjects in the control group who had never been on SSRI medication anytime. Testing on control subjects was carried out twice (round 1 and round 2) to identify if there were test–retest differences in any of the test measures without involving the medication factor. The average time interval between the two rounds of testing for the control group was four months and for the experimental group it was three months.

Case history information indicated that a majority of the experimental subjects complained of difficulty understanding speech in noise and in group conversations. This was true for both unmedicated as well as medicated conditions. On the contrary, none of the control subjects reported any difficulty. Over 25% of the experimental subjects reported tolerance problems to loud sounds whereas only 1 subject from the control group expressed the problem. Table 1 summarizes these findings obtained from the case history information.

3.1. Beck Depression Inventory-II

The Beck Depression Inventory-II provided an assessment of the subject's perception of depression. The control group fell within the minimal depression range obtaining a mean score of 1.73 (S.D. 2.10) and 2.09 (S.D. 2.47) for round 1 and round 2 respectively. As for the experimental group, while unmedicated, the group mean was 18.15 (S.D. 14.49), which scored at the upper level of moderate depression range. During the medicated condition, the mean score was 13.08 (S.D. 8.49), which fell at the upper limit of mild depression. Greater variability was found for the experimental group, especially, for the unmedicated condition. Although all of the experimental subjects complained of depressive symptoms during their unmedicated condition, a majority of the experimental subjects indicated less severe symptoms of depression during the medicated condition (oral communication).

3.2. Blood 5-HT measures

Blood test results indicated mean and S.D. values of 160.6±78 ng/ml for the experimental group while unmedicated, and 26.6±16.5 ng/ml while medicated. The paired-sample t test indicated a significant difference between the two levels ($P<0.001$). The range of blood 5-HT level was noticeably wider for the unmedicated condition. The drop in blood 5-HT levels seen in all experimental subjects while on medication indicated that the SSRI medication had a significant effect on the serotonin level.

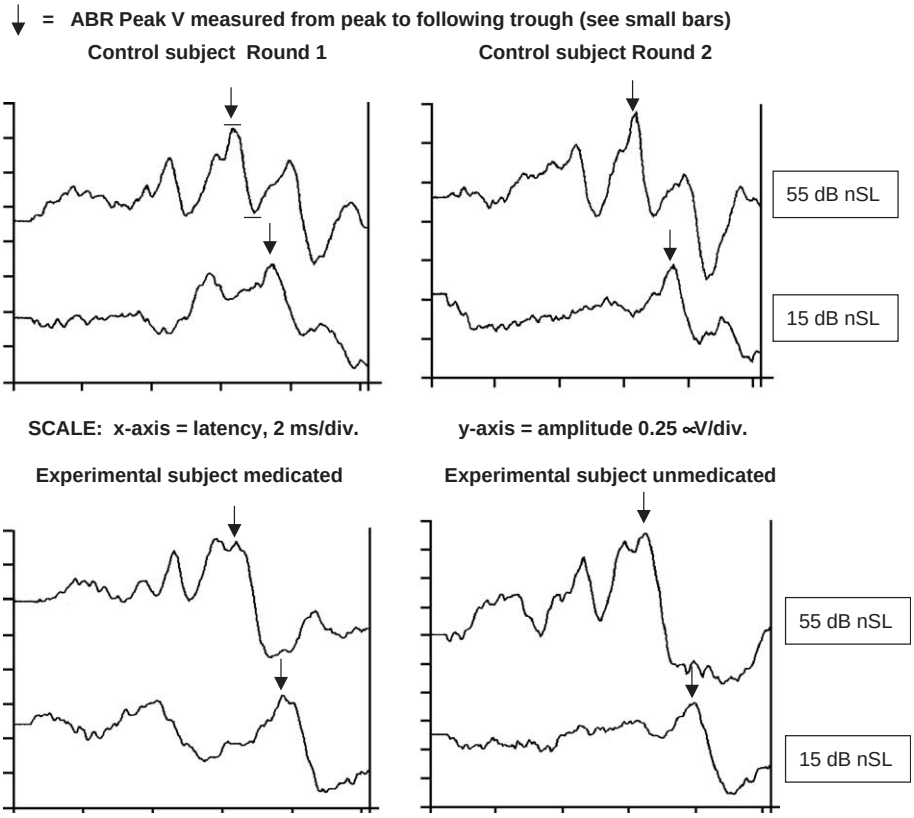

Fig. 2. Auditory brainstem responses (ABR) from a control (upper panel) and an experimental subject (lower panel) obtained at intensities of 15 and 55 dB nSL. Note the difference in Y scale divisions between the two graphs in the lower panel.

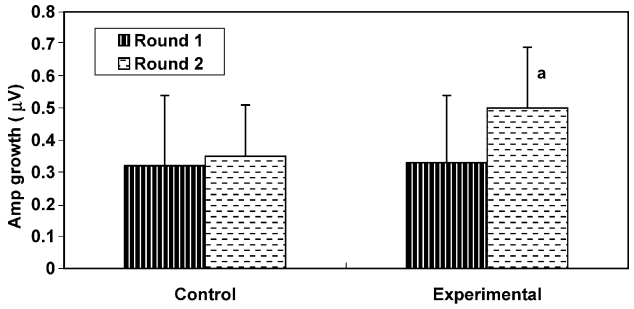

Fig. 3. Amplitude growth for auditory brainstem responses (ABR) peak V, i.e., amplitude difference (μV) between 55 and 15 dB nSL stimuli in control group (round 1 and round 2), and experimental group (round 1=medicated, round 2=unmedicated). Mixed effects ANOVA followed by simple effects analysis indicated significant differences between unmedicated and medicated conditions within the experimental group ($p<0.05$). Note: [a] indicates significant difference.

3.3. Basic audiological measures

Otoscopy revealed clear, unoccluded canals for all subjects. Tympanometry revealed type A tympanograms in all subjects, indicating essentially normal middle ear function. Pure tone averages (PTA) were found to be within normal limits (<25 dB HL) bilaterally for all subjects. Even though the average pure tone thresholds were somewhat elevated in the experimental group, the mixed effects ANOVA results indicated no significant differences for PTAs between the two groups or between two rounds for either group ($P>0.05$). Table 2 presents a synopsis of the above results.

3.4. Acoustic reflex thresholds

Ipsilateral and contralateral acoustic reflex thresholds were averaged for 500, 1000 and 2000 Hz frequencies for each ear separately. Table 2 shows the scores from both groups for each round. ANOVA results indicated no significant differences between groups or within groups between rounds for right or left ears ($P>0.05$).

3.5. Uncomfortable loudness level

Uncomfortable loudness levels were determined for right and left ears in each group. Average uncomfortable loudness levels for all groups are shown in Table 2. The experimental group showed lower mean tolerance values during the unmedicated condition compared to the medicated condition in both ears; however, this difference was not statistically significant ($P>0.05$). The control group average between

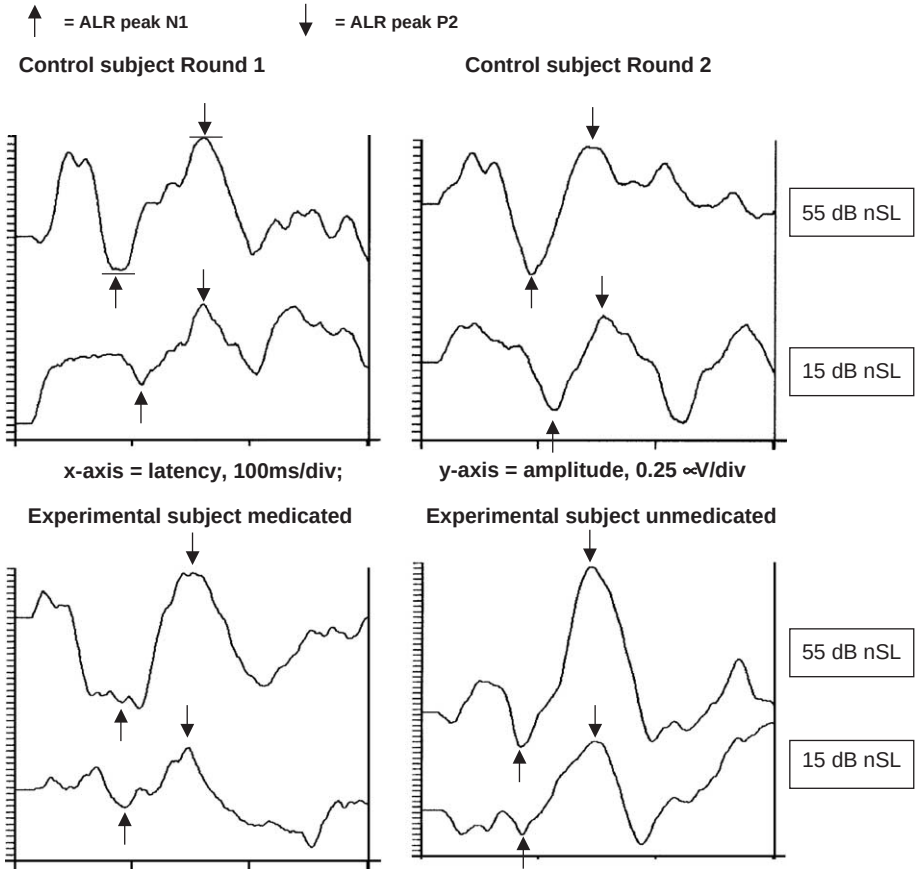

Fig. 4. Auditory late responses (ALR) recordings from a control (upper panel) and an experimental subject (lower panel) obtained at intensities of 15 and 55 dB nSL.

round 1 and round 2 showed no significant differences for either ear.

3.6. Otoacoustic emissions

Transient evoked otoacoustic emissions were obtained for right and left ears separately and were averaged across 1, 1.5, 2, 3 and 4 kHz. As shown in Fig. 1, the mean score for the unmedicated condition showed larger amplitude transient evoked otoacoustic emissions compared to the mean score obtained during the medicated condition. The 2×2 mixed effects ANOVA indicated a significant group by round interaction effect for both ears (right ear: $F_{1,23}=5.38$, $P=0.03$; left ear $F_{1,23}=4.73$, $P=0.04$). Simple effects analysis obtained from pairwise comparisons indicated a significant difference between round 1 (medicated) and round 2 (unmedicated) for the experimental group ($P=0.02$ for right ear, and $P=0.01$ for left ear). No significant differences were found between the two rounds for the control group ($P>0.05$).

Pearson product moment correlation indicated a positive and significant correlation between Beck Depression Inventory-II scores and transient evoked otoacoustic emission amplitudes for both right and left ears for the unmedicated condition in the experimental group. A correlation coefficient of 0.642 and 0.691 was obtained between Beck Depression Inventory-II and right ear transient evoked otoacoustic emission amplitude, and Beck Depression Inventory-II and left ear transient evoked otoacoustic emission amplitude respectively.

3.7. Auditory evoked responses: auditory brainstem responses and auditory late responses

Auditory brainstem response thresholds defined as the lowest intensity at which auditory brainstem response peak V could be repeatedly identifiable was obtained from all subjects for both rounds. The auditory brainstem response threshold ranged from 10 to 20 dB nHL for both control and experimental groups. The average physical stimulus level for auditory brainstem response threshold in the control group was 14 and 12.7 dB nHL for round 1 and round 2 respectively. In the experimental group it was 13.9 and 13.6 dB nHL for round 1 and round 2 respectively. No significant differences were found in auditory brainstem response thresholds between groups or within groups across sessions ($P>0.05$).

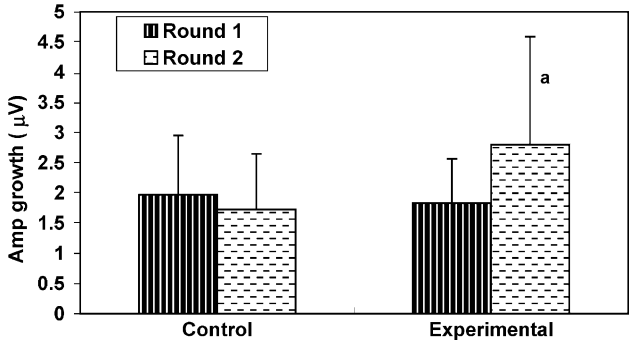

Fig. 5. Amplitude growth for auditory late responses (ALR) peak N_1P_2 depicted as amplitude difference (μV) between 55 and 15 dB nSL stimuli in control group (round 1 and round 2), and experimental group (round 1 = medicated, round 2 = unmedicated). Mixed effects ANOVA followed by simple effects analysis indicated significant differences between unmedicated and medicated conditions within the experimental group ($p<0.05$). Note: [a] indicates significant difference.

Table 3
Mean and S.D. scores obtained on the SCAN-A test for control and experimental groups

Subtest	Control round 1	Control round 2	Experimental medicated	Experimental unmedicated
Filtered words	Mean: 12.36 S.D.: 1.91	Mean: 12.91 S.D.: 1.14	Mean: 1.85 S.D.: 2.76	Mean: 10.31[a] S.D.: 2.98
Auditory figure-ground	Mean: 10.91 S.D.: 2.02	Mean: 11.91 S.D.: 1.87	Mean: 10.61 S.D.: 2.26	Mean: 8.69 S.D.: 2.87
Competing words	Mean: 11.64 S.D.: 2.25	Mean: 11.91 S.D.: 1.81	Mean: 11.31 S.D.: 2.46	Mean: 10.77 S.D.: 1.69
Competing sentences	Mean: 11.18 S.D.: 1.94	Mean: 10.64 S.D.: 2.46	Mean: 10.92 S.D.: 1.61	Mean: 10.38 S.D.: 2.32
Composite score	Mean: 112.2 S.D.: 9.9	Mean: 113.9 S.D.: 8.3	Mean: 110.6 S.D.: 13.7	Mean: 99.9[a] S.D.: 11.8

Mixed effects ANOVA followed by simple effects analyses indicated significant differences between unmedicated and medicated conditions within the experimental group ($p<0.05$). Note: [a] indicates significant difference.

Amplitude growth defined as the difference in amplitude between 55 and 15 dB nSL conditions was measured for auditory brainstem response peak V and auditory late response peak N_1P_2. Fig. 2 depicts analog waveforms from a control and an experimental subject for auditory brainstem response recordings for 15 and 55 dB above their auditory brainstem response threshold. Fig. 3 shows group averages for amplitude growth of auditory brainstem response peak V in control and experimental groups for both rounds. The mixed effects ANOVA results indicated a significant group by round interaction effect ($F_{1,23}=4.91$, $P=0.04$). Simple effects analysis indicated a significant difference between round 1 (medicated) and round 2 (unmedicated) for the experimental group ($P=0.002$). No significant differences were found between round 1 and round 2 for the control group ($P>0.05$).

The amplitude growth for auditory late response peak N_1P_2 was also obtained for both groups. Fig. 4 illustrates an example of auditory late response recordings from a control subject (upper panel) and an experimental subject (lower panel) obtained at 15 and 55 dB nSL. Group average results depicting the differences between the two rounds are shown in Fig. 5. The amplitude growth between 55 and 15 dB nSL was found to be significantly greater for the experimental group in the unmedicated condition

compared to the medicated condition. Again, the mixed effects ANOVA indicated a significant group by round interaction effect ($F_{1,23}=7.84$, $P=0.01$). Simple effects analysis showed significant differences between round 1 (medicated) and round 2 (unmedicated) for the experimental group ($P=0.003$). No significant differences were found between round 1 and round 2 for the control group ($P>0.05$).

3.8. SCAN-A test

Both groups were administered the SCAN-A test at their most comfortable listening level. Results from the composite (standard) and subtest scores (with the exception of the competing sentences portion) indicated that the control group consistently scored better than the experimental group (Table 3). The mixed effects ANOVA results indicated a significant group by round interaction effect for the SCAN-A composite score ($F_{1,23}=4.61$, $P=0.04$). Simple effects analysis indicated a significant difference between the medicated and unmedicated rounds for the experimental group ($P=0.01$).

When interaction effects were scrutinized for each subtest, the filtered word subtest indicated a significant group by round interaction ($F_{1,23}=4.91$, $P=0.04$), and simple effects analysis showed a significant difference between the medicated and unmedicated rounds for the experimental group ($P=0.02$). However, the other three subtests did not show a significant interaction (figure-ground: $F_{1,23}=3.79$, $P=0.06$, competing words: $F_{1,23}=1.21$, $P=0.28$; competing sentences $F_{1,23}=0.09$, $P=0.99$), although the figure ground subtest scores fell close to the significance level. The control group results did not significantly differ between the rounds ($P>0.05$), for the composite or for any of the subtest scores.

4. Discussion

The present study demonstrated that SSRI medication significantly changed certain auditory measures in clinically depressed individuals. To ensure that the changes observed between the medicated and unmedicated rounds of testing were not merely due to session effects, a control group consisting of subjects never exposed to SSRIs, was subjected to two rounds of testing. The control group did not exhibit any significant differences between the two rounds of testing on any of the measures.

The Beck Depression Inventory-II scores obtained from the control group for both rounds fell within the limits of minimal depression. It must be mentioned that the classification system for degree of depression does not include a ‘no depression’ category; hence, the lowest degree of severity is designated “minimal depression”. The experimental group mean for the unmedicated condition was at the upper limit of moderate depression, while the group mean for medicated condition was at the upper limit of mild depression. Although this difference was not significant, most subjects indicated less severe symptoms of depression during the medicated condition.

Blood test results in the experimental group indicated a significant decrease in blood 5-HT levels when the experimental subjects were on SSRI medication, suggesting a drop in the reuptake of serotonin molecules, which in turn is thought to enhance serotonin transmission in the synaptic cleft. These findings are consistent with earlier studies that reported lower neuronal reuptake of 5-HT and lower whole blood and platelet 5-HT levels following SSRI medication (Bourdeaux et al., 1998; Hughes et al., 1996; Narayan et al., 1998).

In this investigation, no significant differences were obtained between groups or within groups across two rounds of testing for pure-tone audiometry, tympanometry, acoustic reflex thresholds, and uncomfortable loudness levels. A majority of the experimental subjects reported difficulty processing signals in noise regardless of the medication status. Similarly, about one fourth of the experimental subjects complained of hyperacusis regardless of the medication state. Uncomfortable loudness testing is one way to assess hyperacusis. Marriage and Barnes, 1995, argue that hyperacusis can be efferent in nature, without obvious cochlear involvement, thus separating the phenomenon from recruitment. They also suggest that 5-HT systems modulate central responses to sensory input, particularly, sensitivity to sound. In this study it was anticipated that the unmedicated experimental group would exhibit reduced tolerance to loud sounds, as measured from their uncomfortable loudness levels. Although the unmedicated scores were about 3 dB lower than the medicated scores in the experimental group, indicating some tolerance problem, the difference was not significant. This non-significant result could be a statistical power issue since the study did not involve a large group of subjects.

Our previous study (Gopal et al., 2000) demonstrated higher transient evoked otoacoustic emission levels in the clinically depressed individual while unmedicated. In the present study, SSRI treatment condition showed a significant reduction in the transient evoked otoacoustic emission levels, drawing the medicated scores closer to the control group. Transient evoked otoacoustic emissions are known to originate in outer hair cells and are innervated by the efferent fibers i.e., the olivocochlear bundle of the eighth nerve. Efferent fibers release the inhibitory neurotransmitter acetylcholine, which is believed to be modulated by serotonin (Gil-Loyzaga et al., 1997; Thompson et al., 1994). Lower levels of serotonin may have possibly reduced the modulatory effect of serotonin on acetylcholine, leading to larger amplitude transient evoked otoacoustic emissions in the unmedicated experimental group. This effect was absent when the subjects were medicated with SSRIs. Recent immunocytochemistry studies have shown serotonergic fibers in the regions below outer and inner hair cells of the

cochlea (Gil-Loyzaga et al., 2000), and biochemical studies have shown evidence of plasma membrane 5-HT transporters in the cochlear serotonergic fibers (Vincete-Torres et al., 2003). Expression of certain serotonin receptor subtypes has been shown in the mammalian cochlea. Serotonin subtypes 1A, 1B, 2B and 6 have been determined in the organ of Corti, lateral wall, and spiral ganglion subfractions of the cochlea, and subtypes 2C, 3 and 5B were found exclusively in the spiral ganglion (Oh et al., 1999). Although the exact role of serotonin in the cochlea is yet to be determined, the presence of serotonergic fibers and serotonin receptor expression in the cochlea support a serotonin-mediated modulation of the auditory signal in the cochlea. Another observation in this study is that each group demonstrated higher transient evoked otoacoustic emission amplitude in their right ear compared to their left ear. These results are in agreement with previous studies, which have shown larger amplitude transient evoked otoacoustic emissions in the right ear, suggesting peripheral asymmetries in the auditory system (Khalfa and Collet, 1996; Morlet et al., 1999). A positive correlation was found between transient evoked otoacoustic emission amplitudes (right and left ears) and Beck Depression Inventory-II scores for the unmedicated condition in the experimental group. In this study, transient evoked otoacoustic emissions was the only measure that correlated significantly with Beck Depression Inventory-II scores.

One of the basic properties of auditory evoked potentials is the growth in amplitude with increasing intensity. Previous studies have indicated a more exaggerated amplitude growth function in people with compromised serotonin levels (Hegerl and Juckel, 1993; Juckel et al., 1999; Gopal et al., 2000, 2004b). This observation has not been supported by some authors, who have suggested no exaggerated or augmented amplitude growth in people with low serotonin (Debener et al., 2002; Dierks et al., 1999). The present investigation found a significant increase in amplitude growth function in clinically depressed individuals while unmedicated for both auditory brainstem response peak V and auditory late response peak N_1P_2. Scores obtained from the unmedicated session showed large variability in amplitude growth probably suggesting a non-homogeneous group. Although all subjects in the experimental group were clinically depressed, the degree of depression varied, which may account for some of the variability. Nevertheless, the amplitude growth that was abnormally large in the unmedicated session returned to levels closer to the control group with medication. We speculate that the auditory evoked potentials also involve the same inhibitory effect that led to larger transient evoked otoacoustic emissions in the unmedicated session.

Group means demonstrated lower scores on most SCAN-A subtests and on the SCAN-A composite score for the depressed group compared to the control group. Although none of the mean scores fell within the disordered range, a statistically significant difference, exhibiting better performance in the experimental group while on SSRI medication, was observed on the composite score. Further investigation of each of the subtests indicated that the filtered word subtest was significantly different between the unmedicated and medicated rounds. The figure ground subtest also showed differences between the medicated and unmedicated rounds, however, the difference was not significant. Poorer performance on the SCAN-A test found in the experimental group in this study is analogous to results obtained by Gopal et al. (2000), wherein the subject exhibited consistently lower scores on the SCAN-A test during unmedicated sessions compared to medicated sessions.

Based on the mean data obtained, there appears to be some differences between the control group and experimental group. For example pure-tone thresholds are slightly higher for the experimental group, regardless of the session. A number of people in the experimental group reported difficulty processing auditory signals in noise. Although no statistically significant differences were identifiable between the groups in the above-mentioned measures, i.e. pure-tones thresholds and figure ground subtest, possible differences in hearing related or unrelated to depression cannot be completely ruled out at this time. Furthermore, there is a pattern that emerges wherein the unmedicated experimental group shows significantly different scores in certain measures from the control group, but this difference is no longer significant when experimental subjects are tested while under medication. Although these findings are somewhat similar to our earlier case study (Gopal et al., 2000), the present study conducted on a larger number of subjects, reiterates the effects of SSRI medication, and in turn the role of serotonin in the auditory system. The present study is also different from our two recent studies (Gopal et al., 2004a, b), in that this study used the same experimental subjects for medicated and unmedicated sessions, whereas the earlier studies used independent groups for medicated and unmedicated sessions. In addition, this study was conducted on females only, in order to control for gender variability. Since this is the first comprehensive study examining the effects of SSRI (and serotonin) on the auditory system in a fairly large group, a broader investigational approach was utilized. Future studies would be aimed at obtaining more detailed information in the areas of auditory function that this study has identified as being important.

In conclusion, the study showed that SSRI medication does have an effect on the auditory system. The effects are exhibited in both behavioral and physiologic test measures. This in turn provides further evidence that serotonin is capable of modulating the auditory system. Low levels of serotonin in the brain can have adverse effects on the auditory structures, but these effects are subtle and are hard to extract from basic pure-tone audiometry. Further evaluation of detailed prognostic values of SSRIs in enhancing auditory skills is definitely needed, wherein sub-categorization of clinically depressed individuals based on the degree of depression, type of SSRI medication, and dosages of medication are controlled.

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