THE EFFECTS OF SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS ON AUDITORY MEASURES IN WOMEN

Kelly Anne Briley, B.A.

Thesis Prepared for the Degree of

MASTER OF ARTS

UNIVERSITY OF NORTH TEXAS

May 2002

APPROVED:

Kamakshi V. Gopal, Major Professor
Kenneth Melnick, Minor Professor
Miriam A. Henoch, Committee Member and
Director of Graduate Studies in Audiology
Jeffery A. Cokely, Chair of the Department of
Speech and Hearing Sciences
C. Neal Tate, Dean of the Robert B. Toulouse
School of Graduate Studies

Briley, Kelly, Anne. The Effects of Selective Serotonin Reuptake Inhibitors (SSRI) on Auditory Measures in Women. Master of Arts (Audiology), May 2002, 86 pp., 5 tables, 9 figures, 57 references.

This study examined the relationship between selective serotonin reuptake inhibitor (SSRI) medication and auditory measures in clinically depressed women. Experimental subjects were tested in both a medicated and unmedicated condition. Experimental subjects were compared to a normal control group; additionally intrasubject comparison was made within the experimental group. Test measures included: audiometry, tympanometry, otoacoustic emissions, uncomfortable loudness level, masking level difference, SCAN-A, Synthetic Sentence Identification (SSI), and the low predictability section of the Revised Speech in noise (RSPIN). The unmedicated group scored significantly less favorably than the control group on the following tests; SCAN-A (composite, filtered words, and auditory figure ground), R-SPIN (0MCR condition in both the right and left ears). Additionally, the unmedicated group scored significantly less favorably than the medicated group on the SSI (-20MCR condition right ear only) and of the R-SPIN (0MCR condition right ear only). Other test measures indicated consistent trends but did reach significance.

ACKNOWLEDGMENTS

I would like to recognize several individuals who have been essential to the successful completion of this process. First, I would like to acknowledge my mentor, Dr. Kamakshi Gopal for instilling within me an appreciation and excitement for research. With her support and enduring patience I have become an enthusiastic researcher, improved clinician, and stronger person. I would like to express my sincere gratitude to Dr. Miriam Henoch, for reminding me why I am doing what I do, and for whom I am doing it. Dr. Kenneth Melnick, for keeping me grounded, helping me maintain a sense of humor, and showing me that dedication brings great rewards.

I would also like to thank my family for the unfaltering encouragement and love. To my mother, in particular, for always believing in me, and giving me an amazingly strong, intelligent, and gifted woman to learn from. To Shane Johnson, for having the love, patience, and courage to go through this journey by my side. And finally Cyrus and Sabrina for devotion and companionship.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

Figure Page

CHAPTER 1

Introduction

Individuals suffering from clinically diagnosed depression are prescribed selective serotonin re-uptake inhibitors (SSRI) for relief of their symptoms, since there is a growing support for the notion that depressed individuals exhibit a compromised balance of the brain neurotransmitter serotonin (5-hydroxytryptamine; 5HT) (Perez, Bel, Celada, Ortiz, Alverez, & Artigas, 1998). Neurotransmitters, such as serotonin, are chemical messengers found in the brain that permit communication between nerve cells. Serotonin has both excitatory and inhibitory effects on neuronal firing in the central and peripheral nervous systems (Jacobs & Fornal, 1993; Thompson, Thompson, Garrett, & Britton, 1994; Vandermalen 1985). Serotonin is released from the neuron into the synaptic cleft and either stimulates the adjacent neuron(s) or is reabsorbed by the first neuron. Serotonin has been reported to have an effect on vertebrate smooth muscles, neuronal cell bodies, dendrites, nerve fibers blood platelets, and glandular functions (Vandermalen 1985). Abnormal function 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. SSRIs are antidepressants that increase the serotonin available in the synaptic cleft by blocking the mechanism responsible for re-uptake. 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).

Clinical symptoms seen in patients with serotonergic dysfunction include; depression, obsessive-compulsive disorder, obesity, migraine, addictive behaviors such as alcoholism, impaired speech perception, intolerance to sensory stimuli and hyperacusis. A pilot study conducted by Gopal et al., (2000), detailed the auditory sensitivity and processing ability of a depressed subject who also suffered from hyperacusis and difficulty understanding speech. The patient was evaluated both in the medicated and unmedicated condition. SSRI medication improved tolerance to loud sounds, and uncomfortable loudness levels were higher in the medicated condition improving the dynamic range of hearing. Auditory evoked potentials and otoacoustic emission amplitudes were more robust in the unmedicated condition, which could be due to lower inhibition. In the medicated condition, SCAN-A (a screening test for auditory disorders) scores were within normal limits; however, in the unmedicated condition the subject scored in the disordered range. The authors attribute these findings to a possible dysfunction in the auditory system. Subsequent research by Bishop (2001) and Carney (2001) made static group comparisons of three groups of subjects including a control group and to experimental groups, one depressed group not taking medication, and one depressed group taking an SSRI. They investigated the relationship between standard audiological tests such as pure tone audiometry, tympanometry, acoustic reflexes, masking level difference (MLD), temporal integration, amplitude resolution, otoacoustic emissions, uncomfortable loudness

level (UCL), along with auditory processing tests such as the SCAN-A, SSI (synthetic sentence inventory), and R-SPIN test (revised speech in noise). Additional test measure included auditory evoked brainstem and late potentials. Significant correlations were found for UCL, amplitude resolution, ABR wave V amplitude, and SSI. It is notable to mention that these investigations differ from this current study in that the experimental group for the medicated and unmedicated condition was comprised of two entirely exclusive groups. The author believes that evaluating intra subject variability, that is evaluating the same individuals in a medicated versus unmedicated condition, as opposed to a static group comparison, would enhance validity.

The purpose of the current study was to evaluate the same individuals in both conditions; that is, medicated and unmedicated, allowing for intra-subject comparison. In order to keep the groups more homogenous, only female subjects were included in the study. Currently, little research has been done on the peripheral and central auditory effects of SSRI medications. Comprehensive auditory evaluation of clinically depressed individuals taking SSRIs would be of value in understanding the role of serotonergic dysfunction in auditory processing. Currently, there is no objective diagnostic test available to diagnose clinical depression. Physicians rely on patient's individual perceptions of how they feel. Developing an objective, noninvasive diagnostic tool to screen for depression would be invaluable not only in identifying and treating more individuals, but additionally in monitoring patient response to medication.

Goal of the Study

The goal of this study was to identify the role of SSRI medication on auditory function in subjects diagnosed with clinical depression. A second objective was to compare the results for the SSRI subjects in their unmedicated condition to normal control subjects. The study consisted of two groups: the control group and the experimental group. The control group included individuals who had never taken an SSRI medication and were not experiencing symptoms of clinical depression. Individuals in the experimental group had to be taking, or planning to take one of five SSRI medications: fluoxetine hydrochloride (Prozac), sertraline hydrochloride (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), or paroxetine (Paxil). The experimental subjects were tested once while on medication and once off medication. The test battery consisted of case history, otoscopy, pure tone testing, Otoacoustic Emissions (OAEs), Masking Level Difference (MLD), dynamic range of hearing based on Uncomfortable Loudness Level (UCL), and behavioral speech tests such as SCAN-A (a screening test for auditory processing in adolescents and adults), SSI (synthetic sentence inventory), low predictability subtest from the R-SPIN (revised speech in noise). This battery allowed for examination of auditory ability from the cochlea to the auditory cortex.

The specific aims of the study were:

1) Is there a difference in any of the test measures while experimental subjects were on medication versus off medication?
2) Is there a difference in the test results between the normal control group and the experimental group?

CHAPTER 2

Review of the Literature

Prelude

This section will begin with a review the pertinent aspects of the serotonergic system, its implication in behavioral and physiological processes, and treatment of serotonergic dysfunction with serotonin reuptake inhibitors. This will be followed by a review of the neurotransmitter's involvement in the auditory system. Past research has consistently linked decreased serotonergic neurotransmission with depression (Perez et al., 1998 Jacobs & Fornal, 1993; Thompson et al., 1994; Vandermalen 1985). Although limited, mounting research points to serotonergic involvement in the central, and peripheral auditory system (Martin & Humphrey, 1994; Thompson et al., 1994, Vandermalen, 1985; Gopal et al., 2000). The current chapter serves to strengthen the role of 5-HT in auditory perception and processing. To provide insight as to why and how the selected test measures were used, a subsequent review of relevant literature will be included.

A routine audiological test battery; comprised of otoscopy, tympanometry, and pure tone testing will serve to assess the basic integrity of the auditory system. Otoacoustic emissions were chosen in light of their documented success in evaluation of outer hair cell function. Also, contralateral masking of OAEs allows for an examination of the suppressive characteristics of the medial olivocochlear efferent system. Masking level difference testing is a well established means of assessing lower brainstem integrity and has also been

implicated in evaluation of auditory processing ability. Uncomfortable loudness level (UCL) testing was selected as part of the test battery in light of earlier research associating hyperacusis and impaired serotonin levels. A compilation of speech tests; including a screening test of auditory processing (SCAN-A), synthetic sentence identification (SSI) and the revised speech perception in noise (R-SPIN) were chosen to assess both brainstem and central functioning of the auditory system.

Anatomy of the Serotonergic System

Jacob and Fornal (1993), noted that the organization 5-HT cell bodies and axon terminals is a primitive one, inherent to essentially all vertebrates. Serotonin cell bodies are exclusive to discrete neuronal groups localized in the dorsal and median raphe regions of the pons and upper brainstem; however, these cells send an extensive network of projections rostral and caudal throughout the nervous system. (Vandermalen, 1985). Prior research has shown serotonergic pathways to interface with the auditory system (Bishop, 2001; Carney, 2001; Gopal et al., 2000; Hegerl & Juckel, 1993; Martin & Humphrey, 1994; Thompson et al., 1994). Understanding this connection between serotonin and the auditory system could provide insight into complaints of hyperacusis and compromised auditory processing in depressed patients with otherwise normal hearing. Animal research by Thompson et. al., (1994) revealed evidence of peripheral 5-HT innervation, showing serotonergic terminals that originated in the midline raphe regions of the brain to terminate in the cochlear nucleus. Staining patterns revealed the heaviest staining to be localized to the midline raphe nuclei and substantia nigra. Lighter

staining of neuronal terminals occurred in the raphe, substantia nigra, pontine nuclei, inferior colliculus, vestibular nuclei, and eighth nerve.

Further research done by Gil-Loyzaga, Bartolome, & Vincente-Torres, (1997) elucidate the presence of serotonin containing fibers in the cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus. Central serotonergic fibers course through virtually all major neuronal structures and additionally make contact with cerebrospinal fluid (CSF) and the walls of blood vessels. Electrophysiological studies on both animals and humans have shown that intensity dependant auditory evoked potentials (AEP) reflect the involvement of serotonin in the auditory cortex (Hegerl & Juckel, 1993; Gallinat, Bottlender, Juckel, Puchner, Stoltz, Kuss, Mavroglorgou, & Hegerl, 1999; Juckel, Hegerl, Molnar, Csepe, & Karmos, 2000). The presence of serotonergic innervation in both the CNS and the periphery leads to the reasonable hypothesis that serotonergic systems may modulate central auditory processing as well as sensory pathways such as those related to tolerance of loud sounds and light (Martin & Humphrey, 1994; Thompson et al., 1994). Although this study focused exclusively on serotonin, and the effects of its dysregulation on the auditory system, one must also acknowledge and understand that serotonin is not the only neurotransmitter implicated in depression. Further examination of these neurotransmitters provides additional insight into the biogenic processes of depression

A Biogenic Monoamine Hypothesis of Depression:

The monoamine hypothesis proposes that depressive symptoms result from central monoamine dysfunction (Kandel & Schwartz, 1985, p. 720). There are five acknowledged biogenic amine neurotransmitters: norepinephrine (noradrenline), serotonin, dopamine, epinephrine (adrenline), and histamine. Functional alterations in one or more of the following systems: serotonergic, dopaminergic, and noradrenergic, have been implicated in the pathophysiology of depression (Charney 1998). Recent research supports this notion, showing that the use of therapeutic medications which function to increase synaptic levels of monoamines in the clinically depressed populations is directly correlated to improvements in symptoms (Bruder, Stewart, Tenke, McGrath, Leiti, & Quitkin, 2001; Menkes, Aghajanian, & McCall, 1980; Pinder, 1997).

Clinical Features of Depression

Clinically diagnosed depression is an overwhelming and debilitating disorder, which if sufficiently bad enough, can affect normal working and leisure life. Depression can be classified as unipolar, which involves episodes of depression, or bipolar, where the individual experiences episodes of depression and mania. Individuals can experience numerous symptoms including thoughts of suicide, guilt, hopelessness, difficulty thinking clearly, agitation and difficulty remembering (Kandel, 1991, p. 718; Lucas, 1992; Simpson & Davies 2000;Whisman, Perez, Ramel, 2000). Currently, there is not an objective test to quantify depression. Physicians depend on descriptors provided by patients when making a diagnosis. The Diagnostic and Statistical Manual of Mental Disorders

Fourth Edition (DSM-IV), published by the American Psychiatric Association, provides standard criteria to aid qualified mental health care professionals in diagnosing mental disorders. Criteria for diagnosis of a major depressive episode (unipolar depression) requires at least one of the following abnormal moods: 1) abnormal depressed mood most of the day, nearly every day, for at least 2 weeks, 2) abnormal loss of interest and pleasure most of the day, nearly every day, for at least two weeks, 3) if 18 or younger, abnormal irritable mood, most of the day, nearly every day for at least two weeks. Further, at least five of the following symptoms must be present during the same two weeks depressed period: 1) abnormal depressed mood as defined in above criteria, 2) abnormal loss of all interest and pleasure as defined in above criteria, 3) appetite or weight disturbances, either loss or gain, 4) sleep disturbances, either insomnia or hypersomnia, 5) activity disturbances, either abnormal agitation or slowing, 6) abnormal fatigue or loss of energy, 7) abnormal self-reproach or inappropriate guilt, 8) poor concentration or indecisiveness, 9) abnormal morbid thoughts of death or suicide. The above symptoms cannot be due to mood psychosis, physical illness, alcohol, medication, recreational drugs, or normal bereavement. It is notable to mention that he two main physicians who referred subjects for this study followed DSM-IV criteria for diagnosis of depression.

Depression and Women

There is general agreement in the literature that the incidence of depression in women is disproportionate to the incidence in men, in fact one of the risk factors

in the DSM-IV for depression is being female (American Psychiatric Association, 1994). Bruder (2001) sited depression as the most critical mental disorder facing women today, with approximately seven million American women implicated. Women have consistently exhibited increased risk rates for depression than men by a ratio of 2:1 (Bruder, 2001). The American Psychiatric Association (1994) report that 12.9% of women between the ages of 15 to 54 will experience a major depressive episode during a 12 month period as opposed to only 7.7% of men. Consequently, 63% of depressive occurrences in a one year time period are accounted for by women. Researchers have attempted to explain the disparity between incidence of depression in men and women. One explanation could be the demands of marriage, educational status, and family obligations increase the risks of depression in women. Other possible explanations include the idea that although men and women undergo a proportional number of negative lifetime experiences, women respond to these experiences with greater levels of stress. Some individuals respond to therapeutic medications and experience an improvement in depressive symptoms.

Depression & SSRIs

Serotonin, or 5-hydroxytryptamine, is synthesized from tryptophan, a common amino acid and essential dietary requirement. The serotonergic system has been shown to be associated with a myriad of behavioral processes including; eating, aggression, libido, personality, bulimia, obsessive-compulsive disorder, manic depression (bi-polar), schizophrenia and alcoholism (Fuller &Wong 1990; Lucas 1992). Physiological processes may include; motor activity, muscle tone,

body temperature, regulation of circadian rhythms, pain transmission, hormone release, gastrointestinal function and vasoconstriction (Pinder, 1997; Jacobs & Fornal 1993; Lucas 1992; Vandermaelen, 1985).

It seems clear that serotonin and depression have a strong correlation given that the majority of 5-HT receptors in the brain are located in regions concerned with mood and anxiety (Martin & Humphrey 1994). Depression appears to be closely coupled to decreased activity of the serotonin neurotransmitter. The synapse is the principal structure in the process of neurotransmission as it provides a connecting link between nerve cells. Concentration of neurotransmitters within the synaptic cleft must be closely controlled by the neuron for synaptic transmission to be effective. To achieve this balance, neurons execute a sophisticated operation of synthesis, packaging, release and degradation. Once released, serotonin affects multiple membrane bound receptor sites. Serotonin travels down the neuron and is released from the presynaptic cleft into the synaptic cleft; a re-uptake mechanism, then propagates transfer of serotonin back into the nerve terminal where it will be re-packaged and stored within synaptic vesicles. When the process of serotonin re-uptake is impaired, depression may result. However, if synaptic activity can be effectively controlled, behavioral and physiological processes governed by these synaptic transmissions could conceivably be regulated if not controlled.

To ameliorate depressive symptoms, individuals often choose antidepressant therapy. The first generation of antidepressants, monoamine oxidase inhibitors and tricyclics, were not selective and allowed for the reuptake

of serotonin, norepinephrine and sometimes dopamine. Second generation antidepressants, selective serotonin reuptake inhibitors (SSRIs), inhibit the serotonin uptake carrier with high specificity, enhancing only serotonergic activity. SSRIs also lack the characteristic side effects of their predecessors, including anticholinergic (such as adverse muscular effects) and cardiovascular effects as well as weight gain (Fuller & Wong 1990). Fluoxetine (Prozac) is likely one of the most widely recognized SSRI and was the first drug of its kind to be prescribed in the United States. (Fuller & Wong, 1990, Lucas 1992).

An objective measurement of serotonin that is not distressing to the patient would be a valuable tool in appraising individual effectiveness of SSRI medications. Serotonin concentrations can be measured centrally in cerebrospinal fluid (CSF) this method is not clinically feasible due to the invasive method required to obtain a valid sample. Although still a matter of debate in the literature, 5-HT can be found peripherally in the blood, intracellularly (platelets) and extracellularly (plasma) (Perez 1998). These two pools are affected differently by certain drugs. Perez (1998) concluded that depressed subjects had a significantly lower concentration of 5-HT in plasma as compared with non-depressed counterparts. Interestingly, Bongioanni & Selvaggi (1991) found subjects displayed a dramatic increase in plasma 5-HT levels following SSRI treatment. Although there has been limited research on the prognostic significance of these measures, this inverse relationship between pre-treatment and post-treatment 5-HT concentrations in blood could be an indicator of the actions serotonergic antidepressant drugs exert on the human serotonin system.

Further examination of the connection between blood 5-HT levels and clinical improvement could benefit in health care providers in the search for individualized treatments for depression.

Currently the therapeutic success of SSRI medications is established through subjective evaluation of patient reported symptom improvement. Research by Rappaport, Coccaro, Sheline, Holland, Fabre, & Bradford, 1996, revealed consistent improvement in depressive symptoms of patients taking Prozac (fluoxetine) as compared to patients who were administered a placebo. This lends support to the theory that SSRI medications increase the quantity of usable endogenous serotonin in the synaptic cleft. Of course to fully comprehend the relationship between depression, serotonin, and the auditory processes, one must first be aware of the intrinsic network of the auditory system.

The Auditory System

A fascinating aspect of the auditory system is the presence of a parallel and sequential network of nerve fibers that send and receive information. Afferent pathways relays neurological information from the cochlea to the auditory cortex, the contrasting efferent pathway transmits from the brain to the cochlea.

Afferent auditory pathways originate in the cochlea. It is through this system that sensory information ascends from the periphery to converge with the brain. Neurons in the cochlear nucleus extend their axons, which converge with subsequent nuclei, including the superior olivary complex, lateral lemniscus, and

inferior colliculus. Once the pathway reaches the inferior colliculus, fibers cross ipsilaterally and contralaterally projecting toward the medial geniculate body. The geniculate axons terminate in the primary auditory cortex (Kandel & Schwartz, 1985).

Recent literature supports the existence of two discrete efferent pathways between the superior olivary complex and the cochlea. The first group synapsing with cochlear afferent dendrites which are proximal to the principle sensory receptors of the auditory system, the inner hair cells. The second group, the crossed, medial olivocochlear efferent system (MOCS), terminates primarily on the outer hair cells which are believed to be the source of active cochlear mechanisms (Morlet et al., 1999; Parthasarathy, 2001). Several studies have related contralateral acoustic stimulation with a peripheral inhibition response (Aran et al., 2000; Collet et al., 1990; Collet, Veuillet, Moulin, Morlet, Giraud, Micheyl, & Chery-Croze, 1994; Graham & Hazell, 1994). Recording otoacoustic emissions with contralateral masking may present a direct means of activating the medial olivocochlear efferent system and observing the suppressive activity of each cochlea.

Serotonin & the Auditory System

Serotonin (5-Hydroxytryptamine, 5-HT), an amino acid derivative, is a neurotransmitter of the monoamine class. It can be found in abundance in the central and peripheral nervous system. In vertebrates, a preponderance of 5-HT producing neurons project from the raphe nuclei and the reticular formation at the

medulla oblongata. Areas indicated as being rich in serotonergic fibers include; the inferior colliculus, olivary complex, and cochlear nucleus (Gil-Loyzaga, Bartolome, & Vincente-Torres 1997; Thompson et al., 1994). Gil-Loyzaga and colleagues (1997), were the first to discover small peripheral distributions of serotonergic fibers in the cat cochlea. The researchers noted that other neurotransmitters such as acetylcholine and dopamine, which are part of the olivocochlear lateral efferent system (OLES), followed similar innervation patterns. This finding suggests that serotonin may belong to the OLES. Stutzman, McEwan & LeDoux (1998), found serotonin-producing cells also interface with the amygdala (an area involved in emotions), and the hypothalamus (which influences appetite, libido and sleep).

Investigating the relationship between auditory and serotonergic pathways could bring forth new, noninvasive methods of evaluating serotonin levels in depressed individuals. Hegerl and Jeckel (1993) examined the difference in auditory evoked potentials as a function of intensity dependence as a means of assessing central serotonin neurotransmission. Findings revealed N1/P1 amplitude to be dependent on stimulus intensity, with larger, more robust amplitudes reflecting low serotonergic transmission.

Recently, a comprehensive study by Gopal et al., has been able to link central and peripheral serotonergic involvement to auditory factors in a human subject. The case study examined the relationship between the auditory and serotonergic systems of a clinically depressed subject undergoing SSRI treatment. Results indicated a change in ABR (auditory brainstem response) intensity

dependant components, otoacoustic emissions, auditory processing skills, and dynamic range of hearing. Similar findings by Bishop (2001) and Carney (2001), investigating the interactions between auditory measures in subjects taking SSRI medications as compared to unmedicated counterparts and controls support these findings

Rationale for Test Procedures used in the Study:

Otoacoustic emissions (OAEs)

Otoacoustic emissions (OAEs) are pre-neural, sub audible sounds generated at the level of the normal cochlea. In the healthy cochlea, the stimulus is processed by the Organ of Corti and as a result a portion of the sound energy is re-emitted through the ossicular chain to the external ear (Kemp, Ryan & Bray 1990; Parthasarathy 2000). OAEs are believed to be the product of intrinsic, nonlinear mechanical activity within the cochlea and provide objective, noninvasive information regarding cochlear function.

Studies indicate that these emitted responses are generated by the stimulus-induced motility of the outer hair cells (OHC). Transient and distortion product are the two types of evoked emissions and can be elicited in individuals with normal hearing. Response amplitude diminishes as hearing loss progresses; elicitation of OAEs will cease once hearing loss reaches approximately 35dB for transient evoked otoacoustic emissions (TOAEs) and 50dB for distortion product otoacoustic emissions (DPOAEs).

(TOAEs) are generated within the inner ear by a brief click stimulus. Averaging (n=260) is used to eliminate environmental noise that may affect amplitude. OAEs follow the tonotopic arrangement of the cochlea, high frequency responses having short latencies and mid and low frequency sounds having longer latencies.

The location of the OHCs is postsynaptic to the medial efferent neurons; consequently OHCs are directly modulated by the medial efferent system, specifically the medial olivocochlear bundle (MOCB) which originates in the medial nuclei of the superior olivary complex (Micheyl, Carbonnel, & Collet 1995; Morlet et al 1999). Efferent fibers release a crucial inhibitory neurotransmitter called acetylcholine (ACh), which is believed to be modulated by serotonin (Duffy 1995; Gil-Loyzaga et al. 1997; Thompson et al. 1994). Stimulation of the MOCB can be achieved through direct electrical stimulation or via contralateral masking (Morlet, Goforth, Hood, Ferber, Duclaux, & Berlin 1999). Contralateral acoustic stimulation results in simultaneous activation of the crossed and uncrossed MOC efferent system, which in turn results in bilateral, peripheral suppression of the auditory system (Aran, Pajor, Charlet du Sauvage, & Erre, 2000; Graham & Hazell 1994). Research suggests that greater reductions in TEOAE amplitude under contralateral stimulation is indicative of a stronger medial efferent system (Micheyl et al 1995). Williams, Brookes, & Prasher (1993) researched the effect of contralateral acoustic stimulation following vestibular neurectomy and found the inhibitory effect of contralateral acoustic stimulation to be lacking postoperatively. It can be concluded from research that

lack of suppressive effects is concurrent with compromised efferent functioning (Berlin et al., 1995; Tavartkiladze, Frolenkov & Artamasov 1996; Williams, Brookes & Prasher 1994). Franklin et al., (1992) found OAEs to have high test re-test reliability, to have low intrasubject variability and to be highly reproducible in individuals over time.

Given this information, the use of OAEs in this study would be advantageous in that changes in test results can be interpreted as indication of change due to outside induced processes (change in medication status), indicating an altered influence of the MOCB in suppression.

MASKING LEVEL DIFFERENCE (MLD)

Masking level difference (MLD) testing evaluates lower brainstem involvement. Release from masking is defined as the improvement in the masked threshold sensitivity for a signal that occurs on transition from a homophasic listening condition to an antiphasic one (Olsen, Noffsinger, Carhart 1976). Homophasic listening involves both the signal and the noise being in phase or out of phase with each other. In the antiphasic condition, either of the two stimuli, signal or masker, are out of phase with itself while the other is in phase. MLDs are typically obtained binaurally using a 500Hz pulsed tone in the presence of narrow band masking noise. The masking level difference is the difference in decibels between the subject's threshold recognition of the tone in the homophasic and then the antiphasic condition. Sweetow and Reddell, (1978)

found tonal MLDs of children with suspected auditory perceptual difficulties to be significantly lower than MLDs of age matched peers. This research indicates MLD testing would be a valuable diagnostic test in central auditory batteries. Patients with subcortical disorders, such as Meniere's disease and 8th nerve tumors exhibit significantly small MLDs. In their comprehensive clinical study, Olsen Noffsinger and Carhart (1976) found patients having higher cortical involvement had normal MLDs; suggesting that release from masking is a phenomenon exclusive of mediation by the auditory cortex

UNCOMFORTABLE LOUDNESS LEVEL (UCL)

Uncomfortable loudness level (UCL) testing is one of the methods used in measuring hyperacusis, dynamic range is evaluated by analyzing the difference between the individual's threshold and UCL. Clinical hyperacusis is an individual's marked intolerance to ordinary environmental sound in the presence of essentially normal hearing (Brady & Lynn 1994). Studies have implicated both the peripheral and central systems in hyperacusis. Anari et al 1997, noted there was a fundamental difference regarding hyperacusis phenomena in several patients with peripheral acoustic trauma, as compared to patients exhibiting central pathologies including neurosis and depression. Brady & Lynn (1994) also support the belief that peripheral hyperacusis involves the middle ear system and cochlea, existing independently from hyperacusis with central and emotional elements. Phillip & Carr (1998) describe the recruitment, a peripheral abnormal

growth of loudness as an afferent phenomenon involving a compromised outer hair cell system. This abnormality regarding loudness function is then twofold, consisting of an elevated threshold and narrowed dynamic range. Marriage & Barnes (1995) offer the hypothesis that hyperacusic phenomena can be efferent in nature without obvious cochlear components. Further, they argue that central 5-HT neural systems exert an inhibitory modulation of central responses to sensory input.

SPEECH STIMULI

SCAN-A:

Keith (1996) describes the SCAN-A as a more progressive version of the SCAN, a screening test for children ages 3 to 11 years old. Specifically, the SCAN-A is used to describe auditory processing abilities in adolescence and adults. The SCAN-A is comprised of four subtests including: filtered words, auditory figure ground, competing words, and competing sentences. In the filtered words subtest, the subject is required to repeat monosyllabic words that have been passed through a 500Hz filter. The auditory figure ground subtest evaluates the subject's ability to understand monosyllabic words in the presence of background noise similar to cafeteria babble presented at 0dB signal to noise ratio. The competing words subtest is a dichotic test (signals presented to separate ears) requiring the subject to repeat the word that was heard in the right ear first (the following task is to identify words heard in the left ear first). The

competing sentences subtest is a directed listening task, the subject is asked to ignore the sentence presented in one ear and repeat only the sentence heard in the test ear.

In a preliminary study by Gopal et al (2000), investigating the processing abilities of a subject exhibiting withdrawn depression, hyperacusis, difficulty understanding speech, lethargy, and hypersensitivity to light, sound and touch revealed significant differences in SCAN-A scores when the subject was evaluated in the medicated (SSRI) condition versus unmedicated condition; scores were found to be normal and in the disordered range, respectively. Subsequent research by Bishop (2001) and Carney (2001) revealed similar findings.

SSI (Synthetic Sentence Identification):

Synthetic Sentence Identification (SSI), developed by Speaks and Jerger (1965), is a closed set procedure that employs sentences that have been modified from standard rules of grammar and syntax paired with a competing message (a narrative about Davy Crockett). Sentences are presented in two different conditions; presentations where the stimulus (sentence) and the competing message are in the same ear are referred to as ipsilateral competing message (ICM), presentations where the stimulus and competing message are in opposing ears are referred to as contralateral competing message (CCM). Sentences are delivered at three different message to competition ratios with regards to a level that usually yields 100% (most comfortable loudness level, or MCL). ICM sentences are presented at 0/0dB and 0/-20dB, while CCM are presented at 0/-

40dB (Willeford & Burleigh 1994). Jerger & Jerger (1974) found significant differences in scores for the ICM condition and the CCM condition in their study of eleven subjects with brainstem lesions. Results revealed the SSI-ICM to be particularly sensitive to brainstem lesion with subjects exhibiting more pronounced difficulty on the ICM task than the CCM task.

Revised Speech in Noise (R-SPIN):

The R-SPIN is a dichotic test presented with background noise or babble serving to mimics an environmental listening situation. The most difficult condition, the 0 MCR, stresses the auditory system and requires the subject to make sense of words that are distorted by the competing stimuli. Research has indicated that the R-SPIN is of significant value in assessing central auditory processing disorder (Jerger, Oliver, & Pirozzolo, 1990). The Revised Speech in Noise test (R-SPIN) consists of both low and high predictability sentences. Low predictability (LP) holding no semantic clues embedded within the sentence and high predictability (HP) holding a controlled number of contextual cues to aid the subject in identification of the final word in the sentence. Due to the more difficult nature, only the low predictability portion was administered in the test battery. There are eight forms of the R-SPIN each consisting of 25 LP or 25 HP sentences (Bilger, Nuetzel, Rabinowitz, & Rzeczkowski (1994)).

Beck Depression Inventory-II (BDI-II)

The Beck Depression inventory is widely recognized as an effective, self-report tool for assessing the severity of depression. The original BDI, devised in

1961 by Beck, Ward, Mock, and Erbaugh, has since been augmented to produce the current BDI-II. This updated design meets the American Psychiatric Association's Diagnostic criteria for diagnosis depressive disorders. A diagnostic criterion was delineated in the 1994 edition of the Diagnostic and Statistical Manual of Mental Disorders-Forth edition (DSM-IV). Respondents are asked to answer questions in regard to "the last two weeks, including today." The quick to administer BDI-II is scored by adding subject responses for each of 21 symptoms. The original inventory evolved from clinical observations of the attitudes and physiological symptoms of depressed psychiatric patients as compared to non-depressed counterparts (Endler, Rutherford, & Denisoff, 1999). The BDI's internal consistency to cognitive and physiological disorders has been affirmed by several studies indicating clinically depressed patients consistently score higher than nonclinical controls (Beck et al., 1999; Kilgore, 1999; Steer, Clark, Beck, & Ranieri 1998).

Symptoms are broken down into a four-point scale that ranges from 0 to 3. Cutoff scoring of the BDI-II assigns a score of 0-12 to be indicative of minimal depression, 13-19 indicating mild depression, 20-28 indicating moderate depression and 29-63 indicating severe depression (Whisman, Perez, & Ramel, 2000). Beck, Steer, Ball, & Ranieri (1999) identified two main dimensions of self-evaluative depression in the BDI-II representing somatic-affective and cognitive dimensions. The somatic portion addresses physiological symptoms such as fatigue and energy loss while the affective dimension represents symptoms such as crying and irritability. The cognitive aspect of the test relates

to psychological symptoms including pessimism and feelings of worthlessness. There is general agreement in the literature that ethnicity and age are not statistically significant factors in the BDI-II. It is notable to mention however, that on average, women scores 4 points higher than men (Beck, Steer, Ball, & Ranieri, 1999; Endler, Rutherford, & Denisoff, 1999; Killgore, 1999).

Summary of Review

The preceding section detailed the serotonergic system and its role in a variety of behavioral and physiological processes that are adversely affected by deregulation of this system. Specifically, the association between 5-HT and depression was explored. A variety of auditory tests measures capable of assessing areas of the auditory system that have documented serotonergic innervation were also detailed. The purpose of this study was to determine central and peripheral effects of selective serotonin reuptake inhibitors (SSRIs) on auditory measures in clinically depressed subjects.

CHAPTER 3

Methods

Subjects

The participants in the study belonged to either the control group (normal) or the experimental group. The control group consisted of eleven women ages 21 to 32, who had never received a diagnosis of clinical depression and had never taken an SSRI. The experimental group comprised of 15 women, all having hearing within normal limits, ranging in age from 18 to 58. Inclusion criteria were 1) diagnosis of unipolar depression, by a physician, based on DSM IV criteria; 2) prescribed one of the following SSRI medications: fluoxetine hydrochloride (Prozac), sertraline hydrochloride (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), or paroxetine (Paxil). Furthermore, the experimental subjects were each evaluated twice, once when medicated and then again after voluntarily abstaining from medication for at least one month. The one month time period was chosen with regards to the SSRI with the longest half life which is fluoxetine (half life=7 or 8 days).

Exclusion criteria were 1) males, 2) the existence of concurrent psychiatric conditions or other neurological condition. The decision to include only women in the study was made to eliminate the variability of gender. Research indicates that women exhibit a greater incidence of depression than men (Bruder et al., 2001) and that women score significantly higher than men by an average of four points (Beck et al., 1999; Endler, Rutherford, & Denisoff, 1999).

Subjects were recruited for the study by means of campus fliers, campus newspaper (NT daily), campus television (NTTV). Subjects were also recruited via the UNT Health Center. All subjects were paid $100 upon successful completion of testing. Subjects were paid from a grant awarded to Kamakshi Gopal, Ph.D., by the Texas Advanced Research Program (TARP). The University of North Texas IRB has approved this study.

Procedures:

Total testing time was approximately four hours. If the patient exhibited or expressed fatigue, two separate sessions were used. Test procedures were randomized and broken into the following sets: 1) Case history and Beck Depression Inventory II (BDI); an SSRI benefit form for medicated condition only, 2) otoscopy, tympanometry and pure tone audiometry, 3) transient evoked otoacoustic emissions with and without contralateral masking, 4) auditory processing tests including the SCAN-A, SSI and R-SPIN, 5) uncomfortable loudness level (UCL) to be used in determination of the subject's dynamic range of hearing 6) masking level difference (MLD).

Instrumentation:

All testing was performed at the University of North Texas. Additionally, raw data for all test procedures is available in the appendices. Further detail regarding the test battery is as follows;

Case History:

All subjects were given the standard case history form used in the University of North Texas Speech and Hearing Center.

Beck Depression Inventory 4th Edition (BDI-VI)

All subjects were given the Beck Depression Inventory 4th Edition and asked to base their answers on general physiological and emotional feelings over the last two weeks.

Otoscopy:

Otoscopic examination of the ear, using a Welch & Allyn otoscope, preceded all test measures to insure that canals were clear and contraindications for the test battery were absent.

Tympanometry:

Tympanometry was conducted using the Grayson-Stradler GSI-33 immitance bridge and classified in accordance with Jerger (1970).

Pure Tone Audiometry:

Testing was done in sound treated rooms using calibrated earphones (TDH-39P) on one of three calibrated audiometers; the Madsen Orbiter 922, Auricle or the Grason-Stadler GSI-10 in sound treated rooms. Air conduction

testing following the classic Carhart & Jerger (1959) method was employed for octaves 250 through 8000Hz.

Otoacoustic Emissions:

Transient evoked otoacoustic emissions (TEOAEs) with and without contralateral masking was obtained using the ILO-96 otodynamic analyzer (Otodynamics Ltd). Each condition was tested twice for both the right and left ears. Stimuli used to evoke subject response was 80 microsecond linear clicks of 70dBpeSPL. It is generally acknowledged that it is possible for the stapedial reflex to affect the emissions reaching the recording microphone (Berlin et al., 1995; Graham & Hazel, 1994). So as a preventative measure to assure the integrity of the samples, the stimulus level did not exceed of 70dBpeSPL (Collet, Kemp, Veuillet, Duclaux, Moulin, & Morgon, 1990). 260 samples were averaged to determine OAE amplitudes for the frequencies 1K, 1.5K, 2K, and 3K. In all conditions, data from the two runs was averaged for the frequencies of 1K, 1.5K and 2KHZ. In the contralateral masking condition, the masker was set at 30dBSL in regards to the subject's threshold for the noise. OAEs were collected separately in each ear. Suppression of OAEs was calculated as the difference between masked TOAE and unmasked TOAE.

Loudness Levels:

Uncomfortable loudness levels (UCL) were obtained via recorded speech in both ears using one of the three before mentioned audiometers. Using Hawkin's (1984) scale the subjects indicated their perception of an intensity

ascending series of sentences. The procedure was repeated twice to ensure accuracy. The dynamic range was established by obtaining the difference between uncomfortable loudness level and pure tone average.

Masking Level Difference (MLD)

MLDs were obtained using the GSI-10 audiometer with TDH-39P headphones. Noise was constant at 65dB. A 500 Hz pulsed tone descended in decrements of 5dB until the subject could no longer detect the stimulus. At this point, a one-dB bracketing technique was used to determine threshold. Threshold measurements were obtained for S0N0, SπN0, and S0Nπ conditions.

Speech Tests:

All tests were completed using calibrated earphones (TDH-39P) on one of three calibrated audiometers; the Madsen Orbiter 922, Auricle or the Grason-Stadler GSI-10 in sound treated rooms. Each individual test material (CD or tape) was calibrated before administering.

SCAN-A

The SCAN-A (screening test for auditory processing disorders in adolescents and adults) was administered in accordance to Keith's (1995) recommendations. The constant level for this binaural test was the subject's most comfortable listening level (MCL) for each ear. Raw score were converted to standard scores that yielded percentile rank.

Synthetic Sentence Identification Test (SSI)

The SSI is a test comprised of recorded non-sense sentences accompanied by a story about Davy Crocket as a masker. Both ears are assessed at presentation levels following one of two formats; ipsilateral competing message (ICM) or contralateral competing message (CCM). The ICM was presented at 0 and –20 message to competition ratio (MCR); the CCM was presented at –40 MCR. The subject's ability to identify sentences heard through the story was calculated and recorded on the scoring form.

Low Predictability Revised Speech Perception in Noise (R-SPIN)

The R-SPIN is a monaural test comprised of 50 sentences selected from the low predictability section. Both ears were assessed at presentations of 0 MCR (message-to-competing ratio) and +8 MCR. Final percentages were immediately tallied and recorded on the score sheet.

Reliability:

The above detailed tests were chosen for their reliability and sensitivity to assess different levels of the auditory system known to posses 5-HT innervation. Threshold for pure tone audiometry and MLD was obtained using a standard bracketing procedure. Minimum acceptable OAE repeatability was judged by the ILO-96 system to be 85% and above. All speech tests in the battery are

standardized for clinical use. All procedures recommended for clinical use will be followed in this study.

Data Analysis:

Statistics Program for Social Sciences (SPSS) software was used to analyze data. Mean and standard deviation was obtained for all test measures from all subjects. To compare the results from the control and experimental groups, Independent Samples t-test test was used. Paired Samples t-test was used to compare the scores of experimental subjects between their medicated and unmedicated conditions. An alpha level of α=0.05 was adopted as the level of significance.

CHAPTER 4

Results and Discussion

Results

This study examined the relationship between SSRI medication and auditory measures in women. Of specific interest was the question of whether auditory function was significantly different between:

1) Experimental subjects medically diagnosed with depression and prescribed with an SSRI as compared to control subjects who had no history of depression or antidepressant drug use.
2) Experimental subjects while on SSRI medication versus off SSRI medication for at least four weeks.

All subjects underwent the following tests: case history, Beck Depression Inventory (BDI), otoscopy, tympanometry, pure tone audiometry, otoacoustic emissions with and without contralateral masking, uncomfortable loudness level (UCL), masking level difference (MLD), SCAN-A, Synthetic Sentence Identification (SSI), and Revised Speech In Noise (R-SPIN, low predictability list).

The following is a summary of test results from each group of subjects. Group means and standard deviation were obtained for all test measures. Raw data for specific test results can be found in the appendices subsequent to this section. Group characteristics of all subjects is illustrated in Table 1. Raw data relative to this descriptive information can be found in Appendix A.

Table 1: Sample Size and Age Information

Group	Control	Experimental
Sample Size	n=11	n=15
Age (years)	Mean: 24.36 SD: 3.61	Mean: 24.73 SD: 6.37

Beck Depression Inventory-II (BDII)

The BDI-II provided an assessment of each subject's perception of their level of depression. Subject's self ratings were then compared to cut off scores: 0-12 implying minimal depression, 13-19 implying moderate depression, and 20-28 implying severe depression. As shown in Table 2, the control group fell into the minimal depression range. As for the experimental group: while unmedicated, subjects fell in the upper limit of moderate depression, and while medicated, subjects fell into the lower limit of moderate depression. Independent Samples t-test for the control and medicated group revealed a statistically significant difference (p=.000) between the BDI scores. Additionally, the Independent Samples t-test for the control and unmedicated group also yielded statistically significant results (p=.000). Paired Samples t-test between medicated and unmedicated groups did not yield statistically significant results (p=.066). Given that the BDI-IV yields ordinal level data, median and semi-interquartile range were chosen as the measure of central tendency. Raw data for the BDI-II can be found in Appendix A

Table 2: Beck Depression Inventory-VI, group means.

Subject Group	Control N=11	Experimental Medicated N=14	Experimental Unmedicated N=14
BDI-II Score	Median: 0 Semi-interquartile range=0.5	Median: 13.5 Semi-interquartile range=6.88	Median: 19 Semi-interquartile range=13.63

Basic Audiological Measures

Otoscopy revealed clear, unoccluded canals for all subjects. Tympanometry revealed type A tympanograms for all subjects except for one control and one experimental subject who presented with type Ad tympanograms bilaterally. It should be noted that both subjects with type Ad tympanograms had normal hearing, case history revealed recurrent otitis media with concurrent use of pressure equalization tubes, this could account for the presence of monomeric membranes. These results are indicative of essentially normal middle ear function. Pure-tone averages (PTAs) were found to be within normal limits (<25dBHL), bilaterally for all subjects. Table 3 presents a synopsis of the afore mentioned results. Raw data for PTA and tympanometry can be found in Appendix B.

Table 3: Results of audiological measures: Otoscopy, tympanometry, and pure-tone averages.

Measure	Control N=11	Experimental Medicated N=15	Experimental Unmedicated N=15
Otoscopy	Normal for all ears	Normal for all ears	Normal for all ears
Tympanometry	Type A=10 Type Ad=1	Type A=14 Type Ad=1	Type A=14 Type Ad=1
PTA-right (dBHL)	Mean: 4 SD: 2.68	Mean: 7.4 SD: 6.11	Mean: 7.5 SD: 6.83
PTA-left (dBHL)	Mean: 3.54 SD: 2.2	Mean: 7.46 SD: 6.44	Mean: 7.13 SD:7.51

Otoacoustic Emissions

Otoacoustic emissions were obtained in two conditions: with and without contralateral masking. An initial unmasked measure was attained, and then OAEs were collected with concurrent contralateral masking. Specifically of interest was the three frequency average (1K, 1.5K, and 2K) for the right and left ears. The decision to include only the above mentioned frequencies was made as a result of research suggesting that the efferent system to be more functional at low and mid frequencies as opposed to high frequencies (Morlet et al., 1999). Although no significant differences were found, a trend was seen wherein the unmedicated group consistently produced more robust OAE amplitudes during unmasked and masked conditions, in both the right and left ears as compared to the control group. Otoacoustic emission p values can be found in table 4a. Another

observation made in this study was that the right ear OAEs were more robust than left ear OAEs, this finding was evident in all groups. Raw data can be found in Appendix C.

Table 4. Transient Evoked Otoacoustic Emissions Means and Standard Deviations.

	Control N=11	Experimental Medicated N=15	Experimental Unmedicated N=15
1000Hz right unmasked	Mean:11.91dBSPL SD: 6.06 dBSPL	Mean:13.08dBSPL SD: 4.82dBSLP	Mean:14.07dBSPL SD: 5.21
1500Hz right unmasked	Mean: 14.86 SD: 5.63	Mean: 17.52 SD: 6.65	Mean: 18.11 SD: 4.47
2000Hz right unmasked	Mean: 12.41 SD: 5.25	Mean: 17.19 SD: 5.37	Mean: 16.3 SD: 6.15
1000Hz right masked	Mean: 10.86 SD: 6.2	Mean: 12.21 SD: 5.3	Mean: 11.17 SD: 6.53
1500Hz right masked	Mean: 13.45 SD: 6.29	Mean: 16.25 SD: 7.73	Mean: 15.47 SD: 7.11
2000Hz right masked	Mean: 11.77 SD: 4.67	Mean: 15.11 SD: 7.15	Mean: 14.67 SD: 8.10
3 freq. ave. right ear unmasked	Mean:13.05 SD: 4.38	Mean: 15.75 SD: 4.15	Mean: 16.16 SD: 4.38
3 freq. Ave right ear masked	Mean: 12.02 SD: 3.86	Mean: 12.59 SD: 4.60	Mean: 13.95 SD: 6.03
1000Hz left unmasked	Mean: 13.41 SD: 4.79	Mean: 11.93 SD: 5.94	Mean:13.77 SD:7.66
1500Hz left unmasked	Mean: 12.95 SD: 4.28	Mean: 14.79 SD: 6.21	Mean: 16 SD:6.65
2000Hz left unmasked	Mean: 11.18 SD:4.95	Mean: 10.82 SD: 6.72	Mean: 12.33 SD: 7.18
1000Hz left l masked	Mean: 12.6 SD: 6.79	Mean: 11.5 SD: 5.39	Mean: 13.3 SD: 7.44
1500Hz left masked	Mean: 13.35 SD: 6.14	Mean: 14.57 SD: 6.35	Mean: 15.83 SD: 6.31
2000Hz left masked	Mean: 11.10 SD: 4.99	Mean: 11.71 SD: 6.61	Mean: 12.07 SD: 7.40
3 freq. ave. left ear unmasked	Mean: 12.50 SD: 2.98	Mean: 12.51 SD: 4.99	Mean: 14.44 SD: 5.28
3 freq. ave.	Mean: 12.35	Mean: 12.59	Mean: 13.94

left ear masked	SD: 4.69	SD: 4.60	SD: 5.94

Table 4a. Otoacoustic Emission (p) Values (A=medicated condition, B=unmedicated condition)

	Independent Samples t-test		Paired Samples t-test	
	Right ear	Left ear	Right ear	Left ear
Control Group 3 freq ave, unmasked	A=.135 B=.055	A=.994 B=.902		
Control Group 3 freq ave, masked	A=.250 B=.464	A=.463 B=.554		
Experimental Group 3 freq ave, unmasked			.731	.608
Experimental Group 3 freq ave, masked			.651	.817

Uncomfortable Loudness Levels and Dynamic Range

Uncomfortable loudness level and dynamic range (calculated as the difference between UCL and PTA) was determined bilaterally for each group. Table 5 illustrates the average UCL for all groups. Figure 1 shows the average dynamic range which was figured as the difference between uncomfortable loudness level and pure tone average. The control group produced the widest dynamic ranges, followed by the medicated experimental group, the unmedicated experimental group had the narrowest dynamic ranges. Although Independent Samples t-test results for the control and unmedicated group did not reach significance, it is interesting to note that there is a difference in dynamic range between the control and unmedicated group of approximately 4 dB, this finding is evident for both ears. When the experimental group was evaluated in the

medicated condition, this gap in dynamic range narrowed. Uncomfortable loudness levels and dynamic range p levels can be found in table 5a. Figure 1 depicts these data graphically. Raw data can be found in Appendix D.

Table 5: UCL for each group.

Measure	Control N=11	Experimental Medicated N=15	Experimental Unmedicated N=15
UCL Right (dBHL)	Mean: 87.27 SD: 7.54	Mean: 88.33 SD: 7.48	Mean: 85.67 SD: 5.63
UCL Left (dBHL)	Mean: 86.82 SD: 8.15	Mean: 88.67 SD: 8.55	Mean: 86 SD: 6.6

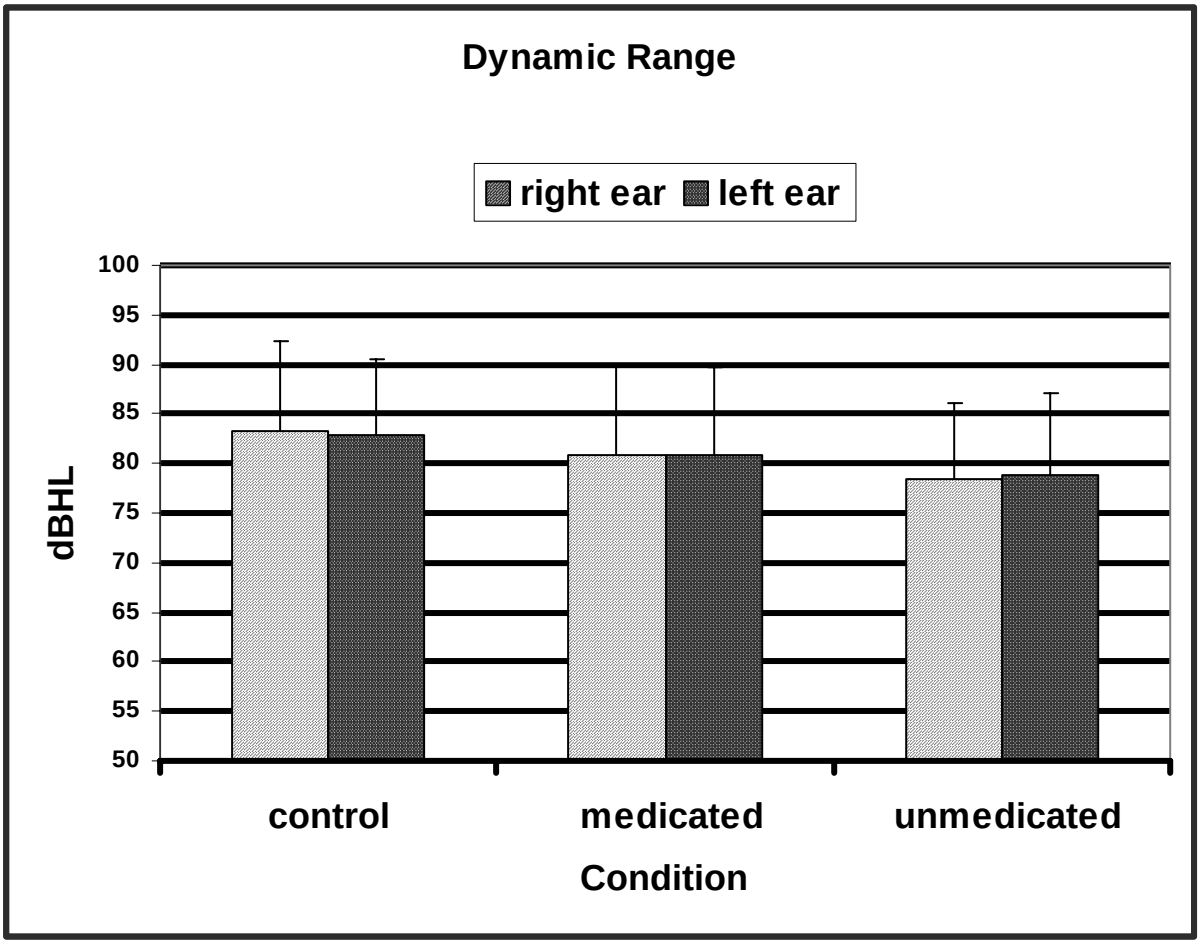
Table 5a: Uncomfortable Loudness Level and Dynamic Range p Values

(A=medicated condition, B=unmedicated condition)

.

	Independent Samples t-test		Paired Samples t-test	
	Right ear	Left ear	Right ear	Left ear
Control Group UCL	A=.725 B=.539	A=.584 B=.780		
Control Group Dynamic Range	A=.520 B=.157	A=.564 B=.231		
Experimental Group UCL			.178	.205
Experimental Group Dynamic Range			.268	.394

Figure 1: Average dynamic range calculated as the difference between UCL and PTA.



Masking Level Difference

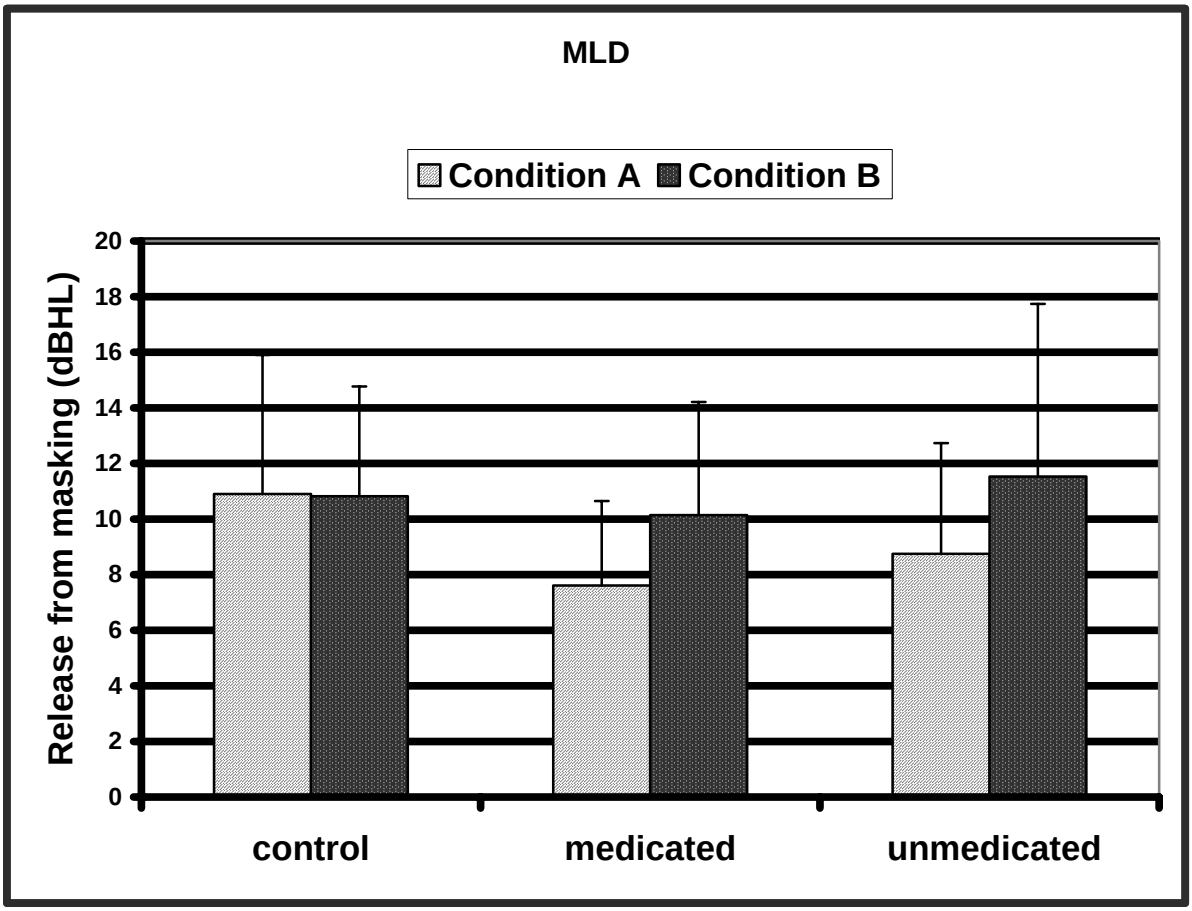
Masking level difference, or release from masking was determined by subtracting the homophasic condition (SONO) from the two antiphasic conditions, SONπ and SπNO. For the SONO-SONπ condition, the control group

had a mean release from masking of 10.90dB. The experimental group, while medicated, exhibited a mean release from masking of 7.62dB, while unmedicated, mean release from masking was 8.75dB. For the SONO-SπNO condition a 10.82dB release from masking was obtained for the control group. The experimental group, while medicated displayed a 10.14dB release and while unmedicated, a 11.54dB release. The group differences were not statistically significant. Independent Samples t-test for the SONO-S⑥NO revealed the following; control group (p= Means and standard deviations for each condition can be found in Figure 2, SONO-SONπ is represented as Condition A and SONO-SπNO is represented as Condition B. Masking Level Difference p levels are located in Table 6. Raw data is shown in Appendix D.

Table : MLD p Values (A=medicated condition, B=unmedicated condition).

	Independent Samples t-test		Paired Samples t-test	
	SONO-SONπ	SONO-SπNO	SONO-SONπ	SONO-SπNO
Control Group	A=.060 B=.263	A=.680 B=.743		
Experimental Group			.807	.778

Figure 2: Masking Level Difference.



Behavioral Speech Tests:

SCAN-A

All groups were evaluated at levels corresponding to the individual's most comfortable loudness level (MCL). The composite score yields percentile ranks for each subject based upon the sum of subtest standard scores. Mean results and standard deviations for the composite test score as well as the subtest scores of

both groups can be found in figures 3 and 4. For the composite and each subtest, with the exception of the competing sentences portion, the control group consistently scores better than the experimental group and the scores of the experimental unmedicated group improved with SSRI medication. Results indicated a significant difference between the control and unmedicated group for the composite, as well as the filtered words and auditory figure ground subtests. Independent Samples t-test analysis of composite scores between the control and unmedicated groups yielded differences that were statistically significant (p=.028). Individual subtests were then evaluated using an alpha level of .0125. Both the filtered words (p=.002) and auditory figure ground (p=.008) were found to be significant for the control and unmedicated group. Although not significant, a trend was observed for the competing words subtest, wherein the unmedicated experimental group consistently scored less favorably than the control group and the medicated experimental group regularly fell in between. Paired Samples analysis did not reveal statistically significant findings between the medicated and unmedicated experimental group. Figure 3 depicts the composite standard score, and Figure 4 presents data from the subtests. Raw data can be found in Appendix F.

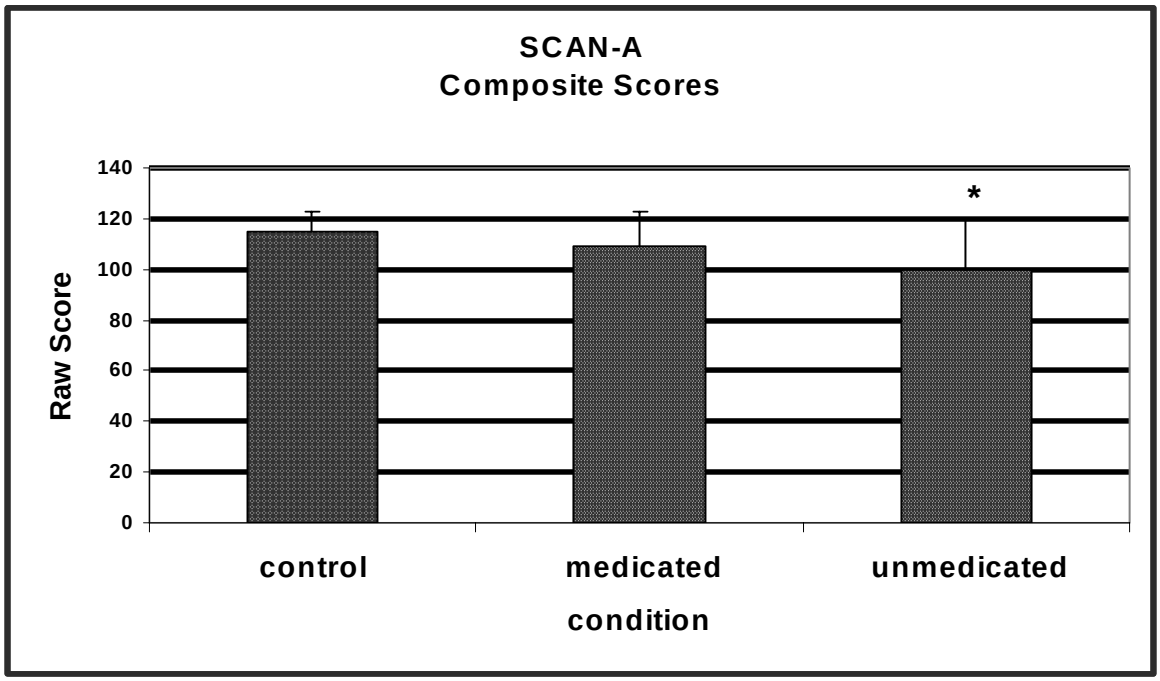


Figure 3: SCAN-A Composite Scores (Control M=114.81, Medicated M=109.47, Unmedicated M=99.67).

Figure 4: SCAN Subtest Scores.

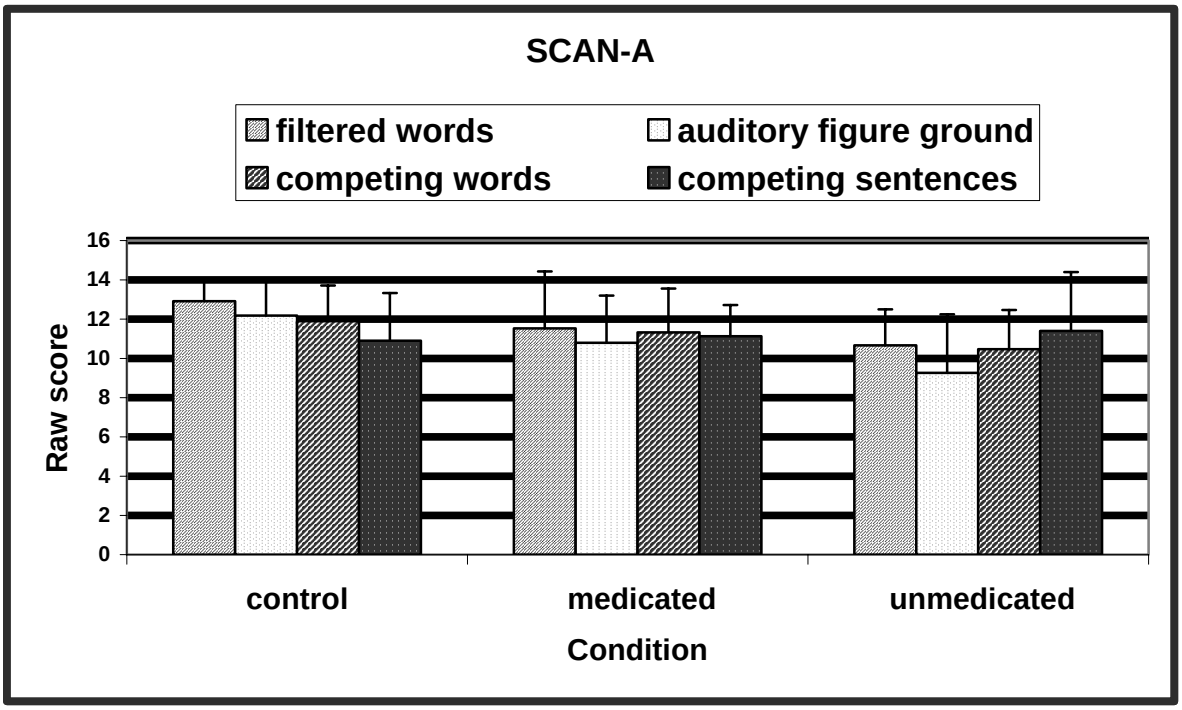


Table 7: SCAN-A p Values (A=medicated condition, B=unmedicated condition). Significant findings are indicated using an *.

Control Group	Independent Samples t-test				
	Composite	Filtered Words	Auditory Figure Ground	Competing Words	Competing Sentences
	A=.249	A=150	A=.120	A=.489	A=.778
	B=.028*	B=.002*	B=.008*	B=.071	B=.960
Experimental Group	Paired Samples t-test				
	Composite	Filtered Words	Auditory Figure Ground	Competing Words	Competing Sentences
	.305	.837	.213	.013	.822

Synthetic Sentence Identification (SSI)

To attain test scores for the SSI, all groups were evaluated with a message-to-competing (MCR) ratio of 0 MCR and –20 MCR, these conditions were monotic tasks where both the signal and the noise were presented in the same ear. The –40 MCR condition was a dichotic task, with the signal presented contralateral to the noise. All groups scored >98% on the –40 MCR portion of the test, and >95% on the 0 MCR portion. Independent Samples t-test for the control and medicated experimental groups reached significance for the 0 MCR condition in the left ear. Independent Samples t-test the control and unmedicated experimental groups did not reach statistical significance, although, it is

interesting to note that the experimental group, while unmedicated scored approximately 10 points lower than the control group for the right ear –20 MCR task (p=0.056). However, in the Paired Samples t-test between the medicated experimental group and the unmedicated experimental group, the –20 MCR condition for the right ear yielded statistically significant differences (p= .027). Figure 5a, 5b, and 5c detail these data. Additionally, SSI p Values can be found in Table 8. Raw data is also presented in Appendix G.

Figure 5a: Mean and standard deviations for 0 MCR portion of the SSI

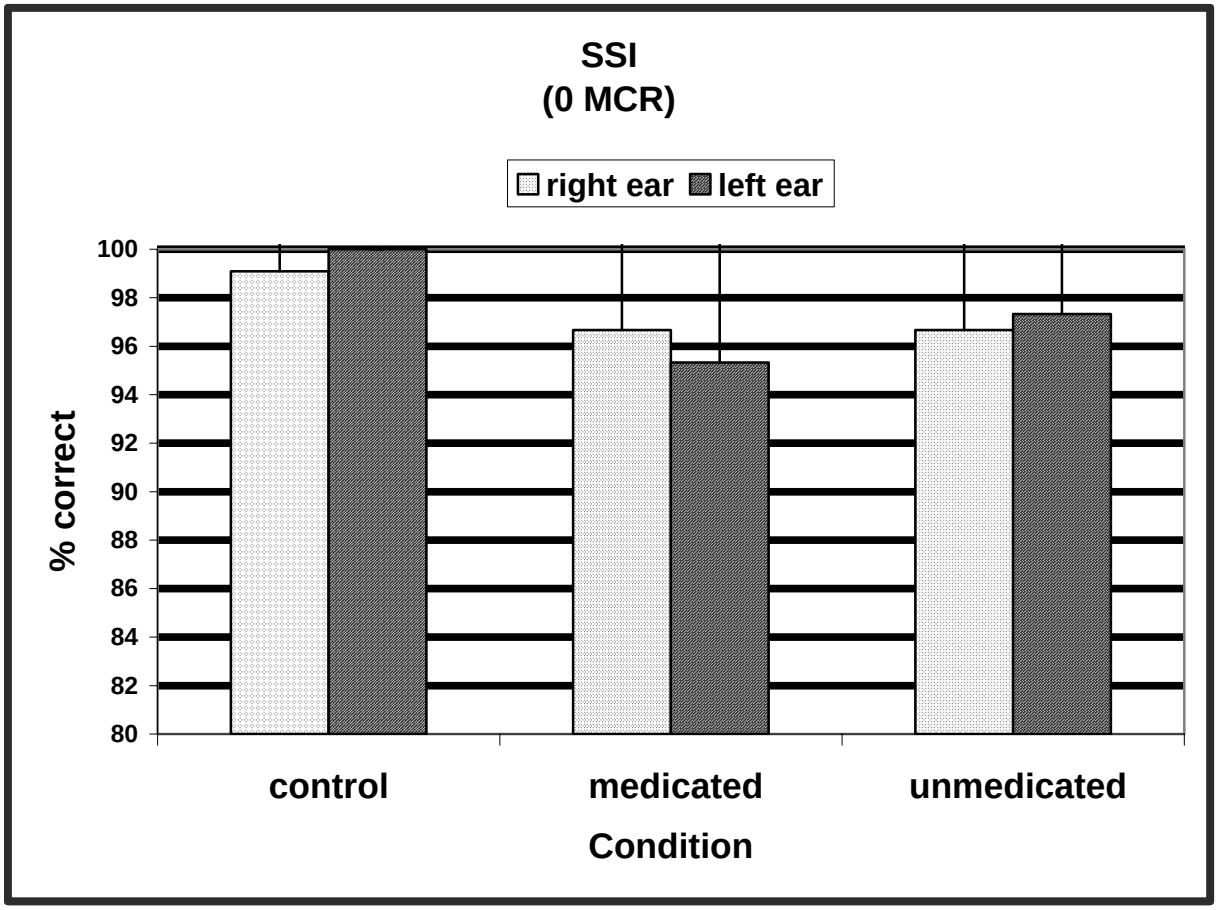


Figure 5b: Mean and standard deviation for –20 MCR SSI.

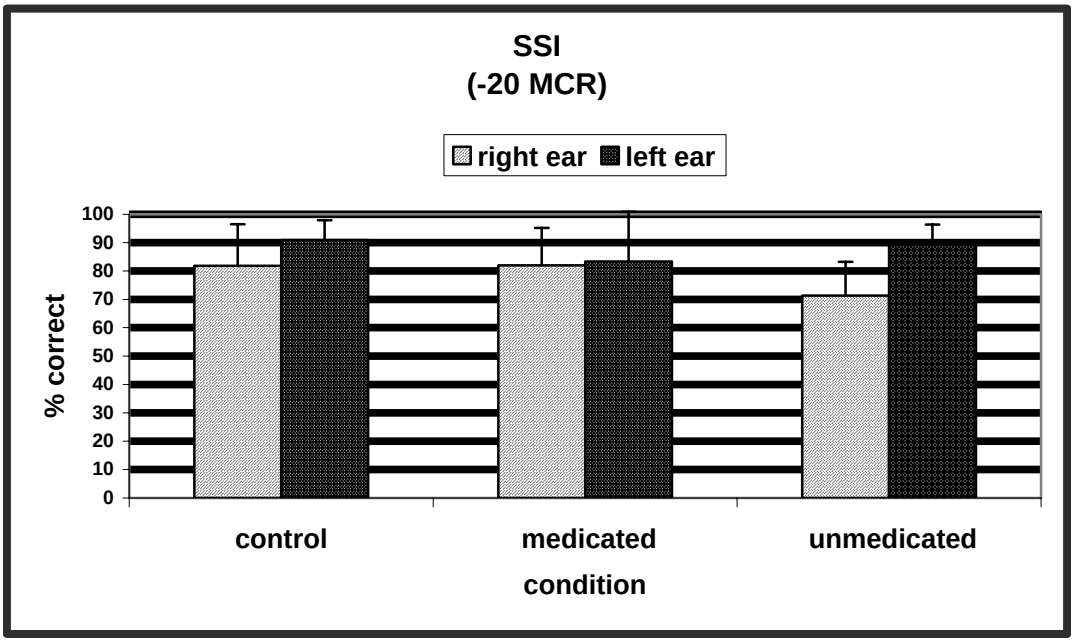


Figure 5c: Mean and standard deviation for –40 MCR SSI.

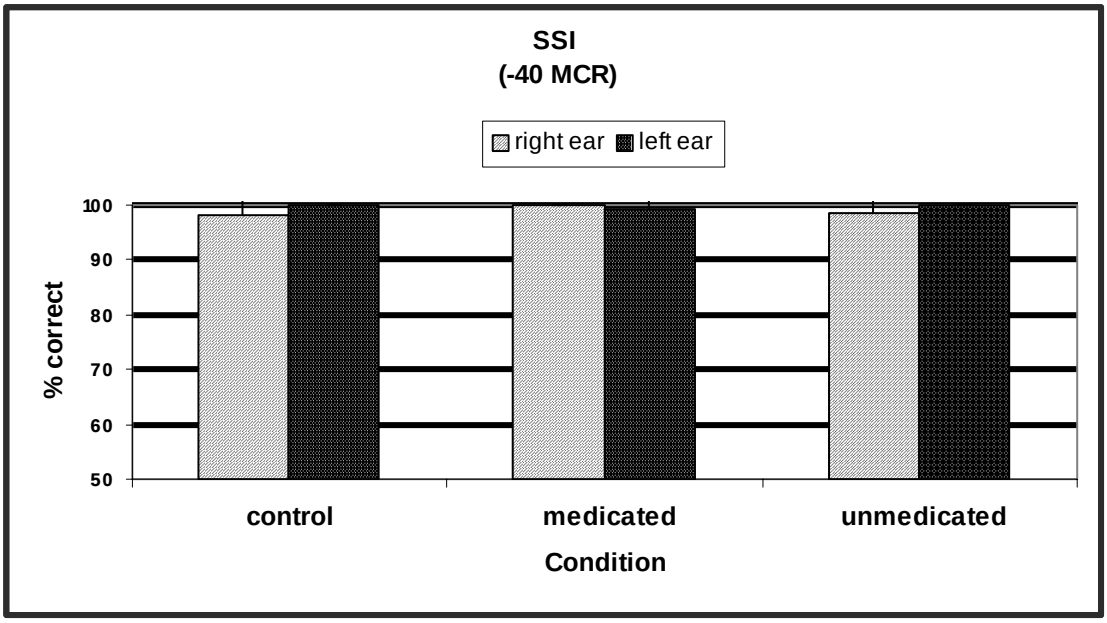


Table 8: SSI p Values, (A=medicated condition, B=unmedicated condition). Significant findings are indicated using an *.

Control Group	Independent Samples t-test					
	0 MCR ICM		-20 MCR ICM		-40MCR CCM	
	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear
	A=.359	A=.240	A=.974	A=.191	A=.251	A=.403
	B=.243	B=.056	B=.056	B=.403	B=.577	B=.164
Experimental Group	Paired Samples t-test					
	0 MCR ICM		-20 MCR ICM		-40MCR CCM	
	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear
	.500	.567	.027*	.237	.164	.336

Low Predictability Sentences of the Revised Speech in Noise (R-SPIN)

All groups were evaluated in the right and left ears with 0 MCR and +8 MCR in the ipsilateral condition. Independent Samples Test revealed a significant difference between the control and experimental unmedicated group for the 0 MCR condition in the right ear ($p=0.035$) as well as in the left ear ($p=0.036$). Paired Samples statistical analysis of the experimental group indicated a statistically significant difference between the medicated and unmedicated results ($p=0.025$), with the unmedicated group showing decreased performance on

the 0 MCR. Figure 6a and 6b below summarize these results. R-SPIN p values can be found in Table 8 below. Raw data can be found in Appendix H.

Figure 6a: Low Predictability R-SPIN, 0 MCR condition.

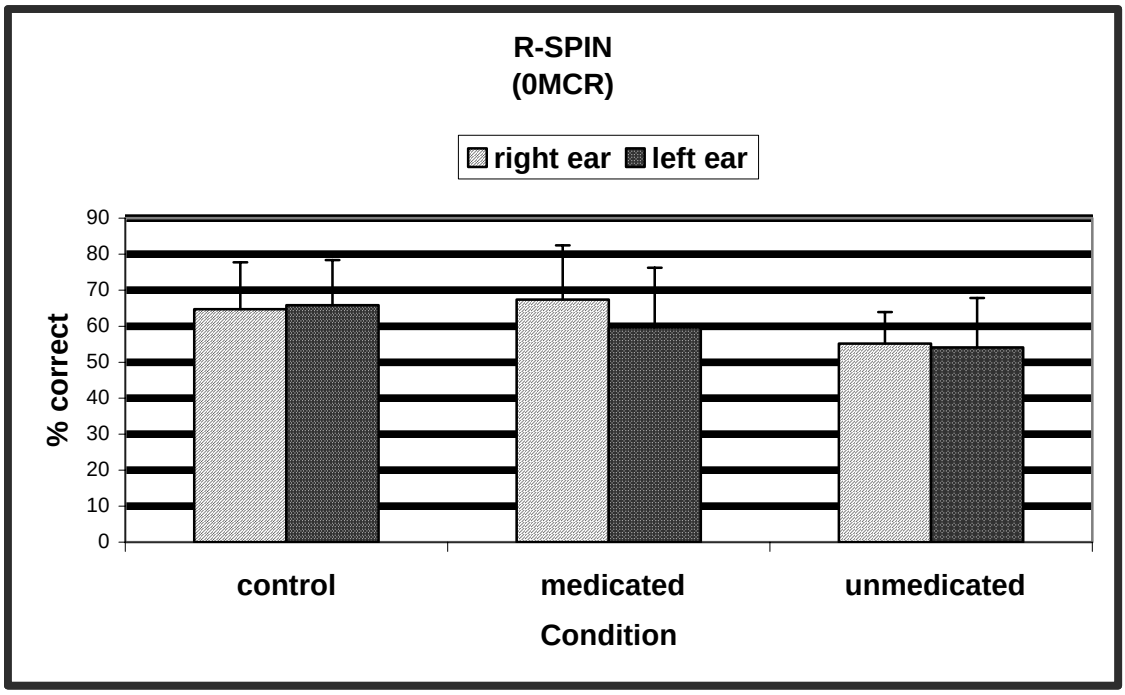


Figure 6b: Low Predictability R-SPIN, -20 MCR condition.

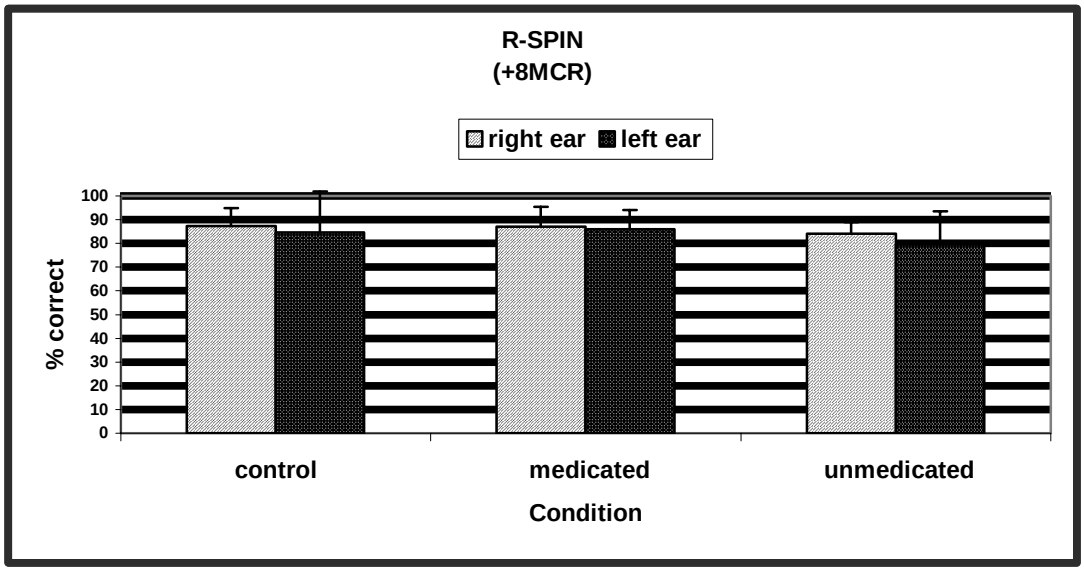


Table 8: R-SPIN p Values, (A=medicated comdition, B=unmedicated condition). Significant findings are indicated using an *.

Control Group	Independent Samples t-test			
	0 MCR		+8 MCR	
	Right ear	Left ear	Right ear	Left ear
	A=.651	A=.325	A=.934	A=.813
	B.=.035*	B=.036*	B=.196	B=..393
Experimental Group	Paired Samples t-test			
	0 MCR		+8 MCR	
	Right ear	Left ear	Right ear	Left ear
	.025*	.704	.490	.797

Summary of Test Results

The data in this study, when considered in its entirety, reveals interesting relationships between its constituents. Of all the tests in the battery, only some of the behavioral speech test results showed statistically significant differences between the groups. Independent Samples t-test revealed differences between the

control and unmedicated group for both the SCAN-A (filtered words, auditory figure ground and composite standard score), and the 0 MCR condition of the R-SPIN for both right and left ears. When experimental subjects were evaluated while on medication versus off medication using a Paired Samples t-test, statistically significant results were found for the 0 MCR of the R-SPIN in the right ear as well as the –20 MCR condition of the SSI, also for the right ear. As results indicated, no significant differences were found for masking level difference, otoacoustic emissions with or without contralateral masking, uncomfortable loudness level or dynamic range

Discussion

The purpose of this study was to explore the effects of selective serotonin re-uptake inhibitors on both peripheral and central auditory processing measures in women. The following test procedures were used: masking level difference, transient evoked otoacoustic emissions (with and without contralateral masking), uncomfortable loudness levels, and behavioral speech tests. The behavioral speech tests: SCAN-A, the low predictability test of the R-SPIN and SSI, were used for their known sensitivity to detecting deficiencies in auditory processing in the lower brainstem and auditory cortex . The battery as a whole was chosen in light of recent research implicating serotonergic pathways in various auditory functions (Gallinat et al., 1999; Hegerl & Juckel, 1993; Martin & Humphrey, 1994; Thompson et al., 1994; Vandermaelen, 1985; Gopal et al., 2000; Bishop, 2001; Carney, 2001; and Marriage & Barnes, 1995). Additionally, the Beck

Depression Inventory was used to ascertain each subject's perception of the magnitude of their depression.

All tests were administered to each of the two groups. The control group consisted of eleven adult women who had never received a clinical diagnosis of depression and had never taken SSRI medications. The experimental group consisted of fifteen adult women who had received a diagnosis of clinical depression and were willing to be evaluated twice, once while on SSRI medication and then again after voluntarily abstaining from medication.

The following section will discuss both significant and noteworthy findings from the study.

Otoacoustic Emissions

Otoacoustic emissions for the frequencies of 1K, 1.5K, and 2KHz were averaged and compared using both an Independent Samples t-test and Paired Comparison t-test. Although not statistically significant, a trend was observed between the groups wherein the control group consistently had the lowest mean OAE amplitude, the unmedicated group consistently had the highest mean amplitude, while the medicated group fell in between.). Efferent fibers release a crucial inhibitory neurotransmitter called acetylcholine (ACh), which is believed to be modulated by serotonin (Duffy 1995; Gil-Loyzaga et al. 1997; Thompson et al. 1994). Efferent fibers release a crucial inhibitory neurotransmitter called acetylcholine (ACh), which is believed to be modulated by serotonin, it is possible that the more robust emissions in the unmedicated experimental group

were indicative of a compromised suppression of the medial olivocochlear efferent system. (Duffy 1995; Gil-Loyzaga et al. 1997; Thompson et al. 1994). These trends remained stable for both the unmasked and masked conditions and in both the right and left ears. Another observation is that each group demonstrated higher OAE amplitude in their right ear compared to their left ear. These results are in agreement with previous studies showing transient otoacoustic emissions to have higher amplitude in the right ear than in the left suggesting peripheral asymmetries in the auditory system (Khalfa & Collet, 1996, Morlet et al., 1999). The topic of auditory asymmetry will be discussed further in the behavioral speech tests results section.

Uncomfortable Loudness Levels and Dynamic Range

Uncomfortable loudness testing is one way to assess hyperacusis. Marriage & Barnes (1985) argue that hyperacusis can be efferent in nature, without obvious cochlear involvement, thus separating the phenomena from recruitment. These researchers go on to suggest that 5-HT systems modulate central responses to sensory input, particularly, sensitivity to sound.

Baseline UCL measurements were taken using Hawkins' (1984) loudness assessment. Dynamic range was then computed as the difference between pure tone threshold and UCL. It was anticipated that the unmedicated experimental group would exhibit reduced dynamic range and increased perception of loudness. Although results failed to reach a level of significance, findings are worth remarking on. The control group had both higher uncomfortable loudness levels

and increased dynamic range as compared to the unmedicated group. In the case of dynamic range, the control group had a wider range, followed by the medicated experimental group and finally the unmedicated experimental group showed the narrowest range. If central 5-HT neural systems do in fact exert an inhibitory modulation of central responses to sensory input, it stands to reason that individuals with serotonergic dysregulation would exhibit lower UCL and more narrow dynamic ranges as did the unmedicated experimental group in this study. Again it is the opinion of the author that taken into account the interesting trends evidenced, a larger sample could result in significant findings.

Masking Level Difference

Masking level difference is the decibel difference between threshold for a 500 Hz tone in an homophasic condition as compared to individual threshold for a 500Hz tone in an antiphasic condition. Release from masking is the phenomena that occurs when a just inaudible tone becomes audible again by switching the phase of the tone through noise. Abnormal performance on MLD testing, in the normal hearing population has been proven to be consistent with brain stem disorders such as 8th nerve tumors and multiple sclerosis indicating MLD to be a good assessment of brainstem integrity and function (Olsen et al., 1976). Given that 5-HT cell bodies exist exclusively in the raphe nuclei of the brainstem, and extend their terminals to both central and peripheral areas, a reasonable assumption is that a diagnostic measure that stresses the brainstem could be

impaired in individuals with impaired 5-HT function. However, in this study, statistically significant differences were not seen between groups.

Auditory Processing Tests Using Speech Stimuli

SCAN-A

Independent Samples t-test analysis showed a significant difference for the composite as well as for the filtered words and auditory figure ground subtests between the control and unmedicated groups. Filtered Word test performance is indicative of processing abilities for minimally distorted speech. The Auditory Figure ground subtest evaluates the subject's ability to discriminate words in the presence of background noise. In all subtests of the SCAN-A, the subject is required to determine the full message by filling in the missing pieces of the distorted message.

The evolving trend of the control group scoring highest, the unmedicated group scoring the lowest and the medicated group falling somewhere in between is again evident. These findings are analogous to prior research by Gopal and colleagues (2000). Bishop (2001) uncovered similar trends wherein the control group consistently scored more favorably than the medicated and unmedicated groups and the medicated group scored more favorably than the unmedicated group; these results did not reach significance.

In the current study, the remaining subtests in the SCAN-A battery failed to reach significance, however, the control group continued to score higher than the

unmedicated group. The Paired Samples t-test failed to reveal any significant differences. Although not statistically significant, the experimental unmedicated groups' performance did improve when medicated as seen in all subtests and the composite score.

Synthetic Sentence Identification (SSI)

Subjects were evaluated in the right and left ears, 0 and –20 message to competition ratio (MCR) was obtained in an ipsilateral condition whereas the –40 MCR portion of the test was obtained in a contralateral condition. Jerger & Jerger (1974) found the ICM portion of the SSI to be particularly sensitive to Brainstem lesion, whereas the CCM task stressed higher levels of the auditory cortex. In this study for the most difficult task, the –20 MCR ICM condition, in the right ear, the control group's mean score (M=81.81) was approximately ten points superior to that of the unmedicated group (M=71.33; p=.056). The Paired Samples t-test showed significant differences for the –20 MCR condition in the right ear only (p= .027) meaning that when medicated, the experimental group performed significantly better on the most difficult right ear task.

Again, given that 5-HT neuronal cell bodies originate in the raphe nuclei of the brainstem, it was anticipated that results from tests that stress that area of the auditory system would prove to be impaired in individuals with a compromised serotonergic system.

Low Predictability subtest of the Revised Speech in Noise (R-SPIN)

This test was administered at a level of 0 MCR and +8 MCR, ipsilateraly to the right and left ears of each subject. Independent Samples t-test revealed a significant difference between the scores of the control and unmedicated groups for the most difficult condition (0 MCR) of the test in both the right (p=.035) and left (p=.036) ears. These results elaborate on earlier findings by Bishop (2001) who found trends in the scores of subjects for both ears, wherein the control group scored higher than the unmedicated group and the medicated group.

Another finding is that significance was found for the right ear only in the Paired Samples t-test. Recent research by Morand et al., (2001) has shown that the MOC system is modulated by the auditory cortex. It has also been suggested by the same researchers that examination of Heschl's gyrus following flumazenil binding revealed a left- right asymmetry in favor of the left auditory cortex (Morand et al., 2001). Taken as a whole, it would be reasonable to expect right ear dominance in subjects with functioning MOCS, while subjects with impaired MOCS would not exhibit a hemispheric dominance and thus a difference in scores between the right and left ears would not occur. Interestingly, upon comparison of the scores for the right and left ears for the most difficult portion (0 MCR) of the R-SPIN, the experimental group's scores improved when medicated. Bruder and colleagues (2001) reported on the possible diagnostic potential of using dichotic tests as a predictor of response to SSRI treatment in depressed individuals. In their study of both men and women clinically depressed outpatients, they found that unmedicated women who later responded to SSRI therapy had a greater right ear advantage for dichotic words, there was no

significant difference in right ear advantage for men. Further research exploring right ear advantage on the SCAN may support Bruder's notion that greater activity in the left hemisphere during dichotic listening tasks is related to better treatment response to SSRI medication. In the present study is that the medicated test results were significantly better than the unmedicated test results only in the right ear. These results, along with Bruder's (2001) results suggests that the right ear which is dominant in most right handed people is more vulnerable to SSRI medication. Furthermore, it can be hypothesized that with SSRI medication, right ear changes may reflect the effectiveness of medication.

Conclusions

The aim of this study was to study the effects of selective serotonin re-uptake inhibitors on peripheral, lower brainstem, and central auditory processing measures in clinically depressed women. The tests selected for this study included basic, clinical audiological tests such as pure tone audiometry and tympanometry. Additionally, tests such as masking level difference, uncomfortable loudness level, and otoacoustic emissions with and without contralateral masking were chosen because of their established sensitivity to peripheral and brainstem processing where serotonin is a suspected modulator. Auditory processing tests using speech stimuli such as the SCAN-A (a screening test for auditory processing in adolescents and adults), the synthetic sentence

identification (SSI), and the low predictability sentence portion of the revised speech in noise (R-SPIN), were chosen in light of their established sensitivity to brainstem as well as cortical lesions. Statistical analysis revealed the following significant results:

1) The unmedicated group scored significantly lower than the control group on the SCAN-A composite score, as well as on the filtered words, and auditory figure ground subtests.
3) The unmedicated group scored significantly lower than the control group on the 0 MCR condition of the low predictability list of the R-SPIN in both the right and left ears.
4) The unmedicated score was significantly lower than the medicated scores on the-20 MCR condition of the SSI test in the right ear.
5) The unmedicated scores were significantly lower than the medicated scores on the 0 MCR condition of the R-SPIN in the right ear.

Although the remaining tests failed to reach significance, there were consistent trends in several of the tests, including:

1) Otoacoustic emissions, wherein the unmedicated group displayed more robust unmasked amplitude in both the right and left ears than the control group, the medicated experimental score was in between.

2) The remaining behavioral speech tests, where the control group repeatedly scored more favorably than the unmedicated experimental group. Additionally, the medicated experimental group often scored less favorably than the controls and consistently scored more favorably than the unmedicated controls.

The behavioral speech tests uncovered some particularly interesting findings. The control group consistently achieved greater scores, sometimes this was seen as a trend but often reached a significant level. Additionally, auditory processing capability improved in the experimental group while the subjects were undergoing therapeutic treatment with SSRI medication. This perhaps suggests that in the experimental group, response to SSRI medications promoted increased serotonergic activity and resulted in an improvement in auditory processing abilities for speech.

Clinical Relevance

Serotonin and its multitude of physiological implications has been the topic of intense research for some time. However, research relating 5-HT to the auditory system is just beginning to scratch the surface. Findings such as those by Gopal et al., (2000), Bishop (2001), Carney (2001), and Bruder, (2001) may contribute to the development of a wide range of clinical tests that aid in identification of impairments in auditory processing, somato-sensory disturbances, serotonergic related disorders, and even predictors of patient response to antidepressant treatment. Several of the tests in this battery, such as the uncomfortable loudness level and behavioral speech tests are quick, noninvasive,

easy, cost effective evaluations. With tools such as these available, a physician could hopefully identify and treat more of the depressed population as well as monitor individual improvement. It is the author's wish that this research will contribute to these goals and potentially contribute to a wide body of research that may improve the quality of life of individuals with serotonergic deficits.

Recommendation:

The primary constraint of the current study was group size. Extending the current study could reveal better the role of 5-HT in auditory measures. Regarding the behavioral speech tests, the author recommends the use of more difficult testing material to further stress the auditory system Additionally, more homogonous groups in terms of medication type and dosage could prove beneficial.

APPENDIX A

Descriptive Information

Appendix A: Descriptive Information.

SUBJECT	AGE	BDI	SSRI	DOSAGE MG/DAY	BLOOD
C1	24	6			161
C2	31	1			136
C3	22	8			
C4	21	1			126
C5	23	0			114
C6	23				219
C7	23	0			157
C8	23	0			448
C9	32	0			158
C10	23	0			171
C11	23	0			156
E1 (1)	20	REFUSED	ZOLOFT	50MG	41
E2(1)	26	14	ZOLOFT	100MG	
E3(1)	21	27	PROZAC	40MG	37
E4(1)	21	6	ZOLOFT	50MG	
E5(1)	32	4	ZOLOFT	100MG	4
E6(1)	27			50MG	24
E7(1)	29	27	PROZAC	40MG	
E8(1)	29	16	ZOLOFT	25MG	
E9(1)	19	11	PROZAC	20MG	24
E10(1)	18	15	PROZAC	20MG	54
E11(1)	23	19	PAXIL	20MG	20
E12(1)	19	6	PROZAC	10MG	31
E13(1)	22	5	ZOLOFT	50MG	31
E14(1)	42	21	ZOLOFT	100MG	7
E15(1)	23	2	PROZAC	20MG	44
E1(2)		REFUSED			298
E2(2)		35			45
E3(2)		10			
E4(2)		29			45
E5(2)		20			135
E6(2)					138
E7(2)		37			
E8(2)		17			
E9(2)		2			148
E10(2)		39			125
E11(2)		18			152
E12(2)		3			143
E13(2)		4			
E14(2)		31			5
E15(2)					158

Appendix B

Pure Tone Averages and Tympanograms

Appendix B: Pure Tone Average & Tympanograms.

SUBJECT	PTA-RE	PTA-LE	TYMPS RE/LE
C1	3	7	A/A
C2	7	2	A/A
C3	8	7	Ad/Ad
C4	5	2	A/A
C5	5	2	A/A
C6	5	5	A/A
C7	1	3	A/A
C8	5	5	A/A
C9	0	0	A/A
C10	5	3	A/A
C11	0	3	A/A
E1(1)	7	5	A/A
E2(1)	8	7	A/A
E3(1)	8	10	A/A
E4(1)	5	7	A/A
E5(1)	3	0	A/A
E6(1)	20	20	A/A
E7(1)	7	5	A/A
E8(1)	0	5	A/A
E9(1)	18	20	A/A
E10(1)	2	2	Ad/Ad
E11(1)	5	3	A/A
E12(1)	3	3	A/A
E13(1)	3	3	A/A
E14(1)	5	5	A/A
E15(1)	17	17	A/A
E1(2)	10	5	A/A
E2(2)	3	3	A/A
E3(2)	3	7	A/A
E4(2)	3	5	A/A
E5(2)	2	0	A/A
E6(2)	22	20	A/A
E7(2)	7	3	A/A
E8(2)	0	2	A/A
E9(2)	20	25	A/A
E10(2)	2	3	Ad/Ad
E11(2)	7	3	A/A
E12(2)	5	6	A/A
E13(2)	3	2	A/A
E14(2)	5	5	A/A
E15(2)	16	18	A/A

Appendix C

Otoacoustic Emissions

Appendix C: Otoacoustic Emissions (unmasked and Contralateral masking right ear).

SUBJECT	UM RE 1KHz	UM RE 1.5KHz	UM RE 2KHz	UM RE 3KHz	CM RE 1KHz	CM RE 1.5KHz	CM RE 2KHz	CM RE 3KHz
C1	15.5	22	18	16.5	15	23.5	15	17
C2	4.5	11	7.5	10	11	11	4.5	9
C3	21.5	13	1.5	10.5	23	8	2	11
C4	11.5	14	19.5	8.5	3.5	8.5	17	7.5
C5	3	9.5	8	12	2.5	9	11	17.5
C6	10.5	11.5	15	15.5	5.5	10	14.5	16.5
C7	5.5	8.5	12.5	19.5	8	9	12	17.5
C8	10	17.5	14	12.5	8.5	15.5	13	12
C9	15.5	21	15.5	15	15.5	17	15	13
C10	20	25	15	18	16.5	26	15	16.5
C11	13.5	10.5	10	8	10.5	10.5	10.5	10
E1(1)	19.5	25	12.5	2	16	23	14.5	5
E2(1)					7	4	6	10
E3(1)	13	19.5	19	16.5	15	19	21.5	17.5
E4(1)	14.5	19.5	19	20.5	12.5	17	17.5	21.5
E5(1)	10	19.5	9	19.5	12	17	7	17
E6(1)								
E7(1)	14	23.5	19.5	16.5	11.5	22	17	14.5
E8(1)	18	20.5	24.5	29	19	22	26	29.5
E9(1)	3.5	17.8	18.5	3	6.5	19.5	18.5	3
E10(1)	5	1.5	12.5	18.5	0	0	5	17.5
E11(1)	12	23	25	22	17	28	25	20
E12(1)	11	15.5	13.5	8	7.5	14.5	10	9
E13(1)	17.5	21.5	21.5	15.5	17	19.5	19	16
E14(1)	15	13	20	14	16.5	14.5	18.5	14.5
E15(1)	17	8	9	3	13.5	7.5	6	3.5
E1(2)	19	15	10.5	2	10	20	8.5	0
E2(2)	15.5	20	14	11	7	4	6	10
E3(2)	11	19	18	14.5	11.5	20.5	19.5	15.5
E4(2)	18.5	19.5	21	23	19	19	21	25.5
E5(2)	17	22.2	13	22.5	15	19.5	14	21
E6(2)	5.5	13	3	14	0	6.5	0	12
E7(2)	14	21.5	20	15.5	13	19	20	13
E8(2)	11.5	19.5	22.5	29	10	18	21.5	29.5
E9(2)	3.5	11	15	4	7.5	13	17	5.5
E10(2)	16.5	13.5	18.5	23.5	0	6	14	20
E11(2)	16.5	26	26	20	18	26	27	21
E12(2)	9.5	18.5	13	10.5	5.5	15.5	7.5	10
E13(2)	19	24	21.5	18	20	23	22	18
E14(2)	22	17	20.5	18	20	18	20	16.5
E15(2)	12	12	8	13	11	4	2	6

Appendix C: Otoacoustic Emissions (unmasked and contralateral masking left ear).

SUBJECT	UM LE 1KHz	UM LE 1.5KHz	UM LE 2KHz	UM LE 3KHz	CM LE 1KHz	CM LE 1.5KHz	CM LE 2KHz	CM LE 3KHz
C1	13	21	20	21.5	17	21.5	20	19.5
C2	15	11	4	18	13.5	11	4	17
C3	20.5	7	15.5	9.5				
C4	14.5	17.5	11	3.5	18	15	10	5.5
C5	11	15.5	15	14	11.5	18.5	16.5	13.5
C6	11	11	4	8.5	9	8.5	5	7
C7	3.5	8.5	13	14.5	0	1.5	13	13.5
C8	11	13	9.5	12	8	14.5	8.5	11
C9	21	10.5	7.5	13	25.5	17.5	10.5	11
C10	14.5	17	14	12.5	10.5	18	14.5	12
C11	12.5	10.5	9.5	12.5	13	7.5	9	13
E1(1)	18	14.5	5	0	19	17	3.5	0
E2(1)	12	12.5	11	11	10	12.5	10.5	8.5
E3(1)	10	18	9.5	18	8.5	20	14	17.5
E4(1)	5.5	12.5	16.5	21.5	10	10.5	17.5	21.5
E5(1)	12	10.5	13	19.5	11	9	13.5	20
E6(1)								
E7(1)	14.5	16.5	11.5	15	12	13.5	13	14
E8(1)	16.5	20	20.5	24	15	21.5	22	24
E9(1)	2	15	0	0	10	19	5	3
E10(1)	9	8	1	20	14	11.5	4.5	20
E11(1)	11	19	21.5	17.5	4	15	22	18
E12(1)	5	7	6	6	8	10.5	7.5	5.5
E13(1)	23.5	31	16	16.5	25	28.5	16.5	16
E14(1)	9	14.5	14.5	8	7	13	13	8
E15(1)	19	8	5.5	0	7.5	2.5	1.5	0
E1(2)	31	26	13.5	6.5	25	23	10	4
E2(2)	18.5	19	12	12.5	17	17	10.5	13
E3(2)	10.5	18.5	10	15.5	9	19.5	9	14.5
E4(2)	11.5	13	17	21.5	9.5	12.5	20	23
E5(2)	18.5	17	16	21.5	18	16	18.5	21.5
E6(2)	3.5	3	1.5	6.5	1.5	3.5	1	6
E7(2)	14.5	16	18	16.5	17	14.5	17.5	16
E8(2)	16.5	21	21.5	27	19.5	21.5	19.5	27.5
E9(2)	3	12	1	0	0	9.5	2.5	0
E10(2)	21	20.5	12.5	28	19	21	12	25.5
E11(2)	9	21.5	23.5	19.5	12	24	23.5	18.5
E12(2)	6	9.5	6	6	3.5	9.5	5.5	5
E13(2)	21.5	24.5	15	15	21.5	23.5	15.5	14
E14(2)	14	13	16.5	14.5	15	14.5	16	14.5
E15(2)	7.5	5.5	1	0	12	8	0	0

Appendix D

Uncomfortable Loudness Levels and Dynamic Range

Appendix D: Uncomfortable Loudness Levels and Dynamic Range.

SUBJECT	UCL RE	UCL LE	D RANGE RE	D RANGE LE
C1	95	95	92	88
C2	80	75	73	73
C3	85	85	77	78
C4	85	85	80	83
C5	85	85	80	83
C6	75	75	70	70
C7	100	100	99	97
C8	90	90	85	85
C9	80	80	80	80
C10	90	90	85	82
C11	95	95	95	92
E1(1)	90	95	83	85
E2(1)	70	70	62	63
E3(1)	95	95	87	85
E4(1)	80	80	75	73
E5(1)	85	80	82	80
E6(1)	90	95	70	75
E7(1)	90	90	83	85
E8(1)	90	95	90	90
E9(1)	100	100	82	80
E10(1)	100	100	98	98
E11(1)	90	90	85	87
E12(1)	85	85	82	82
E13(1)	85	80	82	77
E14(1)	90	90	85	85
E15(1)	85	85	68	68
E1(2)	90	95	80	90
E2(2)	80	75	77	72
E3(2)	90	90	87	83
E4(2)	80	80	77	75
E5(2)	85	85	83	85
E6(2)	80	90	58	70
E7(2)	95	95	88	92
E8(2)	80	80	80	78
E9(2)	90	85	70	60
E10(2)	85	85	83	82
E11(2)	95	90	88	87
E12(2)	85	85	80	79
E13(2)	80	75	77	73
E14(2)	80	85	75	80
E15(2)	90	95	74	77

Appendix E

Masking Level Difference

Appendix E: Masking Level Difference.

SUBJECT	SONO-SONΠ	SONO-SΠNO
C1	16	11
C2	11	14
C3	3	1
C4	11	10
C5	6	10
C6	13	9
C7	22	15
C8	10	15
C9	10	12
C10	10	9
C11	8	13
E1(1)	11	15
E2(1)	10	11
E3(1)	9	12
E4(1)	3	1
E5(1)	10	15
E6(1)	11	7
E7(1)	7	10
E8(1)	3	8
E9(1)	7	9
E10(1)	0	5
E11(1)	0	0
E12(1)	11	16
E13(1)	4	10
E14(1)	5	11
E15(1)	8	12
E1(2)	8	14
E2(2)	7	8
E3(2)	0	0
E4(2)	1	2
E5(2)	12	16
E6(2)	1	1
E7(2)	12	14
E8(2)	9	16
E9(2)	12	16
E10(2)	0	0
E11(2)	10	14
E12(2)	11	16
E13(2)	12	16
E14(2)	10	16
E15(2)	0	1

Appendix F

SCAN-A

Appendix F: SCAN-A (filtered words, auditory figure ground, competing words, competing sentenced, composite score).

SUBJECT	SCAN-FW	SCAN-AFG	SCAN-CW	SCAN-CS	SCAN TOTAL SS
C1	13	12	13	12	119
C2	11	9	10	6	92
C3	14	9	14	12	117
C4	13	12	12	12	117
C5	11	13	13	12	117
C6	14	13	10	12	117
C7	13	15	9	12	117
C8	14	13	13	6	112
C9	14	12	10	12	115
C10	12	13	13	12	119
C11	13	13	14	12	121
E1(1)	12	9	6	9	92
E2(1)	7	8	13	12	100
E3(1)	12	10	10	9	102
E4(1)	14	13	11	13	121
E5(1)	15	13	14	12	127
E6(1)	10	12	11	12	112
E7(1)	15	13	15	12	129
E8(1)	13	12	12	12	117
E9(1)	5	9	10	12	92
E10(1)	13	12	13	12	119
E11(1)	13	13	9	9	127
E12(1)	14	10	13	9	112
E13(1)	9	6	10	12	94
E14(1)	10	14	12	13	100
E15(1)	11	8	11	9	98
E1(2)	8	4	8	9	79
E2(2)	11	12	12	12	113
E3(2)	10	10	12	12	104
E4(2)	12	8	10	12	104
E5(2)	10	6	11	9	92
E6(2)	9	10	10	20	117
E7(2)	12	13	12	12	117
E8(2)	7	12	11	12	104
E9(2)	10	12	6	10	38
E10(2)	12	10	10	6	96
E11(2)	11	4	8	12	90
E12(2)	11	10	14	12	113
E13(2)	14	10	11	12	113
E14(2)	13	6	12	12	113

E15(2)	10	12	10	9	102

Appendix G

Synthetic Sentence Identification

Appendix G: Synthetic Sentence Identification.

SUBJECT	SSI RE 0 MCR	SSI RE -20 MCR	SSI RE -40 MCR	SSI LE 0 MCR	SSI LE -20 MCR	SSI LE -40 MCR
C1	100	60	100	100	80	100
C2	100	100	100	100	90	100
C3	100	90	100	100	80	100
C4	100	100	100	100	90	100
C5	100	80	100	100	90	100
C6	100	100	100	100	100	100
C7	100	70	100	100	90	100
C8	100	80	100	100	90	100
C9	100	80	100	100	90	100
C10	90	60	80	100	100	100
C11	100	80	100	100	100	100
E1(1)	100	100	100	90	60	100
E2(1)	100	100	100	100	100	100
E3(1)	90	70	100	100	70	100
E4(1)	100	80	100	100	100	100
E5(1)	100	70	100	100	70	100
E6(1)	90	60	100	100	100	90
E7(1)	100	90	100	100	90	100
E8(1)	100	80	100	100	100	100
E9(1)	100	100	100	100	100	100
E10(1)	100	80	100	80	100	100
E11(1)	100	80	100	90	70	100
E12(1)	100	80	100	90	70	100
E13(1)	100	70	100	100	60	100
E14(1)	70	100	100	90	100	
E15(1)	100	70	100	90	60	100
E1(2)	100	70	100	100	90	100
E2(2)	100	70	100	100	100	100
E3(2)	80	70	100	100	90	100
E4(2)	100	70	100	100	90	100
E5(2)	100	80	100	100	80	100
E6(2)	90	40	90	60	100	100
E7(2)	100	90	100	100	90	100
E8(2)	100	80	100	100	80	100
E9(2)	100	70	100	100	90	100
E10(2)	100	60	100	100	90	100
E11(2)	90	70	100	100	90	100
E12(2)	100	80	100	100	80	100
E13(2)	90	80	100	100	90	100
E14(2)	100	60	100	100	80	100
E15(2)	100	80	90	100	100	100

Appendix H

Revised Speech in Noise

Appendix H: Revised Speech in Noise (R-SPIN).

SUBJECT	R-SPIN RE 0 MCR	R-SPIN RE +8 MCR	R-SPIN LE 0 MCR	R-SPIN LE +8MCR
C1	68	80	84	92
C2	44	92	72	96
C3	52	92	48	96
C4	68	72	60	88
C5	68	92	64	96
C6	72	92	80	60
C7	84	92	56	92
C8	72	92	60	100
C9	48	92	48	92
C10	56	88	76	48
C11	80	76	76	72
E1(1)	52	91	64	86
E2(1)	76	80	64	92
E3(1)	64	88	56	76
E4(1)	60	80	48	80
E5(1)	60	88	56	76
E6(1)	68	80	56	96
E7(1)	60	100	76	92
E8(1)	68	76	48	80
E9(1)	48	92	44	84
E10(1)	100	100	100	100
E11(1)				
E12(1)	84	96	76	88
E13(1)				
E14(1)	52	80	48	76
E15(1)	84	80	40	92
E1(2)	48	92	60	84
E2(2)	64	84	52	79
E3(2)	56	84	60	88
E4(2)	52	80	24	72
E5(2)	52	88	56	72
E6(2)	60	84	52	92
E7(2)	48	84	80	92
E8(2)	68	76	48	80
E9(2)	48	92	44	84
E10(2)	52	88	48	92
E11(2)	56	88	36	76
E12(2)	44	80	56	72
E13(2)	44	84	60	92
E14(2)	64	76	64	80
E15(2)	72	80	72	36

Appendix I

SSRI Benefit Form

Name: _____ Date: _____

Age: _____ Phone: _____

Please answer the following questions as best you can.

1. Medical diagnosis: Depression_____ Migraine_____

   Other: _____

2. Name of SSRI medication you are currently taking (Prozac, Paxil, Luvox, Celexa, Zoloft). _____

3. Daily Dosage (mg/day) _____

4. How long have you been taking this medication? _____

5. SSRI prescribing physician _____

6. List all other medications, including herbal supplements, such as St. John's Wort. _____

7. Have you noticed any change in you auditory sensitivity and/or speech understanding since taking SSRI medication? _____

   _____

8. It is essential for our research to understand how this medication is affecting you. Please describe how you feel this medication is and/or is not helping you with your symptoms.

REFERENCES

American Psychiatric Association, (1994). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington D.C.: American Psychiatric Association.

Aran, J., Pajor, A., Charlet de Sauvage, R., & Erre, J. (2000). Role of the Efferent Medial Olivocochlear System in Contralateral Masking and Binaural Interactions: An Electrophysiological Study in Guinea Pigs. Audiology, 39, 311-321.

Anari, M., Axelson, A., Eliasson, A., & Magnisson L. (1999). Hypersensitivity to sound. Acta Pschiatrica Scandinavica, 391. 7-13.

Beck, A. S., Steer, R.A., Ball, R., & Ranieri, W., F. (1999). Dimensions of the Beck Depression Inventory-II in Clinically Depressed Outpatients. Journal of Clinincal - Psychology, 55, 117-128.

Beck, A.S., Steer, R.A., & Brown, G.K. (1996). Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation.

Berlin, C. I., Hood, A. E., Wen, H., & Kemp, D. T. (1995). Binaural noise suppresses linear click-evoked otoacoustic emissions more than ipsilateralor contralateral noise. Hearing Research, 87, 96-103.

Bilger, R. C., Nuetzel, J. M., Rabinowitz, W.M., & Rzeczkowski, C. (1994). Standardization of a test of speech perception in noise. American Speech-Language Hearing Association, 27, March, 32-48.

Bishop C. (2001) Unpublished Thesis: A Preliminary study of the Effects of Selective Serotonin Reuptake Inhibitors (SSRI) on Central Auditory Processing Measures.

Bongioanni, M.S., & Selvaggi, G. (1991). Effects of serotonin reuptake inhibitors on plasma and platelet serotonin. Introduction. In G.B., Cassano, & H.S. Akiskal (Eds.), Serotonin-Related Psychiatric Syndromes: Clinical Theraputic Links (pp. 13-19). New York: Royal Society of Medicine.

Brady, W.T., & Lynn J. M. (1994). Audiologic findings in hyperacusis and nonhyperacusic subjects. American Journal of Audiology, 4, 46-51.

Bruder, G.E., Stewart, J.W., Tenke, C.E., McGrath, P.J., Leite, P., Bhattacharya, N., & Quitkin, F.M. (2001). Electoencephalographic and percectual asymmetry

differences between responders and nonresponders to an SSRI antidepressant. Biological Psychiatry,49, 416-425.

Carhart, R., & Jerger, J. F. (1959). Preferred method for clinical determination of pure-tone thresholds. Journal of Speech and Hearing Disorders, 24, 330-345.

Carney L. (2001) Unpublished Thesis: A Preliminary study of the Effects of Selective Serotonin Reuptake Inhibitors (SSRI) on Peripheral Auditory Processing Measures.

Charney, D.S. (1998). Monoamine dysfunction and the pathophysiology and treatment of depression. Journal of Clinical Psychology, 59, 11-14.

Collet, L., Kemp, D., Veuillet, E., Duclaux, R., Moulin, A., & Morgon, A. (1990). Effect of contralateral stimuli on active cochlear micro-mechanical properties in human subjects. Hearing Research,43, 251-262.

Collet, L., Veuillet, E., Moulin, A., Morlet, T., Giraud, A.L., Micheyl, A.C., & Chery-Croze S. (1994). Contralateral auditory stimulation and otoacoustic emissions: a review of basic data in humans. British Journal of Audiology,28, 213-218.

Duffy, J. (1995). Motor Speech Disorders. St. Louis: Mosby Publishing

Endler, N. S., Rutherford, A., & Denisoff, E. (1999). Beck Depression Inventory: Exploring Its Dimensionality in a Nonclinical Population. Journal of Clinical Psychology,55, 1307-1312.

Franklin, D. J., McCoy, M. J., Martin, G. K., Lonsbury-Martin, B. L. (1992). Test/Retest Reliability of Distortion and Transiently Evoked Otoacoustic Emissions. Ear & Hearing, 13(6), 417-427.

Fuller, R. W., & Wong, D. T. (1990). Serotonin uptake and serotonin uptake inhibition. In P. M., Whitiker-Azmitia, & S. J. Peroutka (Eds.) Annals of the New York Achademy of Sciences: Vol. 600. The neuropharmacology of serotonin (pp. 68-78). New York: The New York Achademy of Sciences.

Gallinat, J., Bottlendr, R., Juckel, G., Munke-Puchner, A., Stotz, G., Kuss, H.J., Mavrogiorgou P., & Hegerl U. (2000). The loudness dependency of the auditory evoked N1/P1-component as a predictor of the acute SSRI response in depression.

Gil-Loyzaga,m P., Bartolome', M.V., & Vicente-Torres, M.A. (1997). Serotonergic innervation of the organ of Corti of the cat cochlea. Neuroreport,8 (16), 3519-3522.

Gopal, V.K., Daly, D.M., Daniloff, R.G., & Pennartz L. (2000). Effects of selective serotonin reuptake inhibitors on auditory processing: Case study. Journal of the American Academy of Audiology, 11(8), 454-463.

Graham, R. L. & Hazell, J. W. P. (1994). Contralateral suppression of transient evoked otoacoustic emissions: Intra-individual variability in tinnitus and normal subjects. British Journal of Audiology, 28, 235-245.

Hawkins, D. B. (1984). Selection of a critical electroacoustic characteristic: SSPL90. Hearing Instruments, 35(11), 28-32.

Hegerl, U. & Juckel, G. (1993). Intensity dependance of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biological Psychiatry, 33, 173-187.

Jacobs, B. L. & Fornal C. A., (1993). 5-HT and motor control: a hypothesis. TINS, 16 (9), 346-352.

Jerger, J. F., & Jerger S. W. (1974). Auditory findings in brainstem disorders. Arch Otolaryngology, 99, 342-349.

Jerger, J. F., Oliver, T., & Pirozollo, F. (1990). Impact of central auditory processing disorder and cognitive deficit on the self assessment of hearing handicap on the elderly. Journal of the American Achademy of Audiology, 14, 75-81.

Juckel, G., Hegerl U., Molnar, M., Csepe, V., & Karmos, G. (1999). Auditory evoked potentials reflect serotonergic neuronal activity: a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology, 21 (6), 710-716.

Kandel, E.R.,& Schwartz, J. H. (1985). Principles of Neural Science. New York: Elsevier Science Publishing Company.

Keith (1996). SCAN-A. A Screening Test for Auditory Processing Disorders. San Antonio, The Psychological Corporation, Harcourt Brace & Company.

Kemp, D., Ryan S., & Bray, P. (1990). A Guide to the Effective Use of Otoacoustic Emissions. Ear & Hearing,2(11), 93-104.

Kilgore, W., S. (1999). Empirically Derived Factor Indices For The Beck Depression Inventory. Psychological Reports,84, 1004-1013.

Lucas R. A., (1992). The human pharmacology of fluoxetine. International Journal of Obesity 16, 549-554.

Marriage, J. & Barnes, N.M. (1995). Is central hyperacusis a symptom of 5-hydroxytryptamine (5-HT) dysfunction? Journal of Laryngology and Otology, 109, 915-921.

Martin, G. R., & Humphrey, P.P.A. (1994). Receptors for 5-Hydroxytryptamine: Current perspectives on classification and nomenclature. Neuropharmacology, 33, 261-273.

Menkes, D.B., Aghajanian, G.K., & McCall, R.B. (1980). Chroninc antidepressant treatment enhances adrenergic and serotonergic responses in the facial nuclei. Life Sciences, 27, 45-55.

Micheyl, C., Carbonnel, O., & Collet L. (1995). Medial olivocochlear system and loudness adaptation: differences between musicians and non-musicians. Brain and Cognition, 29, 127-136.

Morlet, T., Goforth, L., Hood, L. J., Ferber C., Duclaux, R., Berlin, C.i. (1999). Development of human cochlear active mechanism asymmetry: involvement of the medial olivocochlear system? Hearing Research, 134, 153-162.

Olsen, W. O., Noffsinger, D., & Carhart, R. (1976). Masking level differences encountered in clinical populations. Audiology, 15, 287-301.

Parthasarathy, P. (2000). In measuring evoked otoacoustic emissions from adults, is age a factor? The Hearing Journal,53,40-46.

Perez, V., Bel, N., Celada, P., Ortiz., Alverez, E., & Artigas, F. (1998). Relationship between blood serotonergic variables, melancholic traits, and response to antidepressant treatments. Journal of Clinical Psychpharmacology, 18 (3), 222-230.

Phillips, D. P., & Carr, M.M. (1998). Disturbances in loudness perception. Journal of the American Achademy of Audiology,9,371-379.

Pinder, R.M. (1997). Designing a new generation of antidepressant drugs. Acta Phychiatrica Scand, 96, 7-13.

Pinel, J.P. (1997). Biopsychology. Boston: Allyn and Bacon.

Simpson, J. J., & Davies W. E. (2000). A review of evidence in support of a role for 5-HT in the perception of tinnitus. Hearing Research145, 1-7.

Speakes, C. & Jerger, J. (1965). Method for the measurement of speech identification. Journal of Speech and Hearing Research, 77, 533-546.

Stutzmann, B. E., McEwen, B. S., & LeDoux, J. E. (1998). Serotonin Modulation of Sensory Inputs to the Lateral Amygdala: Dependancy on corticosterone. Journal of Neuroscience,18, 9529-9538.

Sweetow, R.W., & Reddell, R.C. (1978). The use of masking level difference in the identification of children with perceptual problems. Journal of the American Auditory Society,4, 52-56.

Tavaetkiladeze, G. A., Frolenkov, G. I., Artamosov, S. V. (1996). Ipsilateral suppression of transient evoked otoacoustic emission: Role of the medial olivocochlear system. Acta Otolaryngology, 116, 213-218.

Thompson, G.C., Thompson, A. M., Garrett, K. M., Britton, B.H. (1994). Serotonin and serotonin receptors in the central auditory system. Otolaryngology Head and Neck Surgery, 110, 93-102.

Vandermalen, C.P. (1985). Serotonin. In: Rogawski, M.A., & Barker, J.L., (Eds.), Neurotransmitter Actions in the Vertebrate Nervous System (pp. 201-240). New York: Plenum Press.

Whisman, M. A., Perez, J.E. & Ramel, W. (2000). Factor structure of the Beck Depression Inventory-second edition (BDI-II) in a student sample. Journal of Clinical Psychology, 56 (4), 545-551.

Williams, E. A., Brookes, G. B., & Prasher, D. K. (1993). Effects of contralateral acoustic stimulation on otoacoustic emissions following vestibular neurectomy. Scandanavian Audiology, 22, 197-203.

Williams, E. A., Brookes, G. B., & Prasher, D. K. (1994). Effects of olivocochlear bundle section on otoacoustic emissions in humans: efferent effects in comparison with control subjects. Acta Otolaryngology, 114, 121-129.

Willeford, J.A., & Burleigh, J. M. (1994). Sentence procedures in central testing. In Katz, J. (Ed.), Handbook of Clinical Audiology (4^{th} edition, pp. 25-36). Baltimore: Williams & Wilkins.