Short-Term Effects of Cognitive Training in Adult Cochlear Implant Users

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By

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Changing the brain: Lab-to-bedside approach

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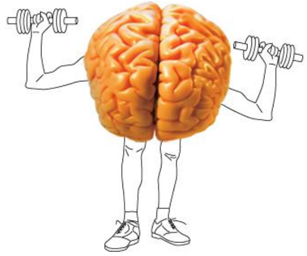

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Abstract

Background: There is growing evidence in support of the cognitive remediation following cochlear implantation in children. To the best of our knowledge, the role of generalized cognitive training (CT) in adult cochlear implant users has not been explored.

Objectives: To determine the effects of computerized CT with standard therapy on adult cochlear implant users' speech comprehension in noise, cognitive functions and auditory ability.

Methods: A prospective, unblinded, single-center, randomized controlled trial with cross-over study design and two treatment arms. Participants (N = 12) from the Maritime Provinces in Canada received CT (via CogniFit) either right after the first assessment or ten weeks later in the immediate (n = 7) and delayed (n = 5) treatment groups respectively. Speech comprehension in noise, assessed by AzBio sentence test, was the primary outcome measure. The secondary outcomes were neuropsychological assessments - CANTABeclipse for Clinical Trials, and self-reported auditory ability - Speech Spatial Qualities questionnaire (SSQ). Data from 2 participants were excluded due to lack of follow-up, data from the remaining participants were analyzed by mixed models in SPSS (version 20) and R (version 3.0.2.).

Results: Based upon analyses combined across two groups, CT with standard therapy (n = 10) *marginally* enhanced sentence comprehension in noise, AzBio score, β = 2.58, 95% CI [-2.84, 8.02], p > .05. Furthermore, CT demonstrated statistically significant, but modest improvement in SSQ total scores, β = 0.60, 95% CI [0.14, 1.05] and certain CANTABeclipse test scores. Namely, (i) SOC number of problems solved in minimum moves, β = 1.12, 95% CI [0.29, 1.94], for Spatial Planning (ii) SWM total errors for problems with 4 to 8 boxes, β = -11.32, 95% CI [-19.82, -2.81] and strategy, β = -3.08, 95% CI [-4.36, -1.81], for Spatial Working Memory, (iii) RVP A′, β = 0.015, 95% CI [0.005, 0.026], for Sustained Attention and (iv) VRM free recall, β = 1.25, 95% CI [0.25, 2.26] and recognition, β = 0.76, 95% CI [0.32, 1.20], for verbal memory.

Conclusion: Ten weeks of cognitive training modestly enhanced executive and working memory skills in adult cochlear implant users. This finding suggests adult cochlear implant users' brains are malleable. The treatment effect estimates for speech comprehension in noise did not reach a statistically significant level. A longitudinal multicentered trial with a large sample size is needed to make evidence-based recommendation for the routine clinical care of cochlear implant users.

Trial Registration: Clinicaltrial.gov unique identifier NCT01732887

Keywords: Cochlear implant, cognitive fitness, cognitive training, deafness, speech intelligibility

List of Abbreviations

CANTAB: CAmbridge Neuropsychological Test Automated Battery

CBI study: Computer-Based Intervention study

CF: CogniFit complementary cognitive training program

CI: Cochlear Implant

CREATE: The Collaborative Research and Training Experience

CT: Generalized Cognitive Training

DM: Diabetes Mellitus

HPAPQ: Healthy Physical Activity Participation Questionnaire

FANTASTIC: Family/Friends, Activity, Nutrition, Tobacco/Toxins, Alcohol, Sleep/Seatbelts/Stress/Safe sex, Type of behavior, Insight, Career

MMSE: Mini Mental State Examination

M. Phil. ICH: Master of Philosophy Degree in International Community Health

MOT: MOtor screening task

NCERC: Natural Sciences and Engineering Research Council of Canada

NCIL: NeuroCognitive Imaging Lab

NS: Nova Scotia

OTS: One Touch Stockings of Cambridge

p: p - value

RADIANT: Rehabilitative and Diagnostic Innovation in Applied NeuroTechnology programme

RCT: Randomized Controlled Trial

RVP: Rapid Visual Information Processing

Std Rx: Standard therapy or standard of care

SNHL: Sensorineural Hearing Loss

SOC: Stockings Of Cambridge

SSQ: Speech, Spatial and Qualities of hearing scale

SWM: Spatial Working Memory

VRM: Verbal Recognition Memory

WM: Working Memory

95 % CI: 95 Percent Confidence Interval

β : Vector of regression coefficients

Definition of Terms

Neuroplasticity

Neuroplasticity (or brain plasticity) is defined as the ability of the nervous system to change its structure and functional organization that persists beyond its inciting internal or external stimuli (Chen et al., 2014).

Generalized Cognitive Training

According to Gates and Valenzuela, the generalized multi-domain cognitive training (CT) consists of training in: (a) applied memory strategies and (b) repetitive cognitive exercises. The former include strategies such as the method of loci, mnemonics and visual imagery, and aim to remediate memory and enhance performance. Repetitive cognitive exercises, however, consist of repeated use of certain cognitive abilities following the ‘reps-sets’ pattern of resistance physical training. In each session, a particular cognitive task is practiced repeatedly. New tasks are introduced and practiced in subsequent sessions. Finally, users train on a higher level version of the original task (N. J. Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; N. Gates & Valenzuela, 2010).

Standard Therapy

Herein, standard therapy (or standard of care) includes the advice and care given by patient’s audiologist, family physician, otolaryngologist, speech-language pathologist and other members of the health-care team.

Hearing

It is essentially a sensory and passive function that helps to perceive sounds by vibrations and discriminate their location, pitch, loudness and quality (Kiessling et al., 2003).

Listening

Listening is an activity and cognitive process where people engage in hearing with intention and attention (Kiessling et al., 2003).

Comprehending

Comprehending is the unidirectional understanding of information, meaning and intent. It is an activity that goes beyond the hearing and listening processes (Kiessling et al., 2003).

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1. Introduction

The brain plasticity, the future of neuroscience, is almost unknown to us.

1.1. Aims of the Present Work

The current study aims to generate high-quality preliminary evidence on the efficacy of generalized multi-domain cognitive training (CT) for adult cochlear implant users. CT will be evaluated with respect to a number of outcome measures, prime among which are the language skills (speech comprehension in noise).

Experts argue that “90% of health research expenditure is on diseases that cause 10% of the global burden of disease, and that diseases that afflict many very poor people are minimally researched reflects a research agenda driven largely by profit motives” (Knut & Omer, 2012). Hence, we should prioritize unresolved areas in the research scheme that affects the world on a bigger scale and find affordable evidence-based solutions. Although cognitive impairment and hearing loss are two of the most prevalent chronic conditions facing the North Americans today, they are still under-reported (Yueh, Shapiro, MacLean, & Shekelle, 2003). Most governmental/personal money is spent in treatment and/or rehabilitation of stroke and other cognitive impairments, whereas mental health promotion and disease prevention should be given a priority.

Ancient physicians had conflicting views on hearing loss, and its relationship with structure and functioning of different brain areas (Findlen & Bence, 2014). Centuries later, the current literature supports that hearing loss is associated with the changes in brain structure. Nevertheless, changes in hearing cannot be explained by an audiogram alone. Working Memory (WM) is well-known to be greatly associated with language and listening abilities. Clinicians are now testing new techniques, which possibly work by changing the brain, such as auditory and/or cognitive training, to help patients who suffer from hearing loss (Anderson, White-Schwoch, Parbery-Clark, & Kraus, 2013; Henshaw & Ferguson, 2013b).

In the following manuscript, I review the cognitive and otology literature with a special focus on functional outcome measure of cognitive fitness, neuroplasticity and translational medicine. Subsequently, I present the main objectives, research methods, results and discussion sections.

1.2. Aetio-pathology of Hearing Loss and its Relationship to Cognitive Impairments

1.2.1. Anatomy of ear. The ear is the organ that detects sound, maintains body balance and a sense of position. It consists of three parts: outer ear, middle ear and inner ear. The outer ear acts as a 'collecting device' for mechanical vibration (i.e., sound) and transfers these vibrations towards tympanic membrane, middle ear and inner ear, more precisely basilar membrane of cochlear duct. The cochlea (Figure 1) is the auditory division of the inner ear which includes the scala vestibuli, scala tympani and scala media (Ropshkow, 2010). A healthy cochlea receives, generates and amplifies sound by active cell-body vibrations of its outer hair cells (i.e., sensory receptors) at the frequency of acoustic signal known as mechanical feedback amplification. Inner hair cells of cochlea are mainly responsible for this acoustic nerve signal.

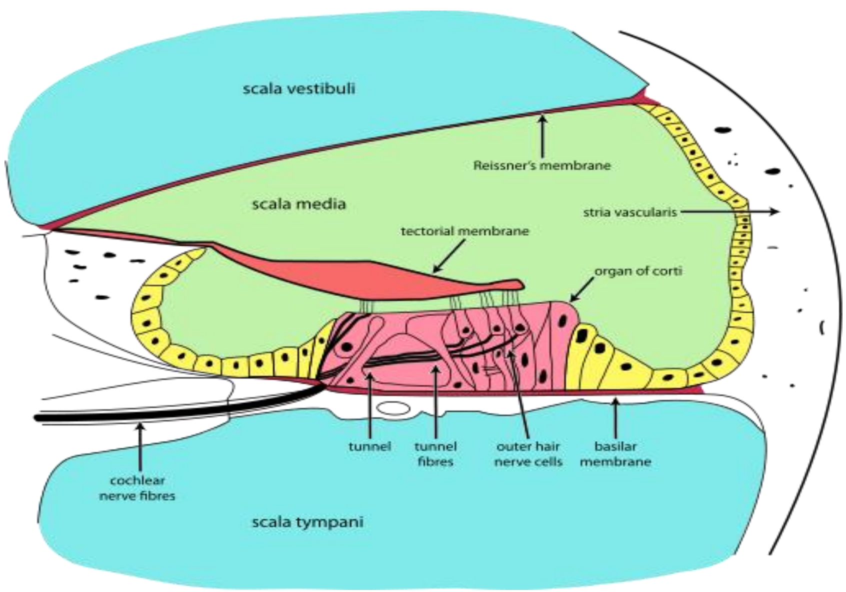


Figure 1: Digital image of cochlea, taken from wikipedia.org (Ropshkow, 2010)

1.2.2. Aetiopathology of hearing loss. Hearing loss occurs when a part of the ear is not working in its normal physiological way. It may stem from an interference with the transmission of sound from the outer ear to the inner ear (conductive hearing loss) or from a damage in the cochlea, the auditory nerve or auditory centers in the brain (sensorineural hearing loss), or a combination of both conductive and sensorineural hearing loss (mixed hearing loss) (National Institute for Health and Care Excellence, 2011). The central auditory processing disorder is another important aetiopathology of hearing loss. Affected patients can 'hear' sound but cannot understand what is heard.

Conductive hearing loss is commonly caused by acute otitis media, serous otitis media, cerumen accumulation in the external auditory canala, and otitis externa. Other causes include middle ear effusion, otosclerosis and ossicular disruption, superior canal dehiscence (Koike, 2006). However, more than 90% of hearing loss is sensorineural, caused by progressive loss in function of hair cells in the organ of corti in the inner ear, leading to deafness (Yueh et al., 2003). Sensorineural hearing loss (SNHL) is mostly permanent. It can be caused by ageing, excessive exposure to noise, infections, inner ear diseases (e.g., Ménière's disease*)*, genetics, metabolic disorders, retrocochlear pathology (lesions affecting auditory nerve through the auditory cortex, e.g., neurofibromatosis type II with acoustic neuroma), and ototoxicity. In addition, both cochlear and retrocochlear pathologies are known to reduce speech discrimination.

Hearing loss can be classified based on the onset of hearing loss and severity. Deafness that occurs before the development of language is described as pre-lingual, whereas deafness that occurs after the development of language is described as post-lingual. Hearing loss can be categorized (Koike, 2006) based on the degree of loss as mild (26 - 40 dB); moderate (41 - 55 dB); moderately severe (56 - 70 dB); severe (71- 90 dB) and profound (91 dB threshold or greater). For children with advancing degree of hearing loss, there is a definite concern for early speech and language development.

1.2.3. Cognitive impairments in relation to hearing loss. Cognition is the interplay of attention, arithmetic skills, decision-making capacity, language comprehension and production, memory, problem solving and reasoning skills. Difficulties in processing these brain functions may lead to physical, psychological, social diffidence and infirmity (Ginsberg, 2005). Here, we briefly describe the anatomical and functional aspects of different cognitive processes:

a) Attention and concentration: It is a cognitive process of focusing on one part of environment or information while filtering or ignoring extraneous information. The reticular activating system which relays signal to thalamus and then to the cerebral cortex plays a major role in normal attention, likewise consciousness.

b) Memory: Simply, the memory ‘system’ includes implicit memory, explicit memory, short-term memory, anterograde memory and retrograde memory. (i) Implicit memory, i.e., motor responses that are learned but not available to conscious access, relies on the basal ganglia, cerebellum and their connections with the cerebral cortex. (ii) Episodic and semantic memories are sub-components of the explicit memory. The limbic system with hippocampus and thalamus plays a major role in the former and the temporal neocortex stores the latter. Early changes in old age typically encompass a decline in episodic memory. (iii) Several researchers' argue about the properties of short-term memory (STM) and WM. More uncertainties exist regarding the role of posterior parietal region, ventral and dorsolateral prefrontal cortex in WM. A clear understanding of short-term memory and WM is crucial for this thesis. WM, a limited capacity system and theoretical concept, represents temporary storage and manipulation of information (Baddeley, 2010; Rothmayr et al., 2007). STM, on the other hand, constitutes information-storage without manipulation. Nelson Cowan, a Psychologist at the University of Missouri, defines WM as a combination of short-term memory and other processing mechanisms that help to make use of short-term memory (Cowan, 2008). He also suggests temporal decay and chunk capacity limits of STM to be the main differentiating features amongst STM and long-term memory.

c) Higher order executive functions, personality and behavior: Normal executive functions rely on the frontal lobes of cerebral hemisphere, particularly the prefrontal cortex. They play a major role in the ability to plan, adapt, handle abstract concepts and solve problems. While social cognition, personality and behavior functions rely on the ventromedial frontal lobes. Clinically, deteriorating verbal fluency, proverb interpretation, cognitive estimates and loss of inhibitory control indicate higher chances of developing frontal dysfunction.

d) Linguistic skills: In most healthy individuals, the left cerebral hemisphere is dominant for language function. Language skills are "localized" in the sense that they depend on specific brain regions and not every part of the brain. Patients with injuries in their dominant hemisphere can present with impairment of linguistic skills and inability to perform complex motor tasks, regardless of their normal muscle power, sensation and coordination, and good comprehension and cooperation. Conversely, the non-dominant hemisphere is mostly responsible for visuospatial skills. Patients with right-sided or non-dominant lesions can present with neglect, and inability to dress properly and/or copy complex shapes. The bilateral parieto-occipito-temporal damage results in more severe visuoperceptual disorders.

Hearing loss has been associated with cognitive impairments. Although both can affect any individual at any age, the incidence and prevalence of cognitive impairments and hearing loss increase with age (Kiessling et al., 2003). Deafness and impaired speech understanding, in particular, may be challenging for a person and the community on a larger scale. People with hearing loss may use sign language as a mode to communicate and may not interpret deafness as a disability, the bigger component of "pre-lingual deaf pride". On the other side of the coin, person will lose the benefits of hearing in everyday life. The absence of hearing sensation may even go ahead to colonization of the auditory cortex by other sensory modalities, which is the main limiting factor for performance of pre-lingual hearing aid and/or cochlear implant users (Teoh, Pisoni, & Miyamoto, 2004a, 2004b). The degenerative changes in the auditory nerve and cerebral cortex also contribute to deteriorating auditory performance but to a lesser extent. Even though an early initiation of aurally based therapies is advocated to preserve the peripheral auditory system and brainstem, adult cochlear implant users' performance typically reach a plateau by 6 months to 1 year past implantation.

Hearing and understanding spoken sentences are closely related but not the same. Speech comprehension in noise is a more complex and demanding task than simply hearing. So, "normal" hearing on an audiogram does not guarantee a good speech comprehension in noise because it depends on hearing plus cognitive abilities. Prior research suggests the association of pre-lingual deafness, prolonged duration of cochlear implant use with increased susceptibility towards deteriorating executive functions (Kronenberger, Pisoni, Henning, & Colson, 2013). In addition, hearing loss may increase the cognitive load, or limit suffers' social interaction, thereby, independently causing cognitive impairments. The presence of concomitant visual and motor impairments can augment cognitive load and divert mental resources from cognitive functions such as memory and comprehension. It is still uncertain whether aural rehabilitation program could have an effect on cognitive functioning (Lin et al., 2011).

1.3. Management Options for Hearing Loss

1.3.1. Aural "habilitation" and "rehabilitation". Based upon each individual patient's characteristics such as age, communicative requirements, degree of hearing loss, etiology, expectations, mental abilities, motivation, and physical abilities; conservative, medical treatment, hearing aids and surgical repair may be recommended for the aural remediation. The intervention is referred to "habilitation" when the training begins prior to acquisition of normal speech and language (i.e., pre-lingual patients). In fact "habilitation" includes a course of action for development of appropriate speech and language. On the other hand, the term "rehabilitation" is used when intervention starts after the acquisition of normal speech and language (i.e., post-lingual patients). Aural intervention options comprise auditory training, cued speech, hearing aid orientation, listening strategies, manual communication, and lip reading.

1.3.1.1. Currently available hearing devices. Most conductive hearing loss cases are temporary, that is, they are often manageable with appropriate treatment as noted above, whereas recurrent otitis media, tympanic membrane perforation, chronic middle ear diseases and head and neck syndromes could result in chronic and relapsing conditions. The moderate or greater degree of sensorineural hearing loss frequently requires an additional aural rehabilitation device such as hearing aids, and/or cochlear implants. Traditional hearing devices such as hearing aids, amplified telephones, and portable devices work by amplification of the sound. The traditional air conduction hearing-aids are best suited for young, middle-aged and independent hard of hearing adults who suffer from significant difficulties in work-life and social interactions. The portable amplification system uses infra-red technology, or more recently a digital processing circuit, to send sound from an external source to receiver. The CROS (Contralateral Routing of Signal) aids are used for people having a normal hearing ear and an unaidable ear with severe hearing loss which contain a microphone to pick up signal and "route" it to the receiver in the "good" or normal ear. If the "good" or "better" ear also has a hearing loss, then, BiCROS arrangement can be used. BiCROS routes acoustic signal from SNHL side to better side and both the microphone and amplifier are placed on the side of the "good" ear.

In case, a person does not receive adequate benefit from traditional hearing amplification devices, an implantable hearing device (cochlear implants, osseointegrated implants, and electrically-driven middle ear implants) may be considered. Bone-anchored hearing aids (BAHA) and osteointegrated implants are now indicated for people with significant bilateral conductive hearing loss, and more recently, single-sided deafness. They are also well suited for people with mixed hearing loss who cannot wear air conduction hearing aids. BAHA is usually placed against the temporal bone of skull with a steel-spring headband. It has limited roles for people with significant degree of cochlear loss, and this is typically a painful procedure which may lead to skull deformities with poor hearing benefits (Janssen, Hong, & Chadha, 2012; Weber, 2013).

The first clinically effective cochlear implant worked by direct stimulation of the human auditory system. It was developed by Drs Djourno and Eyriès in 1957. Although patient consented to undergo this experimental procedure, it would be interesting to note that there was no ethics committee involved at that time and this device was aborted after a short time. Dr Djourno reported their findings in French database and he had a firm belief to keep academia and industry partners separate from each other (Eisen, 2003). Due to the linguistic issue, it took several years before Drs Robin Michelson and William House, the American otologists, first heard of Dr Djournos' work. Since then the field of cochlear implant has been rapidly growing, making it more successful and complex.

Cochlear implantation is the only available option for people with severe to profound bilateral hearing loss that do not receive adequate benefit from acoustic hearing aids (Faulkner & Pisoni, 2013). Notably, cochlear implantation is considered as an option in persons as young as one year and as old as 90 years with severe to profound hearing loss who do not receive adequate benefit from acoustic hearing aids. The reason being that hearing loss can happen at any time in life, from birth to elderly or till death (National Institute for Health and Care Excellence, 2011).

A typical cochlear implant apparatus includes a microphone, a signal processor and transmitter, an implanted receiver and an electrode array. The cochlear implantation procedure, in which electrodes with the stylet are inserted across the skull bones, is performed by a team of healthcare professionals including at least one otologist experienced in cochlear implantation surgery. The said electrode array responds to external auditory stimuli, and in turn transmits the signal to auditory nerve. Consequently, it works by direct innervations of the auditory nerve in scala tympani of cochlea, bypassing the outer hair cells. Finally, the cochlear division of auditory nerve sends information to the auditory cortex of temporal lobe, which interprets this stimulus as sound. The processing occurs at following stages of a classic auditory pathway: cochlear nuclei of the pons and medulla oblongata; superior olivary nucleus of the brainstem; inferior colliculus of the midbrain and medial geniculate nucleus of the thalamus. During the cochlear implantation surgery, there is always a risk of inadvertent trauma to the healthy tissue, resulting in nervous tissue apoptosis/necrosis or a growth of fibrous membrane around electrode array (Behrend et al., 2012).

1.3.1.2. Recent advances in auditory neuroscience. New devices such as Esteem and Lyric are offered in limited number of centers. While Esteem is a surgically implanted middle ear hearing-aid, Lyric is placed directly on ear drum. Long-term effectiveness of both is a matter for further research (Weber, 2013).

Until recently, the stylet-based strategy is used to advance the cochlear implants' electrode array at a "desired depth" inside the inner ear, thereby, avoiding iatrogenic injury to cochlea. New approaches are also being tested to avoid damage to the healthy cochlea, such as "active cannula" robot that delicately senses the contact between the implant and cochlea, robotic skull drilling systems, and robotically assisted implant surgery (Taylor et al., 2013).

1.4. Explanation for Individual Differences in Cochlear Implant users' Language Skills

There are various factors affecting the cochlear implant users' outcome measures. The hearing benefits after cochlear implantation range from normal ability to understanding speech and to having no improvement at all (U.S. Food and Drug Administration, 2010). Speech understanding in noise is challenging for all cochlear implant users. The challenges occur due to high demands on entire brain functions, basic sensory and perceptual capabilities as well as elementary cognitive reserves and processing operations (Faulkner & Pisoni, 2013). The adult cochlear implant users deserve special attention because of the great variability in outcome measures and increasing proportion of cochlear implant users. All patients with cochlear implants struggle with understanding sentences in noise or under a high cognitive load. Hence, a measurable improvement in speech perception abilities may not be considered as a positive *functional* outcome by patients. Despite the overall benefits, in the listed instances and due to inter-individual variations in outcome measures, an individual cochlear implant user can become dependent upon others. Although much research effort has put into early sensory processing and noise reduction algorithms, there is growing awareness to evaluate the role of attention and cognition in cochlear implant users. The median recognition of disyllabic words after one year of surgery was 70%, ranged from low-functioning cochlear implant users with 0 % score to the "stars" with 100% (Faulkner & Pisoni, 2013; Lazard, Giraud, Gnansia, Meyer, & Sterkers, 2012). This extremely large individual variation in cochlear implant users' rehabilitation outcome can be explained by the differences in participant characteristics. Lazard et al. describe factors influencing cochlear implant user's rehabilitation, namely, age at cochlear implantation and age at onset of severe to profound hearing loss, brain plasticity, cochlear implant experience, duration of severe to profound hearing loss, etiology of hearing loss, and peripheral predictors.

The predictive factors for *enhanced* speech comprehension after cochlear implantation are the choice of early intervention, the electrode coupling and processing algorithm, family support, generation of the cochlear implant, higher socioeconomic status, later ages of deafness onset, lip reading abilities, motivation, presence of residual hearing, preoperative hearing aid use, scalar placement and insertion depth of electrode, shorter duration of hearing loss, surgical technique and usage of more auditory training methods (Faulkner & Pisoni, 2013; Finley et al., 2008; Teoh et al., 2004a; van Dijk et al., 1999; Waltzman, 2002). Post-lingually deafened cochlear implant users typically outperform the cochlear implant users with congenital or early acquired deafness due to the considerable neural reorganization of underlying cortical brain circuits in the pre-lingually deafened. At the same time, recent reviews have emphasized that even once these factors are accounted for, still <u>much of the variance in individual outcomes remains unexplained</u> (Faulkner & Pisoni, 2013; Peterson, Pisoni, & Miyamoto, 2010). Research on identification of these unexplained factors combined with patient's unmet-need assessment can assist to revise the existing practice guidelines, and thereby, increase the quality of life of suffers rather than only full restoration to pre-morbid level of function.

2. The Rationale of Present Work

2.1. Global Demographics of People with Cochlear Implants

Prevalence of hearing loss increases with age but age is not the only factor. Despite a large prevalence of hearing loss, several studies have shown a relatively small uptake of hearing aids. Furthermore, a significant proportion of older adults who possess hearing aids do not use it regularly. The United States Food and Drug Administration estimated 219,000 cochlear implant users worldwide as of December 2010. However, this is only a small proportion of the people who could benefit from implants. In the United States, roughly 42,600 adults and 28,400 children have received cochlear implants, while in Canada, there were more than 4200 cochlear implant users (Fitzpatrick & Brewster, 2010). In the emerging economies, despite a large number of eligible candidates for cochlear implantation surgery, the number of cochlear implant users' is comparatively small. For example, in India there are an estimated 1 million profoundly deaf children, over 1.2 million with severe hearing disabilities, but only about 5,000 cochlear implant users (Hindustan Times, 2012; The Hindu, 2011). This minuscule number is due to the high costs for the implant, as well as the cost of subsequent therapy. Cochlear implantation surgery is technically very demanding and costs approximately US$40,000.

Notably, due to limited resources, a great majority of adult cochlear implant users receive a single implant in the North America. It is well known that bilateral cochlear implants provide an ideal option for many deaf individuals. In addition, sound perceived from cochlear implants has less clarity than that of people with normal hearing ability (Kingman, 2012). To solve these problems, Kingman has invented a device where the auditory signal is picked up by the microphone, then amplified by the signal processing circuit, subsequently, converted into minute vibrates of the user's skin by two piezoelectric transducers, thereby, stimulating Pacinian corpuscles in the skin, and eventually transferred the nerve impulses from the skin to auditory cortex. This is definitely an interesting and less costly intervention that could improve the speech intelligibility and comprehension. However, there is limited information about its effect size and as such it cannot be recommended to the patients. Furthermore, the Defence Research & Development Organisation in India is attempting to develop an effective yet affordable cochlear implant. It could potentially reduce the cost to approximate US$2000 (Hindustan Times, 2012; The Hindu, 2011). Due to increased affordability, the number of cochlear implantation procedures is bound to rise. With an aging population and innovative low cost surgeries, we expect that adult cochlear implant users will form an increasing proportion of the population, and yet this is the population for whom outcomes are most difficult to predict (Lazard et al., 2012).

2.2. Access to Specialized Medical Services after Cochlear Implantation in Canada

Cochlear implantation team includes the audiologist, family physician, otologist, and speech-language pathologist. Implant Centre Speech and Language Therapists (ICSLTs) play a major role in delivery of standard therapy in most implant centers (British Cochlear Implant Group, 2010). ICSLTs usually work on the clients' auditory training and developing effective communication skills and assistive listening devices. In a nationwide survey conducted in 12 Canadian implantation centers, there were several rehabilitation concerns such as the cost involved in surgery and rehabilitation, accessibility to the implant center (Fitzpatrick & Brewster, 2010). In the Maritime Provinces, as in many parts of the world, much of the population is widely distributed and living in remote areas with a limited access to specialized medical services. Even people who are able to come to Halifax city for cochlear implantation return to their rural locations afterwards, hence, they cannot readily access speech therapists or audiologists.

2.3. Association between Linguistic Skills and Working Memory

As noted above speech understanding in noise is a complex task, the use of hearing amplification devices may improve the audibility but it does not alleviate the cognitive demand, that is required to process speech understanding in noise (Olson, Stewart, & Effgen, 2010; Sommers et al., 2011). Beyond direct speech training, there is growing evidence that WM is associated with cochlear implantation outcomes. WM is essential for linguistic skills such as recognizing words or understanding sentences (Harden, 2011; Henshaw & Ferguson, 2013a; Kronenberger, Pisoni, Henning, Colson, & Hazzard, 2011; Peterson et al., 2010). WM model (Baddeley, Gathercole, & Papagno, 1998; Baddeley, 2010) have suggested the role of phonological loop component of WM in learning language, to be specific, in speech perception (phonological store) and speech production (articulatory control process). Its other three components: (i) The central executive system controls attentional processes rather than memory storage. (ii) Visuo-spatial sketchpad temporarily stores and processes visuo-spatial information. (iii) Episodic buffer, a 'back up' store, links long-term memory and the subcomponents of WM. Furthermore, phonological loop and visuo-spatial sketchpad components of WM are typically associated with verbal and non-verbal WM respectively (Rothmayr et al., 2007). This concept describes WM as a capacity limited short duration store in which computations are performed in service of task goals. Caplan et al. have further discussed Baddeley's original concept in a book named "Variation in Working Memory" and have suggested that language comprehension requires WM on all levels of language - segmental and lexical phonological representations, morphology, intonational structure, syntax and discourse (Caplan, Waters, & Dede, 2007).

Hearing loss is known to affect language development. Hearing loss is also positively correlated with depression and functional decline (Erlich, 2012; Knudsen, Oberg, Nielsen, Naylor, & Kramer, 2010; Weber, 2013; Yueh et al., 2003). Although most researchers concluded that people with severe to profound hearing loss would mostly rely on visually-based language; the technological advancement and enhanced acquisition of language skills by early exposure to auditory signal have proved them wrong. Now such individuals have diversified linguistic trajectories. The majority of hard of hearing children have delayed developmental trajectories, excluding a small proportion of children who are raised in language rich learning-environments. In addition, children's linguistics skills strongly predict the theory of mind and literacy development skills (Lederberg, Schick, & Spencer, 2013; Lederberg & Spencer, 2009).

2.4. Previous Computerized Post Cochlear Implantation Research

Several studies show that reasoning, speech comprehension in noise and learning tasks require cognitive skills. Furthermore, the complex working memory capacity predicts speech comprehension and aggressive signal processing. Previous studies have also shown a significant demand for designing aural intervention devices, which are learning friendly (Arehart, Souza, Baca, & Kates, 2013; Lunner, Rudner, & Rönnberg, 2009; Rönnberg, Rudner, Foo, & Lunner, 2008; Rönnberg, Rudner, Lunner, & Zekveld, 2010; Rönnberg, Rudner, & Lunner, 2011; Rönnberg, Danielsson, et al., 2011; Rudner, Rönnberg, & Lunner, 2011).

2.4.1. Effects of auditory training on cognitive and linguistic skills of normal and hard of hearing individuals. Auditory training or formal listening activities has been applied to various groups of clinical populations such as the elderly with cognitive deficit, hearing aid users, and cochlear implant users. Training sessions involve either “bottom up” or “top down” approaches. In “bottom up” approach, the auditory signal (building blocks of speech messages) is processed with intent to improve overall speech comprehension. In “top down” approach, the meaningful sentences as training stimuli are presented in background noise. This approach employs trainee’s context and language knowledge to fill up the acoustic gap in the message. Noise level is adjusted depending upon whether the trainee correctly understood the sentence or not. Although enhanced speech recognition has been observed after auditory training in hearing aid users, further research is still warranted before making an evidence-based recommendation for auditory training as a potential aural rehabilitation tool (Bronus, El Refaie, & Pryce, 2011; Miranda, Gil, & Iório, 2008; Wolfe, 2011).

Dr. Qian-Je Fu and his team have shown augmented speech understanding after computerized auditory training in cochlear implant users. One unblinded intervention study (N = 10) assessed the speech recognition of 7 pre-lingual and 3 post-lingual adult cochlear implant users aged 25 to 60 years, using ‘within-subject’ control procedure, after 4 weeks or longer period of moderate auditory training (Fu, Galvin, Wang, & Nogaki, 2005). Results suggested significant improvements in the subjects’ vowel and consonant scores after training. However, there was significant subject variability in improvement across amount, rate and time course. Furthermore, Oba et al. (Oba, Fu, & Galvin, 2011) conducted another unblinded intervention study to improve speech understanding in noise by digit-in-noise training in familiar stimuli with an easy listening task for 4 weeks interval. They used a ‘within-subject’ control procedure in 10 post-lingual adult cochlear implant users. Speech understanding was assessed at baseline (first assessment), after 2 and 4 weeks of intervals, and finally one month after the training period for follow-up. Results suggested improved speech recognition in babble (which was trained) and in steady noise (which was not trained). Further research with a larger sample size is needed to look at the effects of specific training task and to identify potential candidates for computer based auditory training. In addition, a recently patented cochlear implant device presents a continuous noise-based tone sensitivity training or language training for a period of 6 weeks and thereby, it can possibly augment the efficacy (Etienne De, Merzenich, & Zhou, 2012).

Many cochlear implant users can not enjoy music due to the degraded and artificial sound generated by implant. Such patients may benefit from targeted auditory training using complex spectral and temporal patterns (Faulkner & Pisoni, 2013). In conclusion, auditory training can possibly improve speech comprehension skills of cochlear implant users. However, limited evidence exists regarding the contribution of cognitive skills to the main effects of auditory training. It is the time to think beyond the box and develop innovative solutions for betterment of health.

2.4.2. Effects of cognitive training on cognitive and linguistic skills of normal and hearing impaired individuals. There has been an old notion that the brain and nerve pathways are fixed, ended and immutable. Decades of research on neuroplasticity has now shown the brain's ability to change in structure (anatomy) or functional organization (physiology) and even make people faster, smarter and stronger. Across a lifespan, there are waves with different strength of change. No matter how old the person is, his or her brain can change (Chen et al., 2014). Neuroplasticity is "activity or experience-dependent" phenomenon that occurs in normal, day-to-day life. It can result from brain-computer interface devices, CT, healthy nutrition, physical exercise, multi-vitamin and omega-3 fatty acid supplements, non-invasive brain stimulation, virtual learning, as well as by drugs and surgical procedures such as deep brain stimulation and engineered neural tissue construct replacements. Often clinicians describe aggressive lifestyle modification via diet, exercise and behavioral measures as the "miracle" or "wonder" drug for diabetes, hypertension, obesity, varicose veins and many more chronic health conditions. Individual abilities are shaped by environmental experiences. In the real world, we notice that doctors and musicians have attained specific-set of cognitive skills, only after selective training in a repetitive, rigorous environment with self or mentored motivation. On the synaptic level, this means repetitively used synapses have stronger connections and vice versa. The strengthening of *existing* synaptic connections between neurons, refers to “neurons that fire together, wire together” or “neurons that fire apart, wire apart”, is one of the chief justification of neuroplasticity in adults. Whereas, the synaptic pruning refers to the elimination of synapses, and generally is a phenomenon that occurs in normal development, but much less so in adulthood. The exact molecular mechanism of this “activity-dependent” change needs more evidence-based research.

A community of researchers argue in support of neurogenesis, formation of new neurons in the hippocampus, olfactory bulb and cerebellum (Ponti, Peretto, & Bonfanti, 2008), while others say neuroplasticity is primarily due to the active experience-dependent ‘re-wiring’ of brain connections in multiple inter-related neural tissues. The activity in distant ipsilateral tissue and the contralateral hemisphere also contribute towards a functional change (Chen et al., 2014). Another topic for hot debate is whether the number of neurons or size of a particular brain tissue matters most for a functional change in brain.

Three main factors may play a major role in auditory neuroplasticity. Namely, 1)Duration of auditory deprivation; 2) Compensation with the use of sensory devices such as traditional hearing amplification devices, implantable hearing devices and so forth; 3) Learners experiences, with the help of auditory training or CT or language rich environment (Olson et al., 2010; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Hence, adults with cochlear implant may be able to demonstrate neuroplastic change after training. CT depends upon three main factors to deliver a meaningful functional change: intensity, repetition and specificity or suitability of training tasks to person’s abilities.

A small number of research studies have assessed the effects of CT on auditory perception and speech comprehension in cochlear implant users, evidence is limited though. A pilot intervention study (Kronenberger et al., 2011) evaluated the feasibility and efficacy of computerized WM training in pediatric cochlear implant users (N = 9) for 5 weeks. Their report indicated significant improvement in verbal and nonverbal WM (about one-half *SD* or more over pre-training values), parent-reported WM behavior, and sentence-repetition skills (0.69 *SD* over the pre-training value) outcome measures. Based on Kronenberger’ work, researchers from the University of Nottingham are currently conducting a study to determine the effects of WM on cognition, speech perception and self-reported auditory disabilities in hearing aid users aged between 55 and 74 years, by the top-down processing approach of the input signal (Henshaw & Ferguson, 2013b). Researchers from the Speech Processing and Auditory Perception laboratory in the USA, who previously recommended auditory training in pediatric cochlear implant users, assessed the effects of visual digit span (VDS) training on auditory performance of 10 adult cochlear implant users (Oba, Galvin, & Fu, 2013). In VDS training tasks, cochlear implant users are asked recall visually presented sequences of digits for 4 weeks (10 hours). The mean VDS scores significantly improved from 6.72 at baseline to 7.77 and 7.97 after 5 and 10 hours of training respectively, $F_{(3,27)} = 9.73$, $p < .001$. The vocal emotion recognition and melodic contour identification also showed 3.45 and 4.35 post training mean percentage improvement points respectively. However, no significant effect was seen for auditory digit span, hearing in noise test, digits recognized in steady noise and phoneme recognition in quite (*p* - values ranged from .07 to .88). Digit span training alone should not be considered equitable to CT in adult cochlear implant users and moreover, prior CT research insists on <u>longer training sessions</u>. Nevertheless, the above studies suggest CT can improve neurosurgical outcomes for diverse sub-groups of patients.

The data from cochlear implant recipients clearly supports the existence of a “sensitive period” in the development of auditory system. The age at cochlear implantation contributes to the known variation in cochlear implant outcome measures. The normal development is not possible if auditory deprivation lasts beyond the first few years of life. The exact timing of this period may be debated. Different measures suggest permanent deficits if a cochlear implant is not in place by 12-18 months in congenitally deaf children, whereas others showing no deficits until after 3 years of age (Sharma, Nash, & Dorman, 2009). After 7 years of age, speech integration and comprehension becomes very difficult to change (Lazard et al., 2012). For those who are eligible for cochlear implantation, an early surgery is preferred because early sound exposure can create a havoc and long-lasting impact on auditory, cognitive and linguistic outcome measures. Beyond this “critical period”, the existence of auditory neuroplasticity is controversial, although there are number of research studies supporting activity-dependent brain plasticity in older animals and humans (Etienne De et al., 2012). Adults who receive cochlear implants show greater outcome variability than children. The majority of adult cochlear implant recipients, even those pre-lingually deafened, show significant improvements in language abilities, but many do not (Peterson et al., 2010; Teoh et al., 2004a; Waltzman, 2002). Despite different types of available cochlear implants, the overall performance is relatively similar (Teoh et al., 2004a). In order to improve the real world adaptation of new cochlear implant users, family support, and linguistic and social experiences are indispensable. Furthermore, the factors accounting for the unexplained variance can possibly increment the benefits of existing aural interventions. A substantial amount of research suggests lowering of some executive function measures that are highly related to language abilities in cochlear implant and deaf children, compared from normal hearing children. Lowered executive functions obscure the concept learning, phonological reading, and written work. Hence, hard of hearing population suffers from a double-edged sword, firstly, direct effects of hearing loss and secondly, impending reduction of language related neuropsychological functions.

Research shows the benefits of auditory and CT in pediatric cochlear implant users, it should not be inferred to initiate simultaneous auditory and cognitive remediation in all the pediatric cochlear implant users though (Ingvalson & Wong, 2013). *Auditory and cognitive remediation of individual pediatric cochlear implant users should be tailored accordingly to their existing auditory and cognitive processing abilities.* Preliminary evidence suggests that the patients with higher auditory processing abilities may show greater speech and language outcome with CT, but the patients with poor auditory processing skills may not. Auditory training should be prioritized in the latter. More RCTs with a large sample size are needed to make evidence-based recommendations for all cochlear implant recipients regarding auditory and/or cognitive training.

2.5. Finding an Innovative Cost-Effective Solution

With the invention of innovative hearing aids and cochlear implants, people who are hard of hearing can now participate in several activities that were previously inaccessible to them. But, the technology is inadequate and rapidly evolving. Therefore, considering the currently available technology as a “cure-all” services would impose a significant public health risk (Erlich, 2012). Cost-effective therapy to optimize the success of the cochlear implant aural rehabilitation should be a high priority, given the high cost of rehabilitation and the negative effects of poor speech comprehension on individuals’ physical, psychological health and productivity. There are currently five major clinical research issues regarding cochlear implants. Namely, (1) Individual differences in outcome and benefit, (2) Speech understanding in noise,

(3) music perception, (4) neuroplasticity and perceptual learning, and (5) binaural hearing (Faulkner & Pisoni, 2013).

The present study focused on innovative rehabilitation of adult cochlear implant users using a complementary CT program. Here, word “complementary” refers to using standard therapy together with CogniFit-based CT. Rehabilitation is a lifelong process and extremely important to empower implant users. CT is an umbrella term that has been often mislabeled or conflated with other therapies (N. Gates & Valenzuela, 2010). In order to distinguish CT from other similar methods of rehabilitation, Gates et al. have created an operational definition of CT (described in “Definition of Terms” section). There are several commercial CT programs that claim enhancement of cognitive function. For example, Brain age, Brainware safari, Cogmed working memory training, CogniFit, Drivefit, Earobics, Fastforward, fitbrains.com, happy-neuron.com, InSight with cortex, lumosity.com, stresseraser, and so forth.

Cognitive or brain training is a very vague term. Activities like learning a new language, strength or endurance training, or eating an improved diet may enhance cognition of the user and confound the study results. Fernandez and Goldberg reviewed a number of these brain training products (Fernandez & Goldberg, 2009). They discussed each product’s clinical validation status with independent assessment and cost. Furthermore, they compared whether these products target specific brain function or area, present novel challenges, and last but not least, the program’s integration in users’ daily life. They have found very limited to low clinical validation in the programs targeting overall brain maintenance. However, computerized CT is rapidly advancing and clinical validation is ongoing. In the present study, we used CogniFit, a computer-based CT program that has been shown in several published, peer-reviewed studies to improve cognitive skills (e.g., attention, WM) in both healthy participants and people with varied disorders (Peretz et al., 2011). The above mentioned definition of CT is compatible with the trial intervention. CogniFit is the software embedded with comprehensive assessment of more than 18 cognitive skills providing personalized CT experiences for users. In this study, we compared the speech comprehension outcome measure of cochlear implant users after 10 weeks of standard therapy with complementary computer-based CT versus standard therapy alone, regardless of gender, occupation, socio-economic status, etiology, duration and type of implant. CogniFit can be easily delivered through any internet-connected device that supports Adobe Flash, and the rehabilitative costs for running CogniFit are almost negligible. The cost for training basic cognitive functions online via CogniFit is free; however, the outlay for participant's time and commitment, as well as the cost for a computer and electricity, and for follow up visits to clinician or therapist should be noted.

Cochlear implant users formed an ideal group to investigate the effects of CT on cognition, hearing abilities and functional loss associated with hearing impairment. Furthermore, previous research had reported no side effect with the CogniFit program and even shown significant improvements in cognitive skills, error-related negativity in diverse subject groups (Haimov, Hanuka, & Horowitz, 2008; Horowitz-Kraus & Breznitz, 2009; Peretz et al., 2011; Shatil, Metzer, Horvitz, & Miller, 2010). The effects of computerized CT in adult cochlear implant users have not been explored.

For these potential benefits, our study has been investigating the possibility of CogniFit to improve cochlear implant users' speech comprehension in background noise. As noted earlier, language skills are localized functions and our prime interest is to ascertain whether the effects of generalized cognitive training (training of distributed functions) could be transferred to a more local function. The ability to deliver effective rehabilitation over the internet represents an excellent way to provide money-saving services for people who do not otherwise receive them at all, or only rarely. The improved speech comprehension could have significant benefits in terms of social participation, reduction in psychiatric diseases like depression, and increased productivity.

2.6. Designing a Research Study

In health research, there are two distinct types of research methods: qualitative and quantitative research. Qualitative research methods provide good evidence to determine human behavior and the reasons that govern such behavior. We may test knowledge, perception, or other behavioral domains after testing intervention; however, the results are usually very weak to make a representative and generalizable conclusion. On the contrary, quantitative study design, the systematic empirical investigation of data in numeric form, comprise of observational, semi-experimental and experimental types (Hackshaw, 2009). Study design selection depends upon the research questions, hypotheses, outcome measures, and expected treatment effects and/ or natural variations.

2.6.1. Observational study. Importance of anecdotal evidence and observational studies should not be undermined. In observational study, participants are not intentionally involved in intervention in the way individuals live their lives, or how they are treated (Hackshaw, 2009). It can be sub-divided into three groups. Namely,

a) Cross-sectional: It involves data collection from a population or representative sample at one specific point in time. Previous research using this approach for testing the CogniFit training program showed the improvement (albeit small effect) in WM, attention in the healthy elderly volunteers (Peretz et al., 2011). The duration of training is 3 months and CogniFit has never been tested in cochlear implant users. Hence, one snap-shot analysis of CogniFit-based CT is not possible.

b) Case-control study: It is widely used in epidemiology and involves observation of two groups (the ‘‘cases’’, patient with a particular disease/condition and the “controls”, patient without that particular disease/condition) to determine their exposure and outcomes status. A case-control study is usually quicker and relatively inexpensive but the level of evidence is small. The CogniFit intervention has not been exposed to adult cochlear implant users in the past. Hence, being a novel study, we only have option of a prospective cohort or randomized controlled trial (RCT).

c) Cohort study: It is a longitudinal study, where a group of people with a specific exposure is compared to another group drawn from a same population or another cohort with people who are not exposed to the substance under investigation within a defined time period. Here, cohort could be cochlear implant users with exposure to CT within a defined period. Pilot cohort studies may be helpful. However, it would have been time and resource consuming. RCTs are still a superior methodology because they limit the potential of bias by random allocation of participants into intervention or control group and thereby, limit the confounding variables.

In general, observational studies can be useful in evaluating treatment with large effects. There is uncertainty over the actual size of the effect of CogniFit in cochlear implant users and the results can be difficult to interpret especially if there is small or moderate effect.

2.6.2. Semi-experimental study. Trials with historical control: Research shows some evidence of computerized auditory training in cochlear implant users in the past (Fu et al., 2005; Oba et al., 2011). We could have evaluated this effect of auditory training in opposition to a group with cochlear implant users who currently use CogniFit intervention. The plausible limitations with such a design were time, that is, differences in calendar years. On the other hand, RCT's participants are prospectively followed up so time factor can be controlled.

2.6.3. Experimental trial. To test an intervention, the researcher should work on clinical trials. The World Health Organization (Hackshaw, 2009) defined clinical trial as "Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (p.3). Most scientific organizations consider systematic review of all relevant RCT and/ or single properly designed RCT with good internal validity as 'level I' or 'level II' evidence. Experimental trial are broadly defined into four types (phase I, II, III and IV).

a) Phase I clinical trial – First in human studies. Primary aim is to test acceptable level of safety, and establish biological and pharmaceutical effects. Previous intervention based studies were done in healthy elderly, dyslexics, multiple sclerosis patients, and chronic insomnia patients (Horowitz-Kraus & Breznitz, 2009; Peretz et al., 2011; Shatil et al., 2010). No serious adverse events have been reported so far.

b) Phase II clinical trial – Primarily to test the efficacy of trial intervention. This trial is relatively quick, without spending too many resources (participants, time and money) on something that may eventually not work. The phase definitions are not a natural fit for software-based interventions since they were developed for drug trials. Phase II trial is the closest approximation to our study's research question.

c) Phase III clinical trial – If results from phase II studies are convincing, then, further research will be needed to make a reliable conclusion on whether new intervention is a better rehabilitative option.

2.7. Designing a Phase II Clinical Trial

a) Single arm study – Here, improvement is measured as a change from baseline. It is a simple study design. There are several disadvantages. One disadvantage is a positive effect size with treatment can be argued due to treatment or no treatment (placebo effect) or some other factors such as naturally occurring improvement.

b) *Randomized phase II trial with control arm* - Active treatment is compared with standard treatment or placebo.

For computerized online CT based intervention, it is difficult to create an identical placebo group. Moreover, it would be unethical to provide no treatment to cochlear implant user when there is an available existing standard therapy. In this study, we compared standard therapy + CT with standard treatment alone through a 2×2 cross-over design. The benefit of a cross-over trial is that the 'immediate treatment' group participants can be compared with the 'delayed treatment' group. The first group received complementary training earlier. How well did it work relative to existing treatment? This helped us to determine whether complementary CT was better than standard treatment alone. After completion of CT in the 'immediate treatment' group, follow-up evaluations were done to assess whether any gains had been retained. In the 'delayed treatment' group, participants did not receive CT for 1-10 weeks; this determined the pre-existing trend with standard therapy only (i.e., whether the treatment effect was due to some other factor or simply a function of random variation that was present before the intervention was administered). In addition, each participant both in the 'immediate treatment' or the 'delayed treatment' group served as his or her own control.

3. Objectives and Hypotheses of the Study

This thesis is based on a clinical trial entitled: Evaluating The Short-term Effects of Home-based Computerized Multi-domain Cognitive Training in Adult Cochlear Implant Users: A Prospective Randomized Intervention Study

a) Responsible party: Associate Professor Aaron Newman, Dalhousie University, Halifax, Nova Scotia, Canada
b) Sub-Investigator: Dr Amit Bansal, Family Physician and Master of Philosophy in International Community Health Candidate at the University of Oslo, Norway
c) Collaborators: CogniFit Limited, New York, USA and the University of Oslo, Norway
d) Department of Institution where the research was carried out: The study was conducted at the NeuroCognitive Imaging Laboratory in Halifax, Canada. However, adult cochlear implant users (the study participants) were given the opportunity to play the brain training games remotely, from their own personal computers.
e) Outcome Measures: Change in AzBio Sentence Test Score in Noise from the baseline (primary outcome measure). Change in CANTABeclipse neuropsychological test and Speech, Spatial and Qualities of Hearing Scale from the baseline (secondary outcome measures). Refer to methodology section for individual test details.

3.1. Main Objective

To determine the effects of home-based computerized multi-domain cognitive training with standard therapy on adult cochlear implant users' speech comprehension in noise.

3.2. Specific Objectives

i. To determine whether there is an improvement in self-reported auditory abilities in cochlear implant users after using CogniFit based cognitive training.
ii. To see whether there is an effect of cognitive training in adult cochlear implant users' basic cognitive functions.
iii. To evaluate a newer complementary rehabilitative tool for speech comprehension in cochlear implant users and compare its accuracy with a 'delayed treatment' group.

3.3. Research Question

Does multi-domain cognitive training lead to improvement of adult cochlear implant users' speech comprehension in background noise?

3.4. Hypotheses

1. Cochlear implant users will improve on the AzBio Sentence test for speech comprehension in background noise, after 10 weeks of multi-domain cognitive training, but not after the 10 week periods during which no training occurred.
2. Cochlear implant users will improve on the Spatial Speech Qualities questionnaire for self-reported auditory ability after 10 weeks of multi-domain cognitive training, but not after the 10 week periods during which no training occurred.
3. Cochlear implant users aged 19 or above will show an overall increased level of attention, working memory, and other basic cognitive functions after 10 weeks of multi-domain cognitive training but not after the 10 week periods during which no training occurred.
4. At week 20 of study, the outcome measure scores for cochlear implant users in the immediate training group will be maintained at week 10 level and outcome measure scores in the delayed training group will be improved from their baseline and week 10 levels.
5. After 10 weeks of study, cochlear implant users in immediate training group will perform better on primary and secondary outcome measures than in the delayed treatment group.

3.5. Expected Outcomes

Potential benefits to cochlear implant users’ - Improvement of speech comprehension, cognitive skills and reduced auditory disability. The administration of physical activity and FANTASTIC lifestyle checklist questionnaires (Canadian Forces Personal Support Agency, 2005; Canadian Society for Exercise Physiology, 2010; Kason & Ylanko, 1984) may raise focus on the self insight that “how physically active am I?” and “Am I eating a balanced diet?”. In fact, this may initiate behavioral changes within the cochlear implant users. This is something positive; a questionnaire could possibly serve an intervention in itself and later a positive behavior change may reduce incidence and prevalence of obesity among adult cochlear implant users living in Canada.

Benefits to science/society

- Availability of demographic profile of cochlear implant users
- Generalization of new knowledge
- Further insight on neuroplasticity in cochlear implant users
- Newer cost effective complimentary rehabilitative therapy
- Positive results can be used to underpin the justification for a larger trial.

Thereby, the new information on a brain training program can contribute to the development of the evidence-based guidelines for the rehabilitation of cochlear implant users in Canada and later worldwide. After aural rehabilitation, though many cochlear implant users feel independent due to improved hearing, there is still significant individual variation in functional outcome measures, such as speech comprehension and auditory disability. Improving cochlear implant outcomes will provide cochlear implant users the opportunity to be independent and empowered. On the other hand, negative results can be useful information. It means that valuable subjects and resources have not been wasted by having a larger study.

4. Methodology

4.1. Project Methodology

A preliminary prospective, single-center, unblinded, randomized controlled Phase II cross-over superiority-trial with multiple-stage sampling and two arms comparing standard therapy with co-administration of CogniFit-based complementary cognitive training and standard therapy.

Note: CogniFit Limited based cognitive training does not constitute a therapy for language impairment. Training tasks are “complementary” and specifically designed to enhance cognitive functions together with standard therapy. This study attempted to recognize the association between cochlear implant users’ auditory perception and cognitive skills such as attention, cognitive control, executive function, inhibition, learning and memory.

4.1.1. Setting. A home based intervention study conducted through the NeuroCognitive Imaging Laboratory, Dalhousie University, Nova Scotia, Canada.

4.1.2. Screening phase. This section includes description of eligible participants, recruitment and screening process.

4.1.2.1. Advertisement. After obtaining local research ethics board approval, recruitment process was started in January, 2013 via the following channels:

- Audiologists and otologists at the Cochlear Implant Center at VG site in Halifax, Canada
- Internet Ads: Kijiji Halifax, Craiglist Inc., Linking Boomers Halifax
- Poster display at local community sites (Atlantic Provinces Special Education Authority - APSEA, Nova Scotia Community Colleges, Nova Scotia Hearing and Speech Centre, Public Libraries, Restaurants, and Universities)
- Prior research study volunteers
- Private audiology clinics (Hearing Institute Atlantic, Beltone Hearing Aids center etc.)
- National or regional societies such as Society of Deaf and Hard of Hearing Nova Scotians (SDHHNS), Canadian Hard of Hearing Association (CHHA), and Deafness Advocacy Association Nova Scotia (DAANS)

4.1.2.2. Screening. All the volunteers were given necessary information during pre-screening conversations and subsequently, if eligible, written informed consents were obtained. Next, volunteer underwent an initial evaluation consisting of questionnaires. The questionnaires contained the following information about cochlear implant users’ background, contact information, demographics, mini mental state examination, near and color vision testing (“Vision Pocketcard 2nd ed,” 2011). The mini-mental state examination (MMSE) is a brief 30-point questionnaire that is used to assess brain-functions. It is also used to screen brain impairment and to estimate severity brain impairment. It takes about 10 minutes and includes simple questions and tasks. For example, the time and place of the test, repeating list of words, arithmetic such as the counting down from one hundred by sevens, language use and basic motor skills. Color vision test consists of colored dots arranged on a card board so that person with normal color vision can read a number ‘hidden’ in the pattern of the dots (Ginsberg, 2005). Defective color vision may be inherited as a sex-linked recessive trait, or optic nerve disorders, or occipito-temporal disease. Near vision testing was also conducted because of the peculiar nature of trial intervention.

4.1.2.3. Participants. The cochlear implant users who met the below mentioned criteria were invited to join this study.

Inclusion Criteria

- Adult cochlear implant users aged 19 or above
- Access to an internet-connect device that supports flash and basic computer skills
- Medically stable patients

Exclusion criteria

- Patients with epilepsy, severe visual and cognitive difficulties, chronic fatigue syndrome, and serious co-morbid conditions which could be exacerbated by the computer training games were excluded for safety reasons.
- Patients who were unlikely to adhere to the intervention due to dementia, Parkinson’s disease, Parkinson-plus syndrome, movement disorders or disability that could impair the person's ability to perform the training (e.g., problems with attention, alertness, or learning disorders).
- Participants who did not speak English (since CogniFit’s instructions are only in English) or unable to give consent.

4.1.3. Randomization and Blinding. Here, we discuss the available blinding, randomization techniques, and the reasons for choosing treatment order randomization and averting blinding.

Randomization and allocation concealment: During recruitment procedure in the real world, clinical investigators find it difficult to maintain impartiality. Due to the small pool of cochlear implant users in the Nova Scotia and the other Maritime provinces, there was a general issue with recruitment. In addition, assignment of participants into two treatment groups could have lead to an allocation bias. Different randomization methods were available to deal with the issues of allocation, selection bias and confounding variables. Namely,

- Simple randomization: Using random number list, it is possible to get a noticeable imbalance by chance alone when trial size is small.
- Blocked randomization: Minimizes imbalance in treatment group sizes. For two treatments, block size is often four or six, sometimes greater. Each treatment should appear at least twice in each block. A limitation of the random permuted blocks is that the allocation of last subject can be predicted if the previous allocations are known. To solve this problem, mixture of block sizes can be used. *In cross-over trial, ordering of the treatments needs to be randomized, so that a similar proportion of subjects receive 'A' or 'B' treatment first. This is achieved by randomly allocating subjects to receive either 'A' followed by 'B' or 'B' followed by 'A'* (Hackshaw, 2009). So in the present study, subjects had been allocated to receive either 'immediate treatment' first followed by 'delayed treatment' or 'delayed treatment' first followed by 'immediate treatment'.
- Stratified randomization: It could be useful; however, it is difficult to categorize some of the important prognostic factors. For example, duration of auditory deprivation, and age since cochlear implantation.

Blinding: The term blinding refers to keeping trial participants, investigators (usually health-care providers), or assessors (those collecting outcome data) unaware of the assigned intervention, thereby minimizing ascertainment bias. Ideally, blinding is useful to strengthen the RCT design, however, the unblinded designs should not be deemed inferior. In an internet based intervention, firstly, it is difficult to create identical computer games that do not contribute any cognitive skills. Secondly, the non-disclosure of the intervention name in 'delayed treatment' control group was also considered to be difficult. Lastly, there are always ethical issues associated when half of the participants are receiving complementary treatment earlier and they are not allowed to make an informed selection regarding the order of treatment. Blinding is useful to minimize ascertainment bias and placebo effect in the 'immediate treatment' group participants who first receive CogniFit. On the other hand, the 'delayed treatment' group participants may feel deprived or relieved during this time period. Further studies would be beneficial that involve a double or triple blinding and placebo control computer games with English instruction intending to conceal the intervention group identity. In a previous study, effects of CT was compared with computer games that are not designed for cognitive enhancement (placebo control) in healthy elderly individuals and results indicated significant, albeit small, improvement in CT group's visuospatial WM, focused attention and visuospatial learning (Peretz et al., 2011). The placebo computer games were in Hebrew. English conversion would have been time and resource consuming. Therefore, we did not include a placebo control group; rather we compared cochlear implant users receiving complementary CT with those who do not.

4.1.4. Clinical and demographical characteristics of the participants. The clinical and demographical characteristics of cochlear implant users are summarized in Table 1. The trial consisted of 12 adult cochlear implant users (7 males and 5 females) with a mean age of 59 years (Interquartile range: 52.50 - 64.25 years). They belonged to middle age group with range from 47 years to 71 years. Most patients had sensorineural or mixed hearing loss. All volunteers had one cochlear implant and reported no adverse effect related to the present study. In addition, all participants had no previous CT and/or gaming experience. 8 participants spent substantial period (> 9 years) with profound hearing loss without a cochlear implant or adequately working hearing aid. 1 cochlear implant user from both the immediate treatment (user 002) and delayed treatment (user 011) groups dropped out of the study after first assessment due to relocation and worsened general health condition respectively. Their data were excluded from the linear mixed effect analyses. Furthermore, we had missing data regarding user 010's third assessment, which was handled by using maximum likelihood estimation in mixed model analyses.

As noted above, cochlear implant users had been recruited from several channels. Figure 2 describes summary of enrollment procedure. The three Maritime provinces, New Brunswick, Nova Scotia and Prince Edward Island span across 132,416 km^2 (Statistics Canada, 2012). Distance and time-commitment were the main reasons given by patients who did not intend to participate in this clinical trial. 5 participants lived within a driving distance of 50 km from Halifax, Nova Scotia, Canada, and other 7 participants came over a distance of 50 km for lab visits (up to 270 km one-way).

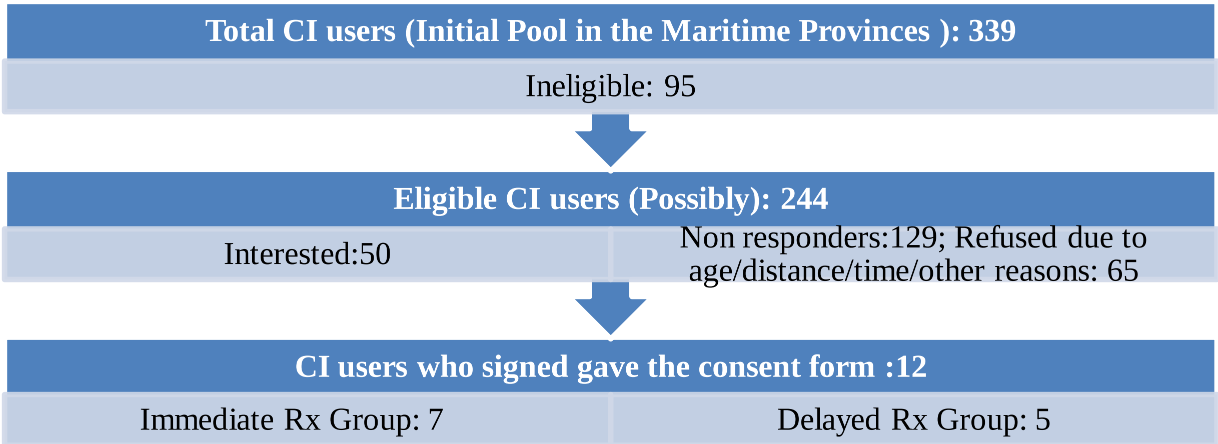


Figure 2: Recruitment and enrollment of adult cochlear implant users

Table 1: Clinical and demographical details of adult cochlear implant users

CI users	Aetiology	Age	Ear	DHL	DPHL	DPwoCI	Edu	Sex	Group
1.	Hereditary	60	L	60	37	24.17	12	M	Immediate
2.	Meniere's disease	62	L	40	27	26.67	16	M	Immediate
3.	Neurofibromatosis II	64	L	34	15	12.42	17	M	Delayed
4.	Perinatal ototoxic antibiotics	47	L	47	47	46.83	13	F	Immediate
5.	Hereditary/Noise-Induced HL	71	L	61	16	9.42	9	M	Delayed
6.	Hereditary	66	R	46	6	5.08	12	F	Immediate
7.	Congenital Rubella	49	R	49	21	9.08	18	F	Immediate
8.	Idiopathic	60	R	38	33	26.08	12	M	Delayed
9.	Idiopathic	51	R	16	6	3.42	16	F	Immediate
10.	Idiopathic	53	L	4	2	0.00	15	F	Immediate
11.	Noise induced SNHL	60	L	33	14	10.33	14	M	Delayed
12.	Noise-Induced SNHL	65	R	20	4	2.33	19	M	Delayed

Abbreviation legend: Age is in years, Edu - Education in years, DHL - Duration of Hearing Loss in years, DPHL - Duration of Profound Hearing Loss in years, DPwoCI - Duration of Profound hearing loss without a Cochlear Implant in years, CI ear (L/R) - Ear with cochlear implant (left/right), HL - Hearing Loss and SNHL - Sensorineural Hearing Loss.

4.1.5. Project methodology study phase. All the eligible volunteer cochlear implant users were invited for a baseline evaluation with questionnaires. Explicitly, the questionnaires used in this study include: Healthy Physical Activity Participation Questionnaire - HPAPQ (Canadian Society for Exercise Physiology, 2010), FANTASTIC Lifestyle Checklist (Canadian Forces Personal Support Agency, 2005), handedness (Oldfield, 1971), history of hearing loss (etiology, age of onset of hearing loss, duration of hearing loss, age of onset of functional deafness, duration of functional deafness), and language exposure (including sign language and lip-reading). Cochlear implant device type was not recorded, because it has not been shown to predict cochlear implant outcomes (Teoh et al., 2004a). Normal or corrected vision was confirmed with the Snellen's eye chart and near vision tests.

The FANTASTIC Lifestyle Questionnaire was chosen because of its simple five-point scale. This scale scores the users' overall lifestyle factors including activity, alcohol, diet, insight, nutrition, sleep, social engagement, stress, tobacco intake, and type of behavior. Questions which were not relevant to study aims such as career, usage of seat belts, and safe sex practices had been removed from the standard FANTASTIC Lifestyle questionnaire. The Healthy Physical Activity Participation Questionnaire - HPAPQ is another brief questionnaire that scores the following users' frequency, intensity and perceived fitness level of current over the last one week, and physical activity based upon gender. Both FANTASTIC Lifestyle and HPAPQ questionnaires rely on participants' recall of previous events that occurred during last one month and one week respectively. They are of course not an ideal method of assessment but they give us a general idea about cochlear implant users' lifestyle and physical activity at different time points.

In addition to the above questionnaires, baseline (before the start of trial), 10 week and 20 week evaluations were done by AzBio speech comprehension test in noise (Spahr et al., 2012), CANTABeclipse for Clinical Trials version 5.0 (Sahakian & Robbins, 2014), CogniFit Neuropsychological assessment (Haimov et al., 2008; Peretz et al., 2011; Shatil et al., 2010; Verghese, Mahoney, Ambrose, Wang, & Holtzer, 2010) and Speech Spatial Qualities of hearing scale questionnaire version 5.6 (Gatehouse & Noble, 2004) in both 'immediate treatment' and 'delayed treatment' groups. In order to prevent contamination of the immediate and delayed treatment groups, CogniFit's name was not disclosed to the delayed treatment group during 1-10 week of the study. The CogniFit neuropsychological assessment was not taken during 1-10 week of the study in the delayed treatment group. As well, later during the 11-20 week, cochlear implant users in the immediate treatment group were asked to refrain from CogniFit. In case, the participant did not follow these instructions, then, this could lead to contamination of groups. Although this trial excluded blinding practice, non-disclosure of the intervention name amongst ‘delayed treatment’ group was attempted.

After the baseline evaluation, *participants were randomly divided into two groups*, namely, the ‘immediate treatment’ and ‘delayed treatment’ groups. The treatments were ordered randomly, that is, allocation of subjects to either 'immediate treatment' followed by ‘delayed treatment’ first or ‘delayed treatment’ followed by 'immediate treatment' was random. The ‘immediate treatment’ group participants received CogniFit based CT and standard of care after one week of pre-assessments. Each subject received a unique username and password to access the website. Username was a new e-mail address based upon participant code number, birth date, sex and location. Any other personally identifiable information such as name, national ID number, driver’s license, occupational or contact information, and social insurance number was not used. In order to maintain online privacy, social engagement through facebook or other social networking websites were not encouraged while playing computer games. On the other hand, after initial screening, the ‘delayed treatment’ group received only standard of care for 10 weeks, after which we gave them access to the intervention. Here, standard of care includes advices and care given by the patient’s audiologist, family physician, otolaryngologist, speech-language pathologist, and other members of the healthcare team.

Cost involved in project was minimal as participants get training from home (via internet) and then, evaluation was done with questionnaires. However, funds were spent in licensing the tests and participants visit compensation ($10/visit). The participants who travel over 50 km to come for lab evaluation were reimbursed with $50/visit. The research scheme was supported by RADIANT training fellowship and Ivar Helles Legat. To make the most effective use of man power, time, and resources, the study was conducted in stages. This allowed us to determine with a relatively small sample whether there was any indication of a treatment effect.

<u>Follow up</u> – 10 week and 20 week follow up assessments were done. Participants from the ‘delayed treatment’ group eventually received the CogniFit assessment and intervention after 10 weeks of postponing. The on call assistance and technical support through email were also provided to participants. During the entire trial period, participants who were not performing the

training as often as requested had been contacted by phone or e-mail to assess their commitment and motivation. Any technical glimpse or query was resolved as soon as possible. During the trial, volunteers were requested not to participate in any additional test or other clinical trial. They were asked to inform the principal investigator about any drugs or medicines they were taking or wish to take, as well as about anything unusual that was happening to their health including any medical problems that seemed to be getting worse. If they had to see another doctor or had to go to a hospital, they were told to let the doctors know that they were in a research study. They were also asked to inform their own doctor as soon as possible for their safety.

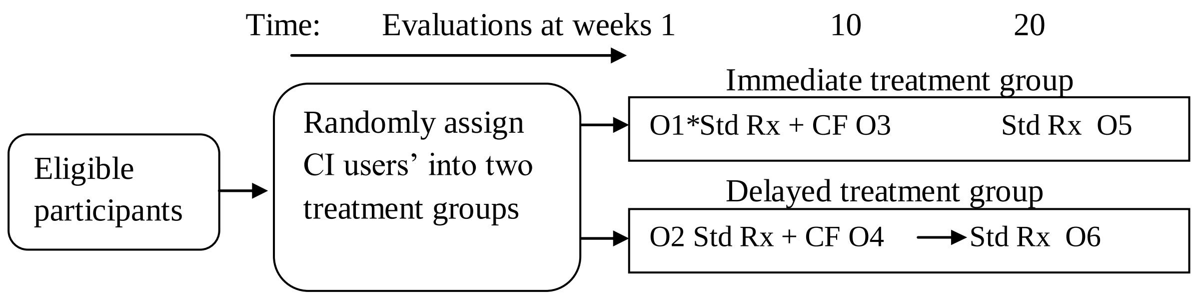


Figure 3: Study design. Note the 2-period, 2-sequence, 2-treatment crossover design. *CF, O and Std Rx represent CogniFit training, an observational measurement and standard therapy respectively. Subscripts are used to distinguish one observational measurement from another. The immediate treatment/Rx group received CogniFit and standard of care after initial screening assessment of one week duration, while the delayed treatment group participants waited for 10 weeks + 1 week pre/post assessment and afterwards, we gave them access to 10 weeks of complementary CT. Follow up assessment were conducted at weeks 10 and 20.

As described in Figure 3, the tasks performed at each visits are listed below:

- First visit at week 1
    - Screening: Participants were asked to answer the background and contact information questionnaires. In addition, sub-investigator performed mini-mental state examination and near and color vision testing.
    - Assessment O1 or O2: If eligible, volunteers were asked to answer the questionnaires on lifestyle, handedness, hearing background, language history, physical activity, and speech spatial qualities; and the tests on a computer such as tests of brain-functions and understanding of spoken sentences.

- Second visit at week 10: Assessments O3 and O4 were conducted. They were similar to assessments O1 and O2. Handedness and language history questionnaires were excluded because they were considered unlikely to change over a period of 20 weeks.
- Third visit at week 20: Assessments O5 and O6 were parallel to assessments O3 and O4.

4.1.6. Outcome Measures. Evaluations were done at recruitment, at 10 weeks (i.e., immediately after training for the immediate-training group; or immediately before training for the delayed treatment group), and at 20 weeks (i.e., 3 months after training for the initial-training group, and immediately after training for the delayed treatment group).

Evaluation included:

1. Primary Outcome Measure: Speech comprehension: Change from baseline in AzBio sentence test in noise
2. Secondary Outcome Measures
   a) Cognitive evaluation: Neuropsychological examination - Change from baseline in CANTABeclipse for clinical trials
   b) Self reported auditory ability: Change from baseline in Speech Spatial Qualities questionnaire

4.1.6.1. Primary outcome measure - AzBio speech comprehension in noise. For people with cochlear implant, Hearing in Noise Test (HINT) and AzBio sentences score are the two standardized tests which are typically used for evaluation of speech comprehension. AzBio sentence test in noise basically gives us an idea about the level of patients “speech understanding” when sentences are presented at a comfortable listening level rather than a test of mere hearing ability. It is a reliable and valid measure for the evaluation of cochlear implant users’ speech understanding ability in noise (Schafer, Pogue, & Milrany, 2012). During this task, participants were asked to repeat what was said on speakers against background noise or babble in a soundproof booth.

The AzBio Sentence Lists were created at Arizona State University, USA and the sentence materials were available on an audio CD. It was designed to be used with a commercial CD player connected with a clinical audiometer (Spahr et al., 2012). Tracks 1-15 contain sentence lists 1-15, each track has a speech channel and a noise channel. Because speech and noise were recorded on separate tracks, the clinician was able to adjust Signal to Noise Ratio

(SNR) and mixing using the audiometer. Track 16 is a white noise for sound-field calibration. Track 17 is a 1000 Hz calibration tone.

Same list number was played for all subjects in each testing sessions. Once they had heard the sentences, it was easier to get them the next time. However, if for some reasons we had to run it twice, we used a different list for the second time. Some clinics prefer to report presentation levels in dB SPL, as measured in the sound field. For this reason, track 16 could be included. The intention is to present the white noise at the same dB hearing loss as the clinician is presenting speech and to then measure the level in both.

The steps for AzBio sentences test administration:

1. Room setup: Testing required a soundproof booth with two speakers, a microphone, a chair and digital analogue mixture. A chair was placed in the centre of the room, facing away from the window. Loud speakers were placed at a distance of one meter and directly in front of the chair. They were positioned at the level of a typical listener head or ears.
2. Test procedure: Run Mackie Onyx 820i analogue mixture and MATLAB to calibrate a sound level and babble level of 70 dB and 60 dB in a soundproof booth. Finally, select the desired sentence list (track 1-15).
3. Instructions: Participant was given the following instructions from minimum speech test battery manual (Auditory Potential, 2011), “This is a test of your ability to understand speech in a noisy situation. You will hear a man or a woman reading a list of sentences in a background of noise that sounds like many people talking in a crowded room. Your task is to repeat all of the words in each sentence. Please repeat everything that you hear, even if it is only part of a word or part of the sentence. It is all right to guess. I will stop after each sentence to allow you to repeat what you heard. I will play each sentence only once” (p. 9).
4. Scoring: Record scores and calculate the percentage of correctly spoken words using printable excel or pdf score sheets (Auditory Potential, 2011). Each word was marked as correct or incorrect (incorrect was anything less than perfect - for instance, if the target word is "walked" and the subject said "walks", that was deemed incorrect).

<u>Alternative methods of audio-logical evaluations</u>: After obtaining a meticulous case history from the patient, physicians or ENT residents complete a physical examination,

systematically. Several audio-logical evaluations are useful for differentiating and monitoring of the patients with outer/middle ear, inner ear and retrocochlear pathologies. Here are examples of different audio-logical evaluations: acoustic reflex delay, audiogram, acoustic reflex, auditory steady state response, central auditory processing, electrocochleography, electornystagmography/videonystagmography, neurological auditory brainstem response, threshold auditory brainstem response, tympanogram, and otoacoustic emissions (Koike, 2006). These tests are useful for management of patients in the otology clinics. However, they are not relevant to our hypotheses and/or research questions.

4.1.6.2. Secondary Outcome Measures. Herein, we describe the secondary outcome measures. In addition, the following text also includes clarification for using them.

a) <u>CANTABeclipse for clinical trials</u> (Sahakian & Robbins, 2014) is a method of assessing the cognitive functions of a person using a battery of computerized tests, developed at the University of Cambridge. CANTAB is an abbreviation for CAmbridge Neuropsychological Test Automated Battery. It has been widely used in clinical research to accurately and effectively assess cognitive effects of a particular intervention, following over 25 years of validation and underpinning the paradigm. Besides it can be easily administered by graduate students after short instructions. This clinical trial included the following CANTAB tests. Namely, MOTor screening tasks (MOT), Spatial Working Memory tasks (SWM), Rapid Visual information Processing tasks (RVP), One Touch Stocking of Cambridge tasks (OTS), Stocking Of Cambridge tasks (SOC) and Verbal Recognition Memory tasks (VRM).

i. First the participant was asked to complete a MOtor screening Task (MOT). It provides a user-friendly introduction to the CANTABeclipse for clinical trials and gives a general idea about their sensorimotor and comprehension abilities. Here the participant was asked to touch the cross Xs in turn when they flashed pink or green (Figure 4). This test has two attention domain outcome measures: Mean Latency (i.e., delay in participant’s speed of response) and Mean Error (error in accuracy of participant’s pointing). The lower the score is, the better the participant’s sensorimotor performance is. Sometimes these two outcome measures give a counter intuitive finding due to a speed-accuracy trade-off (Bootsma, Fernandez, & Mottet, 2004).

Figure 4: A screenshot of MOtor screening Task (MOT). Participants are asked to touch the cross X when its flash color is pink or green.

ii. Spatial Working Memory Task: In the beginning, the participant was shown a number of colored boxes on the screen. Subsequently, he/she was asked to touch the boxes, find one blue token in each of boxes, and use them to fill up an empty column on the right hand side of the screen (Figure 5). The participant used a process of elimination while searching for blue tokens. The number of boxes was gradually increased until the eight box task. This test requires retention and manipulation of visuo-spatial information in WM. It measures executive functions by calculating total errors for 4 to 8 boxes (touching boxes that have been found to be empty and revisiting boxes which have already been found to contain a token) and measures strategy as well. The lower the score is, the better the participant's performance is.

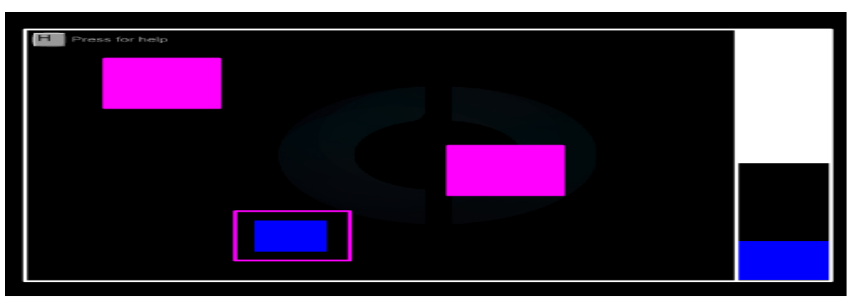


Figure 5: A screenshot of Spatial Working Memory Task. Participants were asked to touch a number of boxes, find each blue token in each of those boxes and use it to fill the empty column on the right.

iii. One Touch Stocking of Cambridge Task: This test requires executive function, spatial planning and WM abilities. In the beginning, the participant was shown a pattern of three colored balls hanging in stocking/socks at the top and bottom of the screen (See the Figure 6). There was also a row of numbered boxes along the bottom of the screen. The sub-investigator demonstrated for the participant how to use the balls in the lower display so that both the upper and lower halves of the screen have a similar pattern. Using Tower of Hanoi test, OTS measures the number of problems solved in the first choice (higher score is better), and mean choices to correct response (lower score is better).

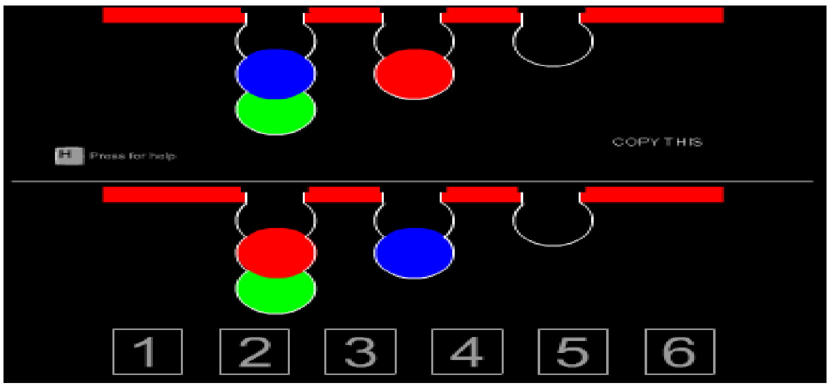


Figure 6: A screenshot of One Touch Stocking of Cambridge Task.

iv. Verbal Recognition Memory (Free Recall): It assesses visual memory and new learning by measuring immediate and free recall of verbal information. The participant was shown a list of 12 words and then asked to repeat them without any hint.

v. Stocking of Cambridge Task: It is an executive/spatial planning domain task, based on the Tower of London test (Baker et al., 1996) which gives a measure of frontal lobe function. The test begins with a screen containing three colored balls in both the upper and lower half of the screen (Figure 7). This arrangement makes a 3-D concept where these colored balls can easily be perceived as stacks of balls in stocking/socks suspended from a beam. The participant was asked to move the balls on the lower half of the screen so that both halves of the screen had a similar pattern. One ball was moved at a time by touching to the required position using participant’s planning abilities. This test measures the number of problems solved in minimum moves and mean moves for n-move problem.

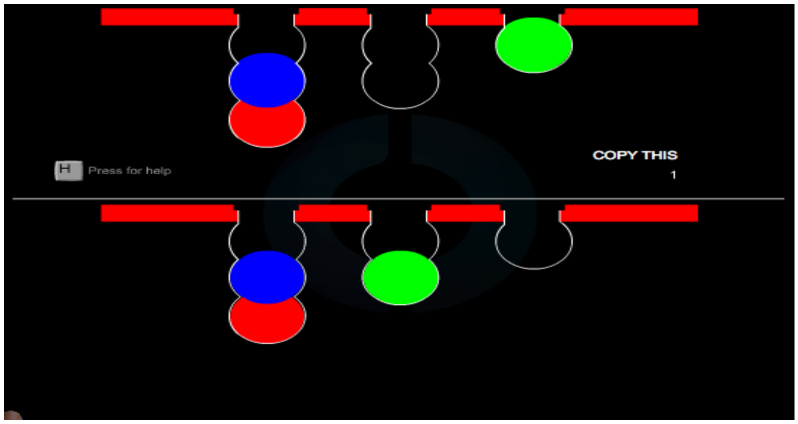


Figure 7: A screenshot of Stocking of Cambridge Task.

vi. Rapid Visual Information Processing Task: It is a sensitive measure of sustained visual attention and concentration abilities. Participants were asked to detect a target sequence of three digits (2-4-6, 3-5-7 and 4-6-8) and then respond immediately after they see the last digit (6, 7 and 8 respectively) (Figure 8). This test approximately takes 4 minutes. Outcome measure for this test is RVP A′, a ratio of the probability of hits and the probability of false alarms. Higher score is considered better. Patients with parietal cortical disease often fail to report the sensory stimuli on the side contralateral to the site of damage, the visual inattention phenomenon (Ginsberg, 2005).

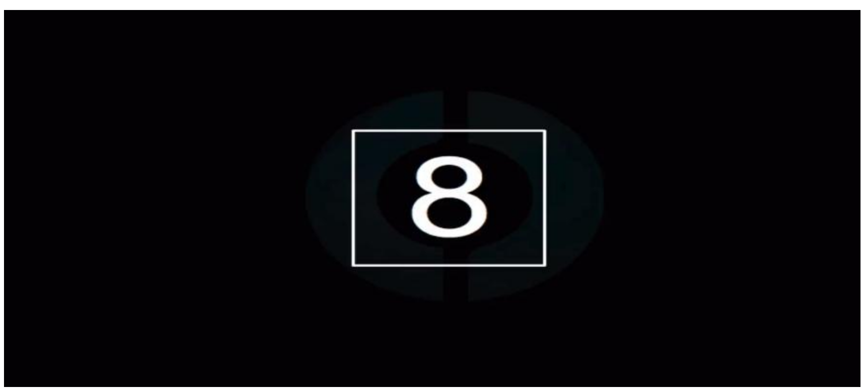


Figure 8: A screenshot of Rapid Visual Information Processing Task.

vii. Verbal Recognition Memory (Recognition phase): It is a measure of delayed recall and recognition of verbal information. The participant was shown a list of 24 words and then asked to recognize the words they have seen before from a list containing the original words and distracters (Figure 9).

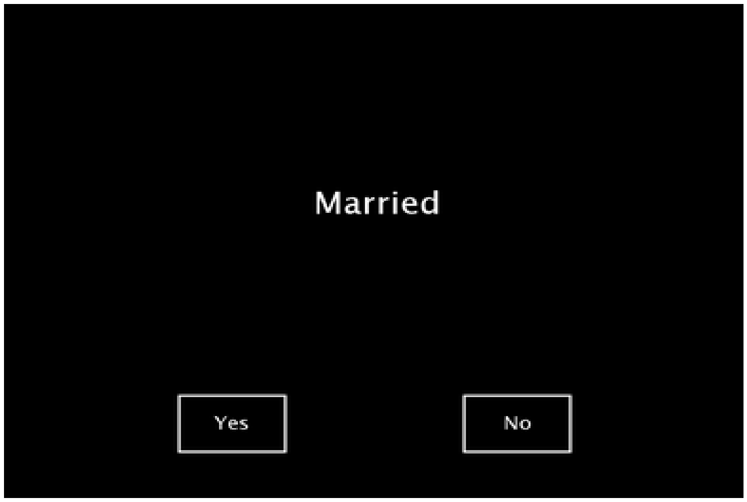


Figure 9: A screenshot of Verbal Recognition Memory (Recognition phase)

Alternative clinical research tests for evaluation of cognitive functions:

- Attention and concentration include orientation in time and place, digit span and serial sevens.
- Memory include bed-side tests such as recall of complex verbal information and geometric figures – for verbal and non-verbal anterograde episodic memory, respectively; recall of autobiographical details – for retrograde episodic memory; tests for general knowledge and vocabulary – for semantic memory.
- Higher-order executive function, personality and behavior: Verbal fluency, proverb interpretation, and cognitive estimates.
- Language: Fluency, comprehension, repetition, naming and reading/writing.
- Structural brain imaging to evaluate brain structure, and pathophysiologic conditions, if any. Modalities include computed axial tomography (CAT), magnetic resonance imaging (MRI), and positron emission tomography (PET).
- Functional brain imaging modalities to evaluate both cognitive and affective processes. Namely, Electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and positron emission tomography (PET). Apart from cost, they also have their own pros and cons with regards to invasiveness, spatial and temporal resolution.

CANTAB assesses several above mentioned measures in a standardized way. Currently there is a definite requirement of neuropsychological tests adapted to cochlear implant user's characteristics. It would have been remarkable to measure the brain activity after stipulated period of CT by functional imaging (fMRI). However, this may be a time and resource consuming endeavor for the MPhil. Furthermore, an implanted magnet and/or metallic device can interfere with MRI images by extending image and artifact (shadowing).

b) Self-reported auditory ability: Speech Spatial Qualities of Hearing scale questionnaire (SSQ) was created by Gatehouse and Noble (Gatehouse & Noble, 2004). SSQ version 5.6 was used to assess the self-reported hearing abilities across several domains such as hearing, speech in challenging contexts, and to the directional, distance and movement components of spatial hearing (Gatehouse & Noble, 2004). This questionnaire was also suggested by the local team of ENT surgeons. It includes functional, emotional and physical aspects of hearing in everyday life. The lower the score is, the more severe the perceived auditory disability will be. Thus, a subjective score may shed more insight into how cochlear implant patients are functioning in the "real-world". Three parts of SSQ includes 50 questions, on a scale of zero to ten with 14, 17 and 19 questions in Speech, Spatial and Qualities subcomponents (Gatehouse & Noble, 2004). Following is question examples for each section:

   i. Part 1 - Speech Hearing: "You are talking with other person in a quiet, carpeted lounge-room. Can you follow what the other person says?" (p.2).
   ii. Part 2 - Spatial Hearing: "You are standing on the footpath of a busy street. Can you hear right away which direction a bus or truck is coming from before you see it?" (p.6).
   iii. Part 3 - Qualities of Hearing: "Do you find it easy to recognise different people you know by the sound of each one's voice?" (p.9).

We focused on *functional and behavioral* outcomes - that is the outcomes that matter the most to patients. These include language perception, both under standard audio-logical testing conditions, and in real world environments where spatially distributed sources and background noise create unique challenges. Evaluation were done at recruitment, at 10 weeks (i.e., immediately after training for the initial-training group; or immediately before training for the delayed treatment group), and at 20 weeks (i.e., 3 months after training for the initial-training group, and immediately after training for the delayed treatment group)

4.2. Intervention

During training period, the participants were given access to general cognitive and memory training applications. CT included a set of online games designed to enhance general cognitive abilities and memory rather than auditory skills. During the entire wait-list period in the delayed treatment group, the name of the training program was not disclosed. No participant in the 'delayed treatment' group came to know about the intervention. The participants were explicitly asked to refrain from the intervention during 1-10 week wait-list period in the delayed treatment group, if they know. Likewise, the participants in the immediate treatment group were asked to refrain from using CogniFit during 11-20 weeks duration. After completion of the study, both groups are at their will to continue using the intervention. Computer-based training of basic cognitive functions via CogniFit had activities under following two headings,

a) General training applications (Whack-a-mole, mouse challenge and mahjong)

- <u>Whack-a-mole</u>: The user was required to find and hit the mole that matches the target color - the color of the mole on the sign on the left of the screen. This task trains **response time** in the first level. In the more advanced levels, this task also trains *inhibition and shifting*.
- <u>Mouse challenge</u>: The user was required to press all the cows on the screen in a particular order (from the least spotted cow to the most spotted cow), as fast and accurately as possible. The tasks became harder when the mouse start acting 'eccentric' and goes left instead of right, up instead of down and so forth. During the first level this task trains primarily **eye-hand coordination**, in the more advanced levels, when the mouse manipulation begins, it also trains *inhibition*.
- <u>Mahjong</u>: The user was required to match to tiles of the same type. The tiles could be matched only if they were not block by any other tile on top, or on side of them. During the lower levels, this task trains primarily **visual scanning**. On more advanced levels, it also trains *planning* to some degree.

b) Memory training applications (Water lilies, piece making and candy factory)

- Water lilies: The user was required to remember the sequence in which the flowers are highlighted and repeat it after the computer showed it. This task trains the **WM span**.

- Piece making: The user was required to remember three shapes that appear next to each other and chose them from four options later on. The levels varied on the distance. This task trains the **visual memory**.
- Candy factory: This task had two steps: during the first step there was a combination of candies shown to the user. After the candies disappear, the user had to remember the type and location of candies and drag with the mouse the correct type of candy to the correct place. This task trains primarily **WM** as well as **visual memory**.

Each individual session in both groups included playing specific computer games for *at least ½ hour a day, 3 days per week, throughout the 10 week interval*. Daily adherence data on the number of minutes spent in each cognitive task (e.g., general training and memory) were also recorded.

4.3. Data Collection and Management

All cochlear implant users were evaluated by the Dr Bansal, supervised by Dr Newman, as well as otolaryngologists as required. Baseline assessment for cognitive functions, auditory ability and speech comprehension was done and participants were enrolled consecutively when they met the study criteria.

A non-nominal linked information method was used for data collection. Every eligible cochlear implant user who agreed to participate was given a code number that linked their data with a list of names. The code number was based upon the sequence of recruitment. The list that links names to code numbers was stored at the NeuroCognitive Imaging Lab and only the authorised study staff had access to the list. Participants were given a unique e-mail address and password to access the CogniFit website. E-mail address was based upon participant's code number, date of birth, sex and location. In order to maintain anonymity, their real name, personal e-mail address and facebook or other personally identifying information was not be processed. However, in the "account information" section of the CogniFit website, participants had the option of entering information that could personally identify them, such as their name, personal email address, and Facebook account. We asked the participants not to provide any of this information on the website. If someone did so, this information would be available to the company, and to other users of their website. In lieu of this, we could not completely guarantee their privacy with regard to this study. After the study, it was up to the participants what information they would provide on the company's website, if they chose to continue using it.

Confidentiality and privacy was maintained at all times even during publication and announcement of results to the media (if possible). Participants were not identifiable during this entire trial or afterwards.

The rights and authorization to access CogniFit training tasks, collection and storage of data, and monitoring the adherence have been obtained. Data was stored on CogniFit's servers and copied to the NeuroCognitive Imaging lab. Any data on CogniFit's servers was coded by non-identifying ID codes only. However, it was made clear that participants would have to provide an email address to CogniFit, and this would be stored on their server along with their training and assessment data. The study-specific email addresses were created at ncilab.ca web domain. CogniFit received information on the participant's year of birth and sex. They also knew that all of these participants use cochlear implants. In addition, CogniFit collected and stored CogniFit personal coach neuropsychological assessment at baseline (for immediate treatment group only), weeks 10, and 20 (both groups). Furthermore, they recorded the time spent training at each session (start time and end time), performance on the individual training tasks (if possible). CogniFit may use the data that they collect for their own purposes, including product development, scientific publications, and marketing. This was made clear to participants in the Consent Form. It is important to note, however, that CogniFit did not receive any of the study data that we collect aside from each participant's lab assessment date, year of birth, sex, and the fact that they use a cochlear implant.

4.4. Timeline of the trial

November 2011 to May 2014. The project idea was conceived well around November, 2011. Afterwards, we started working on designing the project proposal for ethical clearance and grant application. First cochlear implant users visit was scheduled in the last week of April 2013 whereas third visit of the twelfth user occurred in February 2014.

4.5. Statistical consideration

In this clinical trial, the primary independent variable was the CT intervention (i.e., CT with standard therapy and standard therapy alone). The dependent measures were the AzBio sentence speech comprehension score in noise, CANTABeclipse for clinical trials assessment scores and speech spatial qualities assessment scores. Outcome measures had been evaluated at the beginning of trial (week 1 or baseline time point), and after 10, and 20 weeks of participation. This crossover trial gave us data for each participant both when they were on standard therapy with complementary CT and standard therapy alone. We evaluated the data for each adult cochlear implant user to compare the effect of complementary CT at weeks 10 and 20. As noted earlier, there were several factors accounting for subject variation that can influence outcomes of post aural rehabilitation, notably whether individual suffered from pre-lingual or post-lingual deafness, duration of auditory deprivation, age at implantation and type of profound hearing loss (whether meningitis, congenital, progressive etc.). Crossover trial has an ability to reduce the confounder co-variation because cochlear implant users serve as his/her own control (Hackshaw Allan, 2009). The participants in the study were drawn from three Canadian provinces: New Brunswick, Nova Scotia, and Prince Edward Island. The recruitment was done through cochlear implant centre at VG site in Halifax, Nova Scotia. Crossover trials are also known to be statistically significant and require fewer subjects than non crossover trials (Hackshaw, 2009). The expected sample size consists of 100 cochlear implant users, with 50 assigned to immediate intervention group and 50 to the ‘delayed treatment’ group. However, an interim analysis had been performed after 10 cochlear implant users have completed the training. This allowed us to determine with a relatively small sample whether there was any indication of an effect, and if so to perhaps estimate treatment effect. A similar assessment will be done at 20 participants. The benefit is that we can stop the study when clinically important differences are achieved and the power calculations indicate that the sample size is reasonable; say at sample size less than 50 participants/group or larger.

Relationships between dependent and independent variables were explored through linear mixed effect models for correlated data with random intercept, based on maximum likelihood methods, in R (version 3.0.2.) and SPSS Inc., Chicago, IL (version 20.0). Mixed models are known to be asymptomatically efficient, regardless of whether data are balanced or not. Each dependent measure was examined as a function of predictor variables including participant characteristics and cognitive measures (background, handedness, FANTASTIC lifestyle checklist, healthy physical activity participation, language, hearing background), and the experimental manipulation. Covariates such as age, duration of cochlear implant usage/hearing loss/profound hearing loss, education, physical activity, subject effect and nutritional status were adjusted and controlled in the linear mixed effect models.

In most clinical studies, there is always possibility of measuring and adjusting more variables. In this study, the potential confounding factors which were not adjusted in mixed models include aetiology of hearing loss, ethnicity, existing co-morbidities, implant generation, occupation, geographical location, side effects of previous or current treatment and the presence of functioning auditory nerve/cochlea. Ethnicity, implant generation, and the presence of functioning of auditory nerve/cochlea were not recorded. Aetiology of hearing loss and occupation showed no systematic variance between the immediate and delayed treatment groups.

The change in scores on each dependent measure from the baseline assessment was compared with two different time points (10 week, and 20 week assessments), and as a function of two treatment groups (i.e., whether or not the CogniFit intervention occurred in each time period). Furthermore, combined group analyses was also conducted wherein all the participants ($n = 10$) scores were compared immediately before vs. immediately after, the treatment, ignoring the fact that for some people these were the week 0 and 10 visits, and for others they were the week 10 and 20 visits. The raw or unstandardized regression coefficients (β), vector of fixed-effects parameters, were calculated and a significant effect of CT was concluded in the event that scores on the dependent measure improve by a statistically significant amount ($p < 0.05$) between before and after CT time points, as compared to that of before and after the 10 week no-intervention period.

4.6. Ethical and safety issues

Project has been approved by the National Committee for Research Ethics in Oslo, Norway and the Capital District Health Authority in Halifax, Canada on 28.06.2012 and 27.11.2012 respectively. This study represented a low physical risk as both the ‘immediate treatment’ and ‘delayed treatment’ groups incorporated standard of care for cochlear implant users. The risk associated with internet and computer usage was minimal. Due to the pervasiveness of internet usage and computer games, it was reasonable to expect that participants would encounter these in their daily life. CogniFit general brain training is available free and on-line to anyone who wishes to use it. Clinical validation of CogniFit games is ongoing. Several studies have been published but none conducted in cochlear implant users. Research suggests that CT may have moderate-to-large therapeutic benefit, and there have been no reports of adverse outcomes (N. J. Gates et al., 2011; N. Gates & Valenzuela, 2010). Similarly, previous research has shown *no reported side effect* with the CogniFit program (N. Gates & Valenzuela, 2010; Haimov et al., 2008; Horowitz-Kraus & Breznitz, 2009; Peretz et al., 2011; Shatil et al., 2010; Thompson et al., 2011; Verghese et al., 2010). However, as the study standard therapy with complementary CT program is experimental, there may be side effects that are not yet known. The participants were asked to inform the Principal Investigator or a member of the research team about any new symptoms they experience. There may be a few potential at-risk populations, for example, epilepsy patients. Photosensitive epilepsy is a form of epilepsy in which seizures can be triggered by visual stimuli such as flashes of light from computer screen. It is advisable to exclude the people at risk. So, in order to avoid any discomfort to participating cochlear implant users, people with epilepsy, chronic fatigue syndrome, motor or attention difficulties, visual and cognitive difficulties were excluded. Written informed consent was obtained from all the participants after providing necessary information in lay terms. Participants were at their freewill to participate, and they could withdraw at any moment during the study without stating any particular reasons.This does not cause any consequences for their further treatment.

5. Results

Below we describe results of the present study accompanied by applicable statistics. Our plan is to compare standard therapy with standard therapy + CT for adult cochlear implant users' speech comprehension in noise, cognitive functions and self-reported auditory ability. Following text is divided into four sub-sections where group level analyses for hearing and cognitive measures, between and within individual participant analyses for hearing and cognitive skills, and finally analyses across all the participants (immediately before vs. immediately after CT) are respectively presented.

5.1. Group Level Analysis for Hearing and Cognitive Outcome Measures of the Adult Cochlear Implant Users

The Tables 2 and 3 demonstrates a change in outcome measures of the immediate and delayed treatment groups over a period of 20 weeks. Outcome measure scores at week 1 or baseline are considered as a reference. We found statistically significant effects in five and seven variables in the immediate (n = 6) and delayed (n = 4) treatment group.

In the following four pages, I summarize the major findings from group level analyses:

a) Changes seen in outcome measures from baseline in the immediate treatment group

(i) AzBio speech comprehension in noise scores augmented (which were not trained), ten weeks after playing brain training games, however, this finding was not statistically significant, $n = 6$, β =3.83, 95% CI [-3.73, 11.40] at week 10 (Post-training/Rx) and β = 6.61, 95% CI [-1.44, 14.67] at week 20 (Follow-up).

(ii) CT enhanced Speech Spatial Quality Questionnaire - total scores (which were not trained), $n = 6$, β = 1.13, 95% CI [0.35, 1.91] and $p = .007$ at week 10 (Post-Rx).

(iii) CT enhanced SWM scores (which were trained) after 10 weeks of training and findings were preserved after 10 weeks of follow up. (a) SWM Total errors for problems with 4 to 8 boxes, $n = 6$, β = - 16.35, 95% CI [-28.23, - 4.47] and $p = .009$ at week 10 assessment (Post-Rx) and $n = 6$, β = - 12.74, 95% CI [-25.48, - 0.01] and $p = .05$ at week 20 assessment (Follow-up). (b) SWM Strategy, $n = 6$, β = - 5.11, 95% CI [-6.91, - 3.31] and $p < .001$ at week 10 assessment and $n = 6$, β = - 5.50, 95% CI [-7.43, - 3.57] and $p < .001$ at week 20 assessment.

(iv) Verbal recognition memory scores (which were trained) were also enhanced by trial program in the immediate treatment group ($n = 6$), VRM free recall, β = 2.86, 95% CI [1.33, 4.40] and $p = .001$ at week 10 (Post-Rx) and β = 3.61, 95% CI [1.97, 5.25] and $p < .001$ at week 20 (Follow up).

(v) CT also modestly improved sustained attention scores (which were trained) in the immediate treatment group ($n = 6$), RVP A′, β = 0.03, 95% CI [0.001, 0.05], $p = .037$ at week 10(Post-Rx) and β = 0.04, 95% CI [0.01, .07], $p = .005$ at week 20.

b) Changes seen in outcome measures from baseline in the delayed treatment group

(i) AzBio speech comprehension in noise score (which were not trained) increased with both standard therapy only and CT + standard therapy, however, this finding was not statistically significant, $n = 4$, β = 4.67, 95% CI [-4.30, 13.64] at week 10 (Pre-Rx) and β = 6.44, 95% CI [-2.88, 15.78] at week 20 (Post-Rx).

(ii) CT enhanced sensorimotor functions (which were trained), MOT mean latency, $n = 4$, β = -236.60, 95% CI [-384.64, -88. 57], $p = .004$ at week 20 (Post-Rx). However, a similar trend was also present during week 1 - 10 when the CI users received standard therapy only, β = -207.74, 95% CI [-350.76, -64.71], $p = .007$

(iii) SWM scores (which were trained) deteriorated after 10 weeks of standard therapy only as seen on SWM Total errors for problems with 4 to 8 boxes scores, $n = 4$, β = 14.51, 95% CI [0.21, 28.81] and $p = .047$ at week 10 assessment. The estimates were non-significantly increased with CT.

(iv) OTS outcome measures, for executive function, spatial planning and WM (which were trained), were enhanced by CT. However, a similar pre-existing trend was present beforehand with standard therapy only. (a) Number of problems solved in first choice, $n = 4$, $\beta = 2.38$, 95% CI [0.58, 4.19], $p = .011$ at week 10 (Pre-Rx) and $\beta = 2.15$, 95% CI [0.29, 4.00], $p = .025$ at week 20 (Post-Rx). (b) Mean choices to correct response, $\beta = -0.22$, 95% CI [-0.41, -0.03], $p = .024$ at week 10 (Pre-Rx) and $\beta = -0.37$, 95% CI [-0.57, -0.18], $p < .001$ at week 20 (Post-Rx).

(v) Verbal free recall memory (which was trained) scores were augmented by the CT in the delayed treatment group, $n = 4$, $\beta = 3.36$, 95% CI [1.46, 5.25], $p = .001$ at week 20 (Post- Rx). A similar but weaker pre-existing trend was noted in the first ten weeks of participation with standard therapy only, $\beta = 2.64$, 95% CI [0.80, 4.49], $p = .006$ at week 10 (Pre-Rx). Similarly, verbal recognition memory (which was trained) scores were enhanced after ten weeks of CT in the delayed treatment group ($n = 4$), $\beta = 1.50$, 95% CI [0.74, 2.21], $p < .001$ at week 20.

(vi) CT also augmented spatial planning, a function of frontal lobe and which was trained, for the delayed treatment group participants ($n = 4$) as seen in SOC outcome measures: (a) problems solved in minimum moves, $\beta = 2.60$, 95% CI [0.93, 4.27], $p = .003$ at week 20 assessment. (b) Mean moves taken to solve 4-move problems, $\beta = -1.00$, 95% CI [-1.85, -0.15], $p = .022$ at week 20 assessment. Similar trend was also noted in first ten weeks of participations with standard therapy only, $\beta = -0.93$, 95% CI [-1.76, -0.11], $p = .028$ at week 10 assessment.

Table 2: Treatment effect estimates for the change in outcome measures from baseline to week 10 and 20 in immediate treatment groups

No.	Outcome Variable	Immediate Treatment Group			
		Week 10 (Post-Rx)		Week 20 (Follow Up)	
		Estimate [95% CI]	*p*	Estimate [95% CI]	*p*
Hearing Outcome Measures					
1	AzBio sentence test in noise	3.83 [-3.73, 11.40]	> .05	6.61 [-1.44, 14.67]	> .05
2	SSQ total	**1.13 [0.35, 1.91]**	**.007**	-0.49 [-1.33, 0.34]	> .05
Cognitive Outcome Measures					
3	MOT mean latency	17.03 [-102.67, 136.71]	> .05	25.00 [-102.89, 152.90]	> .05
4	MOT mean error	0.26 [-1.11, 1.63]	> .05	-1.81 [-3.28, 0.34]	> .05
5	SWM total errors for problems with 4 to 8 boxes	**-16.35 [-28.23, 4.47]**	**.009**	**-12.74 [-25.48, -0.01]**	**.05**
6	SWM strategy	**-5.11 [-6.91, -3.31]**	**< .001**	**-5.50 [-7.43, -3.57]**	**< .001**
7	OTS number of problems solved in first choice	-0.03 [-1.53, 1.46]	> .05	0.61 [- 0.99, 2.22]	> .05
8	OTS mean choices to correct response	0.002 [-0.155, 0.159]	> .05	-0.108 [-0.276, 0.060]	> .05
9	VRM free recall	**2.86 [1.33, 4.40]**	**.001**	**3.61 [1.97, 5.25]**	**< .001**
10	VRM recognition	0.49 [-0.10, 1.08]	> .05	0.55 [-0.08, 1.19]	> .05
11	RVP A′	**0.03 [0.001, 0.05]**	**.037**	**0.04 [0.01, 0.07]**	**.005**
12	SOC problems solved in minimum move	1.10 [-0.24, 2.45]	> .05	0.70 [-0.75, 2.14]	> .05
13	SOC means moves taken to solve 2 move problems	0.089 [-0.29, 0.47]	> .05	0.187 [-0.22, 0.59]	> .05
14	SOC mean moves taken to solve 4 move problems	-0.19 [-0.87, 0.49]	> .05	0.70 [-0.03, 1.44]	> .05
15	SOC mean moves taken to solve 5 move problems	-1.03 [-2.20, 0.15]	> .05	-1.88 [-3.14, -0.62]	.005

Table 3: Treatment effect estimates for the change in outcome measures from baseline to week 10 and 20 in delayed treatment groups

No.	Outcome Variable	Delayed Treatment Group			
		Week 10 (Pre-Rx)		Week 20 (Post-Rx)	
		Estimate [95% CI]	*p*	Estimate [95% CI]	*p*
Hearing Outcome Measures					
1	AzBio sentence test in noise	4.67 [- 4.30, 13.64]	> .05	6.44 [-2.88, 15.78]	> .05
2	SSQ total	-0.40 [-1.34, 0.54]	> .05	-0.42 [-1.39, 0.55]	> .05
Cognitive Outcome Measures					
3	MOT mean latency	**-207.74 [-350.76, -64.71]**	**.007**	**-236.60 [- 384.64, -88.57]**	**.004**
4	MOT mean error	-0.82 [-2.47, 0.83]	> .05	-0.90 [-2.60, 0.80]	> .05
5	SWM total errors for problems with 4 to 8 boxes	**14.51 [0.21, 28.81]**	**.047**	3.86 [-10.85, 18.58]	> .05
6	SWM strategy	0.033 [-2.13, 2.20]	> .05	-1.70 [-3.93, 0.54]	> .05
7	OTS number of problems solved in first choice	**2.38 [0.58, 4.19]**	**.011**	**2.15 [0.29, 4.00]**	**.025**
8	OTS mean choices to correct response	**-0.22 [-0.41, -0.03]**	**.024**	**- 0.37 [- 0.57, -0.18]**	**< .001**
9	VRM free recall	**2.64 [0.80, 4.49]**	**.006**	**3.36 [1.46, 5.25]**	**.001**
10	VRM recognition	0.38 [- 0.34, 1.09]	> .05	**1.50 [0.74, 2.21]**	**< .001**
11	RVP A′	0.007 [- 0.024, 0.038]	> .05	- 0.007 [- 0.035, 0.021]	> .05
12	SOC problems solved in minimum move	1.12 [-0.49, 2.75]	> .05	**2.60 [0.93, 4.27]**	**.003**
13	SOC means moves taken to solve 2 move problems	0.34 [-0.109, 0.798]	> .05	-0.13 [-0.60, 0.34]	> .05
14	SOC mean moves taken to solve 4 move problems	**-0.93 [-1.76, - 0.11]**	**.028**	**-1.00 [-1.85, -0.15]**	**.022**
15	SOC mean moves taken to solve 5 move problems	0.79 [-0.62, 2.21]	> .05	-0.097 [-1.55, 1.36]	> .05

In the Table 4, we compared the change in outcome measures in the immediate and delayed treatment group after first ten weeks of study period. The effect size estimates of standard therapy + CT in the immediate treatment group when compared with standard therapy only in the delayed treatment showed statistically significant improvement in four outcome measure variables: SSQ total scores (which was not trained directly), SWM strategy, SWM total error scores, and SOC mean moves taken to solve a 5 move problem (which were trained). However, three outcome measures demonstrated significant deterioration of cognitive functions with CT + Std Rx compared from Std Rx: MOT mean latency, and two OTS test scores (which were trained).

Table 4: Treatment effect estimates for the change in outcome variables in the immediate treatment group after complementary cognitive training compared to the delayed treatment group without CT assessed at week 10

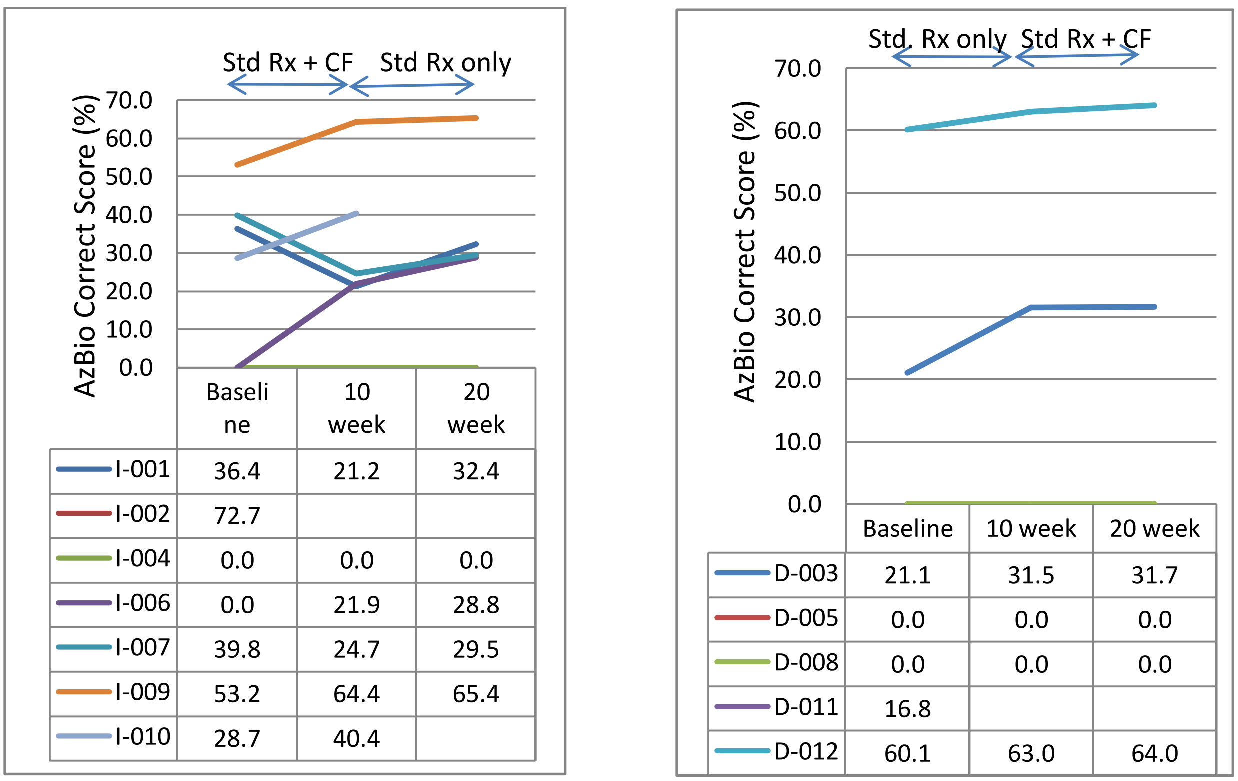
No.	Outcome Variable	Effect Estimate at Week 10 [95% CI]	*p*
Hearing Outcome Measures			
1	AzBio sentence test in background noise	-0.27 [-12.22, 11.67]	> .05
2	SSQ total	**1.61 [0.52, 2.70]**	**< .001**
Cognitive Outcome Measures			
3	MOT mean latency	**220.63 [44.37, 396.90]**•	**.017**
4	MOT mean error	1.07 [- 1.04, 3.20]	> .05
5	SWM total errors for problems with 4 to 8 boxes	**-31.31 [- 49.35, - 13.26]**	**.001**
6	SWM strategy	**-5.06 [-7.78, -2.35]**	**.001**
7	OTS number of problems solved in first choice	**-2.36 [-4.62, -0.09]**•	**.042**
8	OTS mean choices to correct response	**0.21 [-0.02, 0.45]**•	**.071**
9	VRM free recall	0.26 [-2.09, 2.60]	> .05
10	VRM recognition	0.12 [-0.79, 1.04]	> .05
11	RVP A′	0.02 [-0.01, 0.06]	> .05
12	SOC number of problems solved in minimum move	0.032 [-1.34, 3.98]	> .05
13	SOC means moves taken to solve 2 move problems	-0.24 [-0.81, 0.33]	> .05
14	SOC mean moves taken to solve 4 move problems	0.80 [-1.31, 1.74]	> .05
15	SOC mean moves taken to solve 5 move problems	**-1.88 [-3.65, -0.11]**	**.038**

•Note: MOT mean latency and two OTS test scores which were better with standard therapy only versus CT + Standard therapy

5.2. Individual Level Analysis for Hearing Outcome Measures of the Adult Cochlear Implant Users

It includes AzBio Sentence Test and Speech Spatial Qualities Questionnaire.

5.2.1. AzBio sentence test scores in background babble in two treatment groups. Figure 8 showed a change in AzBio sentence test scores over a period of 20 weeks in the immediate and delayed treatment groups. Cochlear implant users' had a different baseline AzBio sentence understanding scores among two treatment groups. Findings also suggested a dramatic between subject variation and analyses per user would be beneficial to identify the drivers for this change. At baseline, four participants show a mere 'zero' speech comprehension in noise while five participants show more than thirty. Although there was a general trend for improvement in participants' AzBio sentence understanding scores after the CT, these results were not statistically significant (Refer to the Tables 2 and 3 for details).



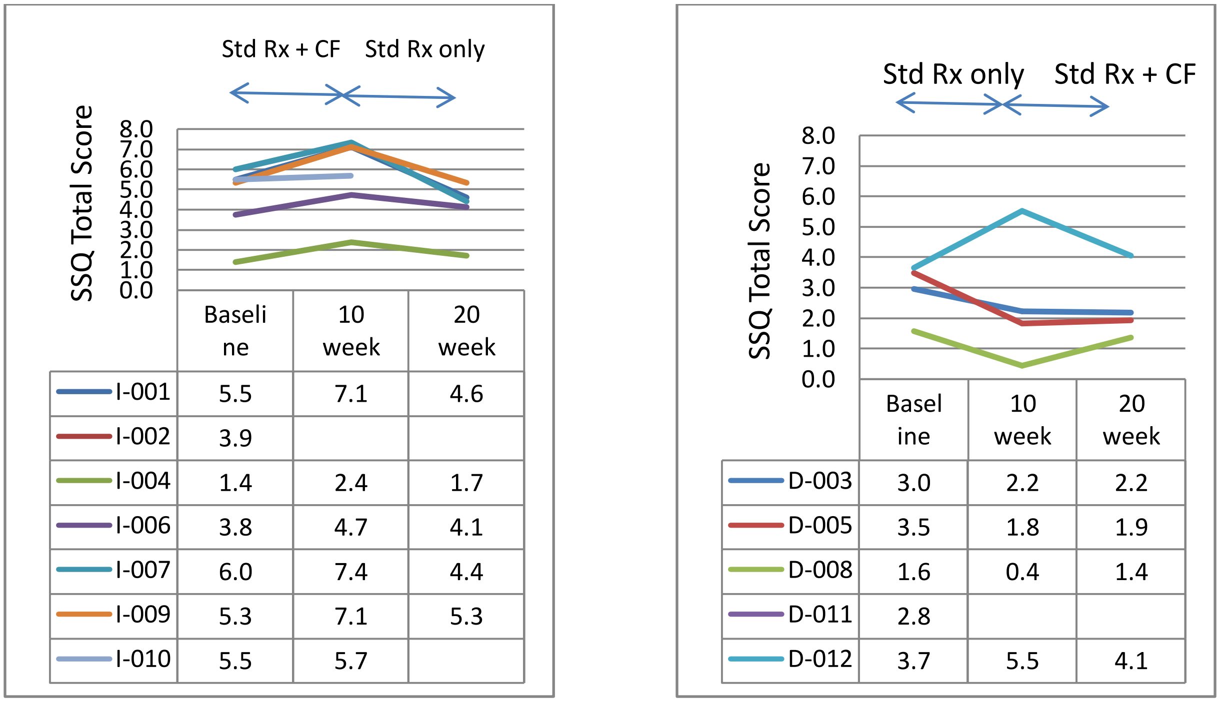
	Baseline	10 week	20 week
I-001	36.4	21.2	32.4
I-002	72.7		
I-004	0.0	0.0	0.0
I-006	0.0	21.9	28.8
I-007	39.8	24.7	29.5
I-009	53.2	64.4	65.4
I-010	28.7	40.4	

	Baseline	10 week	20 week
D-003	21.1	31.5	31.7
D-005	0.0	0.0	0.0
D-008	0.0	0.0	0.0
D-011	16.8		
D-012	60.1	63.0	64.0

10A 10B

Figure 10: AzBio Sentence Test in Babble. 10A and 10B denote the immediate and delayed treatment groups. AzBio Sentence Understanding Scores range from 0 to 100 %. Higher score denotes a better speech understanding ability in background noise. CF and Std Rx represent CogniFit training and standard therapy respectively

5.2.2. Speech Spatial Qualities Questionnaires, SSQ, total scores in two treatment groups.



11A 11B

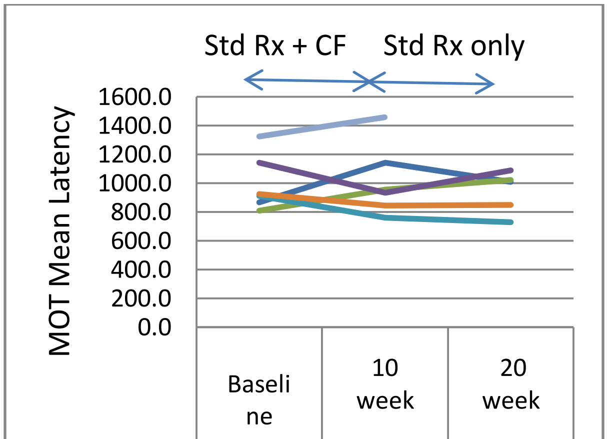
Figure 11: Speech Spatial Qualities Questionnaire - Total Score. 11A and 11B denote the immediate and delayed treatment groups. SSQ total score ranges from 0 to 10. Higher score demonstrates a better the functional self-reported hearing ability.

A change in Speech Spatial Qualities scores over a period of 20 weeks in the immediate and delayed treatment group is shown in Figure 11A and 11B. It is quite evident here that SSQ total score had increased in all of the volunteers in immediate treatment group after the CT (p < .05). However, this change did not sustain after receiving standard therapy for ten weeks (not significant, p > .05). Participants' functional hearing ability had decreased after a ten-week waiting period with standard treatment only period in the delayed treatment group. Interestingly, the speed of decline seems to be reduced during the next ten-week period with CT.

5.3. Individual Level Analysis for Cognitive Outcome Measures (CANTABeclipse Version 5.0) of the Adult Cochlear Implant Users

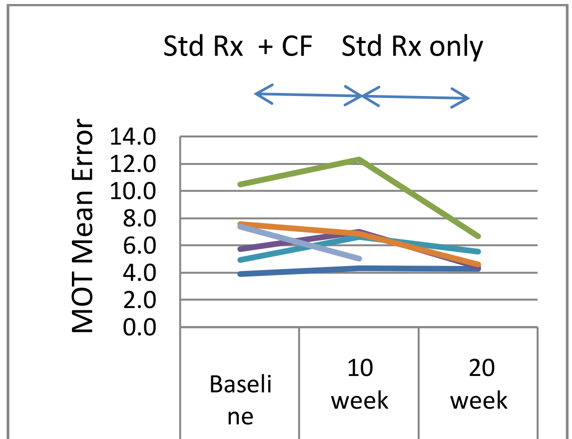
It includes 13 outcome variables. The CANTABeclipse outcome measures were described in the methodology section.

5.3.1. MOtor screening Test (MOT). The trend graphs for the mean error and mean latency scores in the immediate and delayed treatment groups are described in Figures 10 and 11 respectively. MOT neuropsychomotor tests screen the users' ability to cooperate with the battery of CANTAB tests.



	Baseline	10 week	20 week
I-001	867.4	1142.3	1010.1
I-002	979.2		
I-004	811.5	959.8	1024.2
I-006	1142.9	932.8	1091.1
I-007	911.8	761.4	729.3
I-009	924.3	847.4	850.3
I-010	1323.4	1459.9	

12A

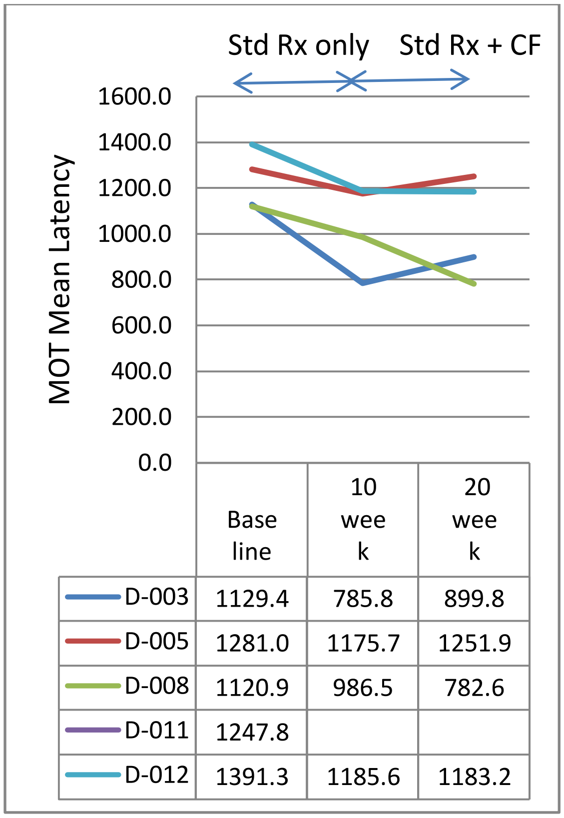


	Baseline	10 week	20 week
I-001	3.9	4.3	4.3
I-002	5.4		
I-004	10.5	12.3	6.7
I-006	5.7	7.0	4.4
I-007	5.0	6.6	5.5
I-009	7.6	6.9	4.6
I-010	7.4	5.0	

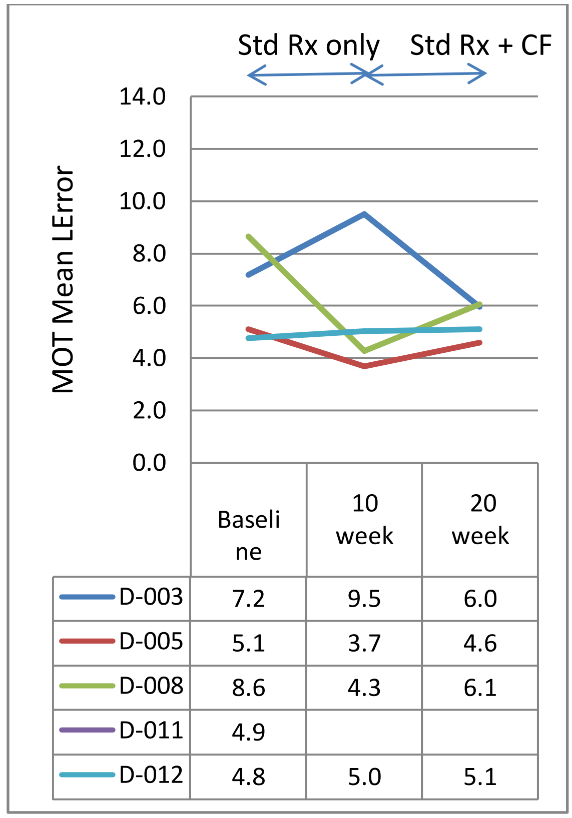
12B

Figure 12: MOT Immediate Treatment Group. 12A and 12B denotes Mean Latency and Mean Error. Lower score in Mean Error and Latency indicates a better comprehension and sensorimotor skills.

Users 001 and 004 showed an increased value of MOT Mean Error and Latency scores after first ten weeks of CT period whereas their value reduced during next ten weeks of standard therapy only. On the other hand, reverse happened for the user 006 and 009. Also, User 007 and 010 scores show improved scores from baseline but this picture seem more in favor of speed-accuracy trade off. On a group level, mixed findings were seen for cochlear implant users in the immediate treatment group. Moreover, results were not statistically significant.



13A

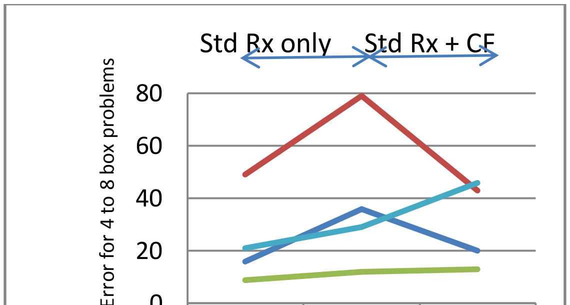


13B

Figure 13: MOT Scores in Delayed Treatment Group. 13A and 13B denote Mean Latency Score and Mean Error. Lower score in Mean Error and Latency indicates a better comprehension and sensorimotor skills.

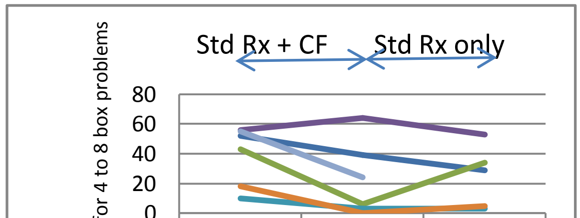
Figure 13 demonstrates that cochlear implant users' mean latency scores were improving over the whole 20 week study period. So, we cannot give sole credit to CT for this optimistic change. User 003 scores show improved mean latency scores but these pictures seem more in favor of speed-accuracy trade-off.

5.3.2. Spatial Working Memory (SWM) scores in two treatment groups. SWM test is widely used to assess visuospatial WM and executive functions. Figure 14 and 15 demonstrate trend graphs in SWM total errors for problems containing 4 to 8 boxes and SWM strategy. Most users show enhanced SWM measures after CT rather than time period with only standard therapy. As well, mixed models analyses indicated that the results were statistically significant effects (Refer to Tables 2 and 3 for details).



	Baseline	10 week	20 week
D-003	16	36	20
D-005	49	79	43
D-008	9	12	13
D-011	41		
D-012	21	29	46

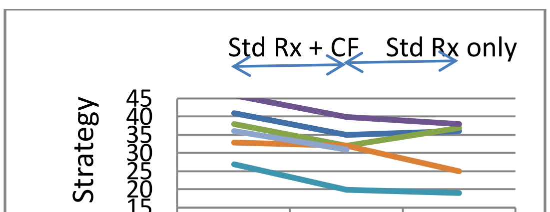
14A



	Baseline	10 week	20 week
I-001	52	39	29
I-002	33		
I-004	43	6	34
I-006	56	64	53
I-007	10	3	3
I-009	18	0	5
I-010	55	24	

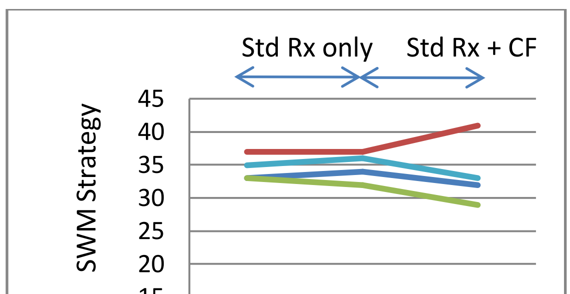
14B

Figure 14: SWM Total Error for 4 to 8 box problems. 14A and 14B denote the immediate and delayed treatment groups. Lower scores indicate a better visuospatial WM and executive functions.



	Baseline	10 week	20 week
I-001	41	35	36
I-002	39		
I-004	38	32	37
I-006	46	40	38
I-007	27	20	19
I-009	33	32	25
I-010	36	31	

15A



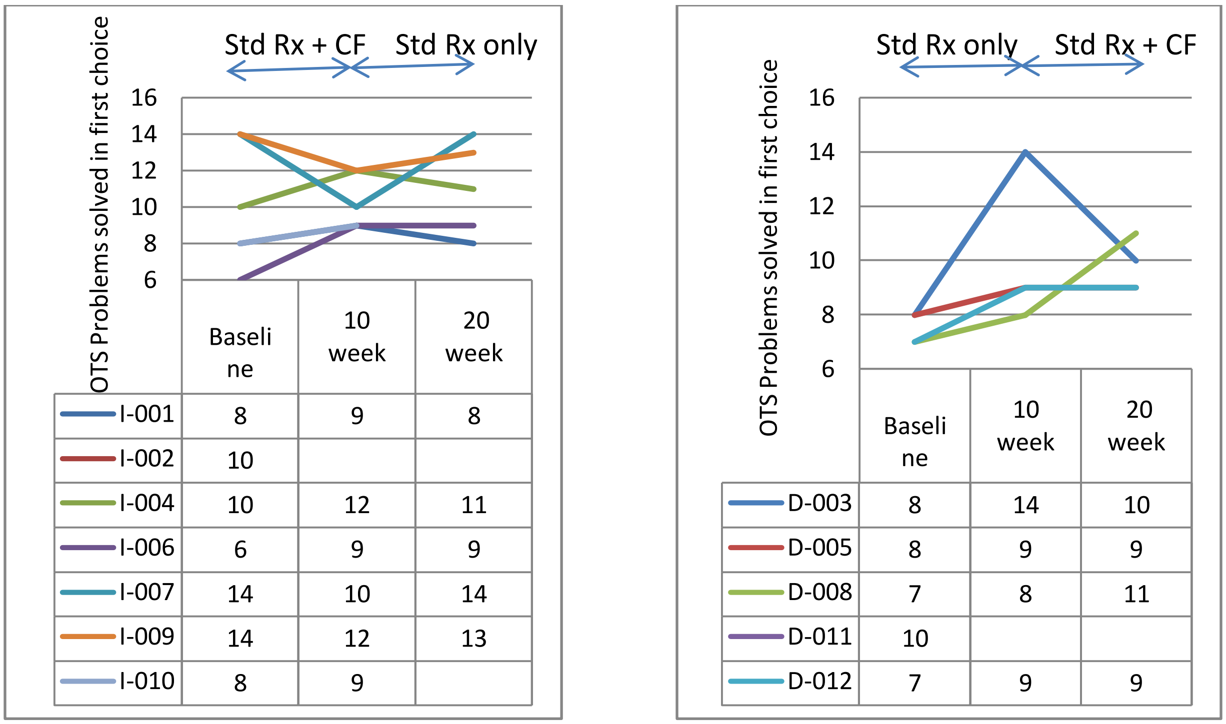
	Baseline	10 week	20 week
D-003	33	34	32
D-005	37	37	41
D-008	33	32	29
D-011	38		
D-012	35	36	33

15B

Figure 15: SWM Strategy Scores. 15A and 15B denote the immediate and delayed treatment groups. Lower scores show a better visuospatial WM and executive functions.

5.3.3. One Touch Stockings of Cambridge (OTS). OTS is a test of executive function, spatial planning and WM based upon the Tower of Hanoi test. It includes the following task:

a) OTS Number of problems solved in first choice



	Baseline	10 week	20 week
I-001	8	9	8
I-002	10		
I-004	10	12	11
I-006	6	9	9
I-007	14	10	14
I-009	14	12	13
I-010	8	9	

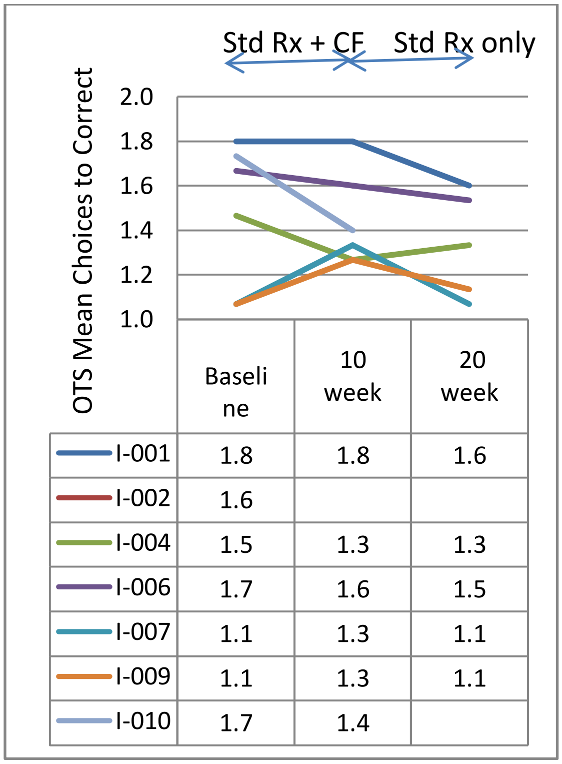
	Baseline	10 week	20 week
D-003	8	14	10
D-005	8	9	9
D-008	7	8	11
D-011	10		
D-012	7	9	9

16A 16B

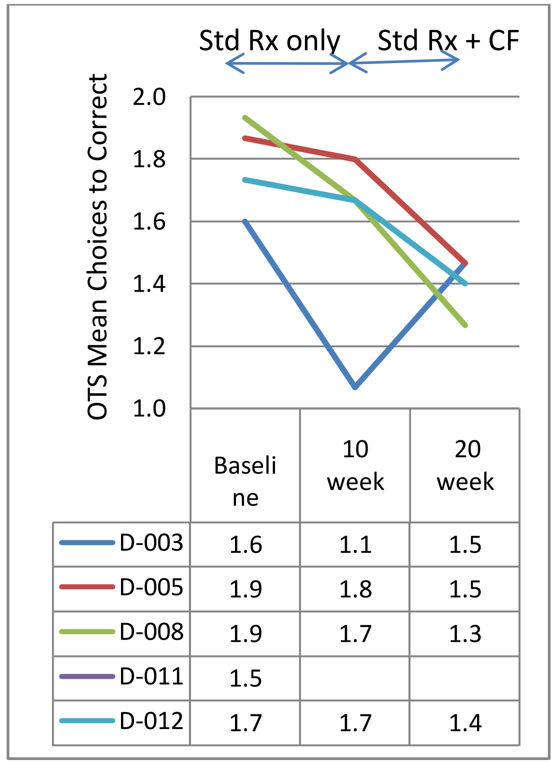
Figure 16: OTS Problems solved in first choice Score. 16A and 16B denote the immediate and delayed treatment groups. Higher score point toward a better executive, spatial planning skills and WM.

Figure 16 describes the changes in OTS problems solved in first choice score over a period of 20 weeks. Note that four users from the immediate group showed improvement in their scores after ten weeks of playing certain games where two CI users' scores deteriorated immediately after training. Change in scores from baseline was not sustained at 20 week assessment though. Most cochlear implant users' OTS number of problems solved in first choice scores returned to close to baseline values except user 006 who showed sustained results. On the other hand, majority of participants in the delayed treatment group showed a statistically significant improvement, subsequent to both the waiting and training period (Refer to Table 2). Hence, in the delayed treatment group, there was an underlying trend driving this spontaneous improvement despite CT. Also, why some of these users get this benefit and what are the driving factors for this change remain largely unknown.

b) **OTS Mean choices to correct response**



17A



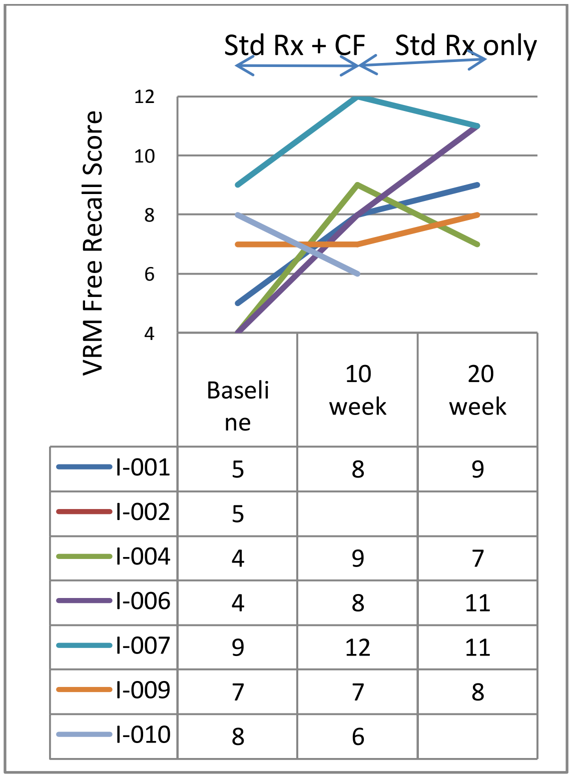
17B

Figure 17: OTS Mean Choices to Correct Score. 17A and 17B denote the immediate and delayed treatment groups. Lower score is better executive, spatial planning skills and WM.

Figure 17A shows that all the cochlear implant users in the immediate treatment group acquire a favorable outcome except user 007 and 009. However, scores returned back to baseline for user 007 and 009 when they receive only standard therapy. Similar to the other OTS measure finding in the delayed treatment group, most cochlear implant users demonstrated enhancement in both assessments, after the waiting and training period (Figure 17B).

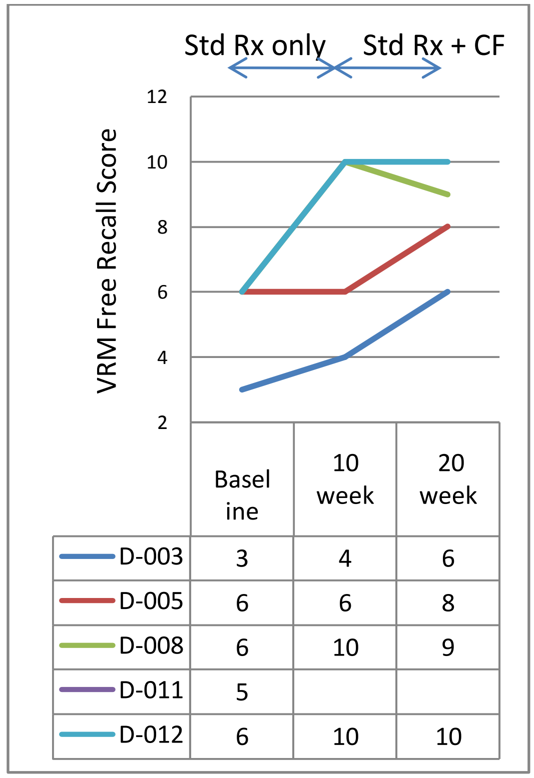
5.3.4. Verbal Recognition Memory.VRM assesses visual verbal memory and new learning.

a) Free recall - total correct



	Baseline	10 week	20 week
I-001	5	8	9
I-002	5		
I-004	4	9	7
I-006	4	8	11
I-007	9	12	11
I-009	7	7	8
I-010	8	6	

18A



	Baseline	10 week	20 week
D-003	3	4	6
D-005	6	6	8
D-008	6	10	9
D-011	5		
D-012	6	10	10

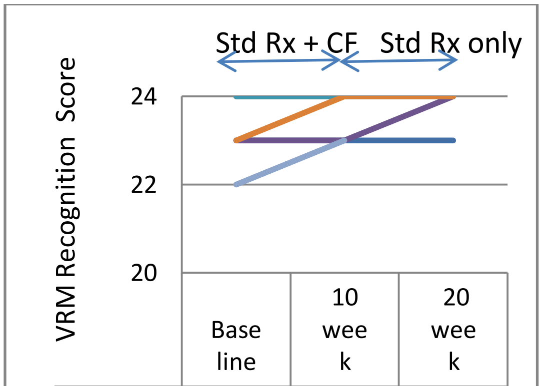
18B

Figure 18: VRM Free Recall Score. 18A and 18B denote the immediate and delayed treatment groups. Score ranges from 0 to 12 and a high score indicate better performance.

Although users from both groups showed a statistically significant improvement in free recall, subsequent to the waiting period and/or intervention. Improvement was further boosted with CT.

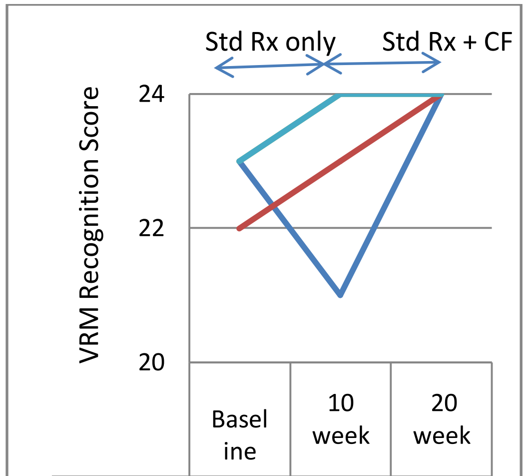
b) VRM Recognition - total correct

There is a general trend and improvement in visual memory across all patients (Figure 19) except user 001 whose score did not change. VRM recognition scores in the delayed treatment group varied both positive and negatively after standard therapy only. In the delayed treatment group, all participants had recognized all the words correctly after ten weeks of CT.



	Base line	10 week	20 week
I-001	23	23	23
I-002	21		
I-004	24	24	24
I-006	23	23	24
I-007	24	24	24
I-009	23	24	24
I-010	22	23	

19A

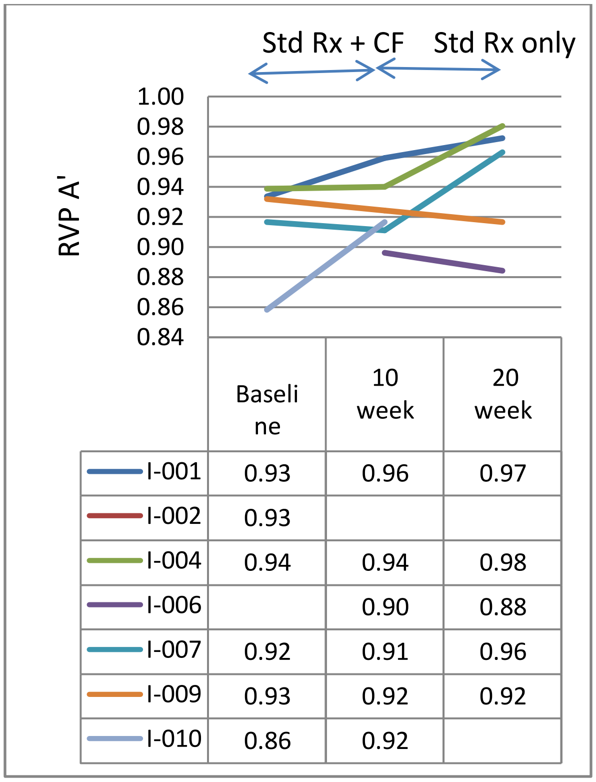


	Baseline	10 week	20 week
D-003	23	21	24
D-005	22	23	24
D-008	23	24	24
D-011	24		
D-012	23	24	24

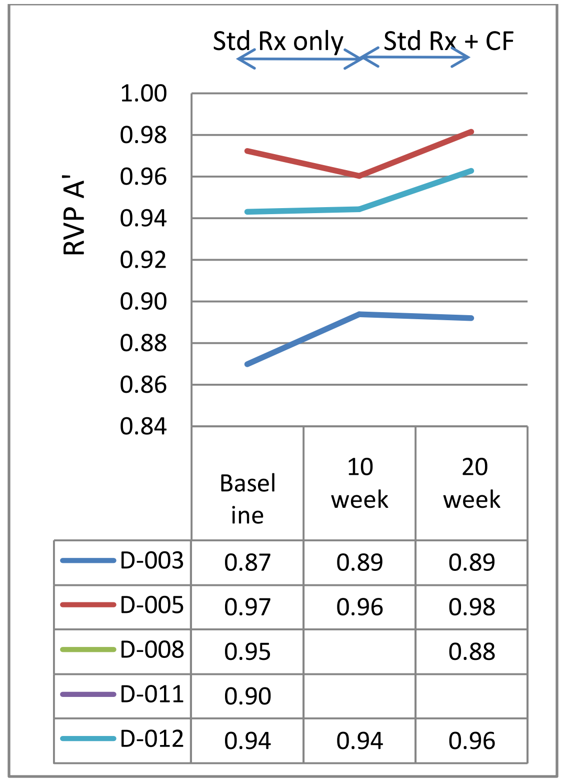
19B

Figure 19: VRM Recognition - Total Correct Score. 19A and 19B denote the immediate and delayed treatment groups. Score ranges from 0 to 24. Increased in VRM recognition scores suggest better verbal memory.

5.3.5. Rapid Visual information Processing (RVP) – A'. This test measures sustained visual attention abilities. As shown in Figure 20A, most participants RVP A' scores increased after ten weeks of training in the immediate treatment group. Notably, user 006 could not complete this task on the baseline assessment because it was too challenging or stressful for her. However, on the subsequent visits, she did not notice any undue discomfort and she successfully completed this task. Interestingly, most users have preserved these gains as seen in the follow up visit. Users from the delayed treatment group showed mixed results after the ten week waiting period (Figure 20B). However as seen on 3rd assessmentat 20 week, cochlear implant users' RVP A' scores or visual attention scores have improved with the CT.



20A



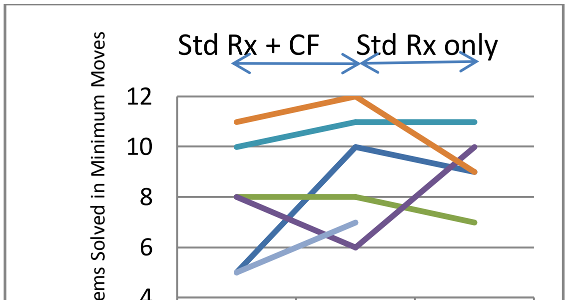
20B

Figure 20: RVP A'. 18A and 18B denote the immediate and delayed treatment groups. RVP A' ranges from 0 to 1 and higher score indicates a better attention function.

5.3.6. Stockings Of Cambridge (SOC).

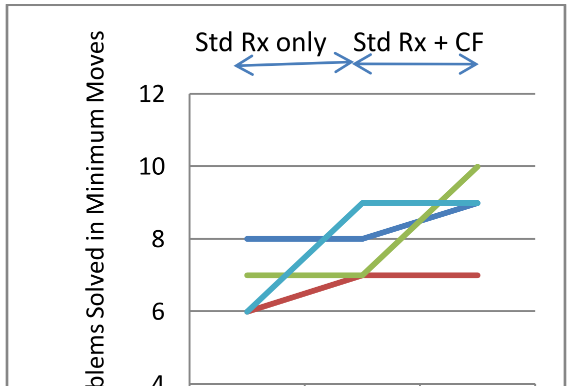
a) **SOC Problems solved in minimum moves:** It is a measure of spatial planning and motor control, that is, it SOC tasks assess frontal lobe functioning.

In the immediate treatment group, most cochlear implant users (except user 006) showed a marked improvement in their spatial planning and motor control functioning outcome measure after ten weeks of training (Figure 21A). During follow up visit, most cochlear implant users showed a slight reduction in this outcome measure. User 006 potentially showed a delayed effect and her score bounced by 50% change from baseline. In the delayed treatment group (Figure 21B), all participants showed an improvement at 20 week time from baseline but there was a pre-existing wave of improvement in users 005 and 012, even at 2nd visit after ten weeks of waiting period.



	Baseline	10 week	20 week
I-001	5	10	9
I-002	9		
I-004	8	8	7
I-006	8	6	10
I-007	10	11	11
I-009	11	12	9
I-010	5	7	

21A

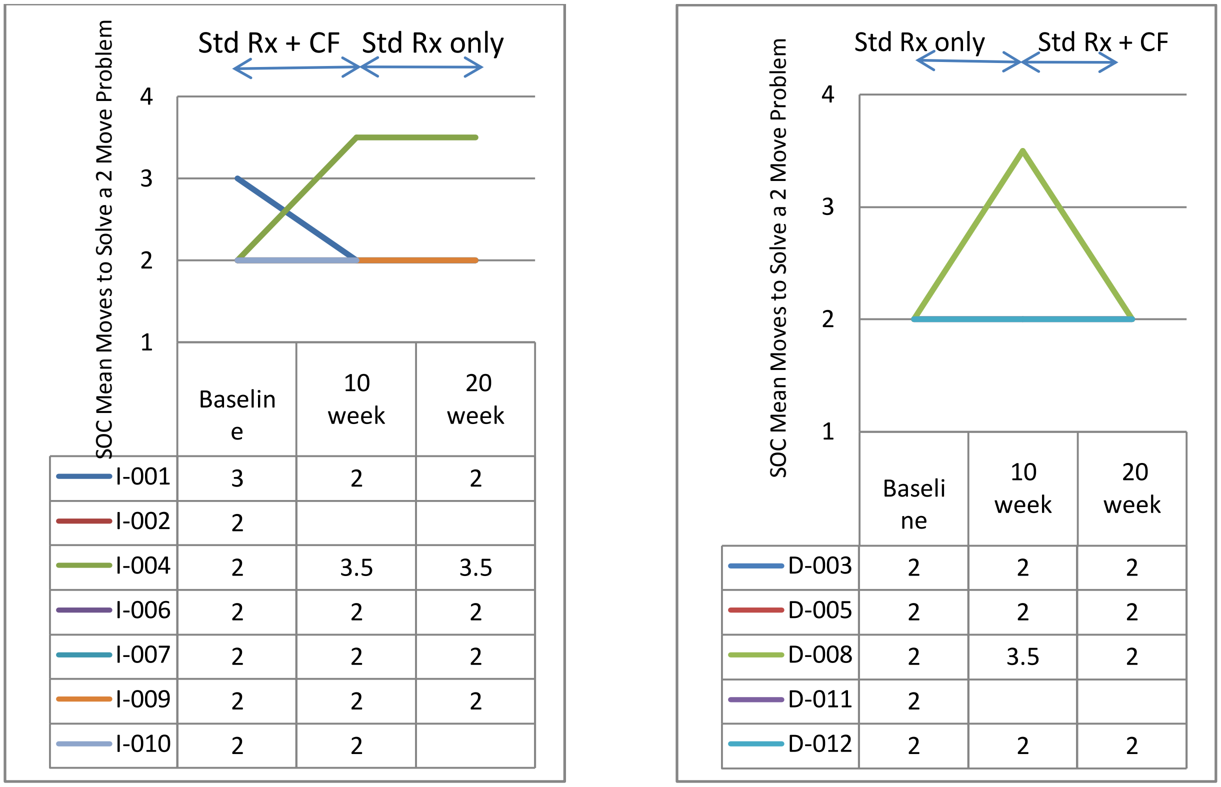


	Baseline	10 week	20 week
D-003	8	8	9
D-005	6	7	7
D-008	7	7	10
D-011	8		
D-012	6	9	9

21B

Figure 21: SOC Problems Solved in Minimum Moves Score. 21A and 21B denote the immediate and delayed treatment groups. Higher score illustrate better spatial planning and motor control abilities.

b) SOC Mean moves to solve a 2 move problem. As shown in Figure 22, majority of the cochlear implant users' scores remained stable in both groups except the change seen in user 001 and 004. This finding could be a result of ceiling effect associated with SOC mean moves to solve a 2 move problem outcome measure.

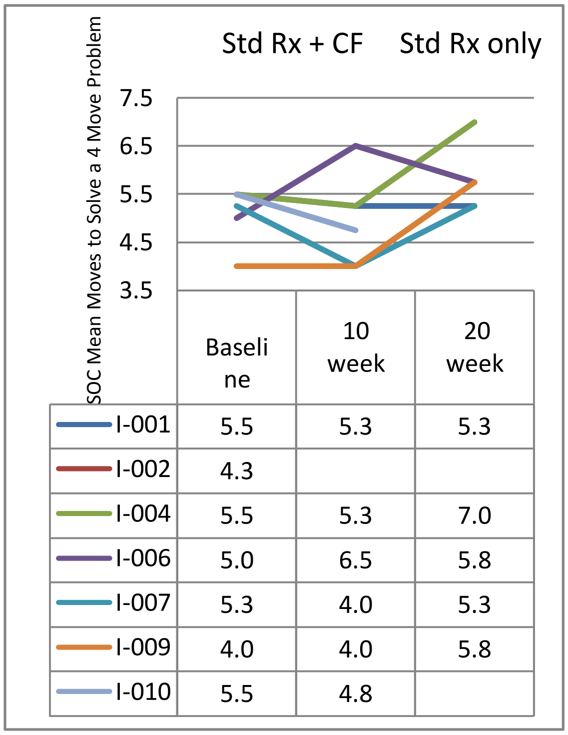


22A 22B

Figure 22: SOC Mean Moves to Solve a 2 Move Problem Score. 22A and 22B denote the immediate and delayed treatment groups. Lower score illustrate better spatial planning and motor control abilities.

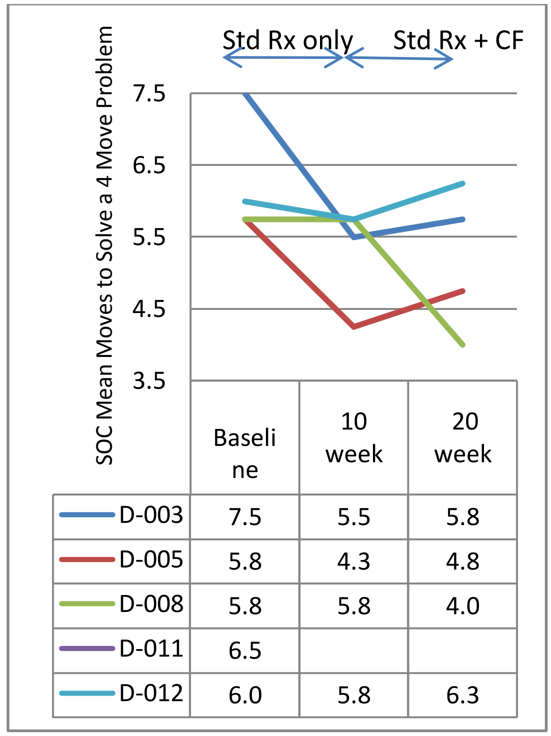
c) SOC Mean moves to solve a 4 move problem.

SOC planning/executive functions improved for many cochlear implant users, seeing that apparent change in SOC mean moves to solve a 4 move problem in cochlear implant users 001, 004, 007, 010 (Figure 23A). On a follow up visit, this change was not maintained for some participants (e.g., users 004 and 007). For the delayed treatment group (Figure 23B), the changes in test scores demonstrated a statistically significant improvement in planning function, even after only standard treatment.



	Baseline	10 week	20 week
I-001	5.5	5.3	5.3
I-002	4.3		
I-004	5.5	5.3	7.0
I-006	5.0	6.5	5.8
I-007	5.3	4.0	5.3
I-009	4.0	4.0	5.8
I-010	5.5	4.8	

23A



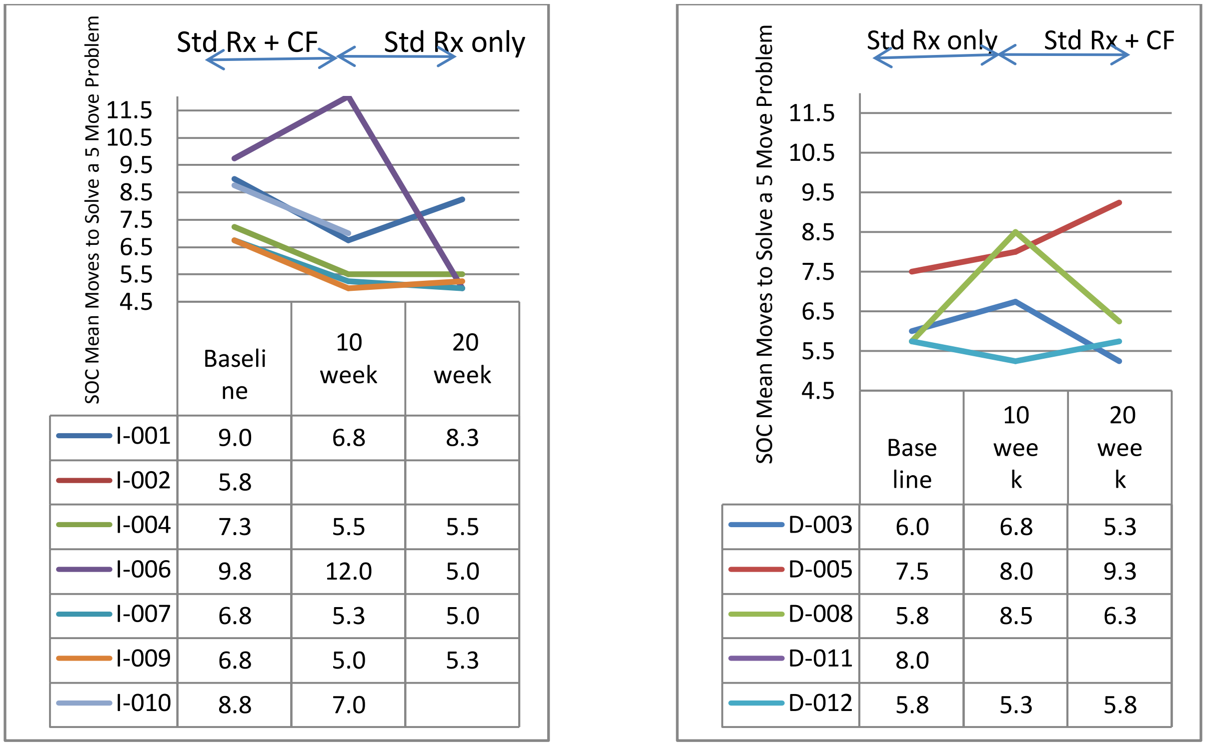
	Baseline	10 week	20 week
D-003	7.5	5.5	5.8
D-005	5.8	4.3	4.8
D-008	5.8	5.8	4.0
D-011	6.5		
D-012	6.0	5.8	6.3

23B

Figure 23: SOC Mean Moves to Solve a 4 Move Problem Score. 23A and 23B denote the immediate and delayed treatment groups. Lower score illustrate better spatial planning and motor control abilities.

d) SOC Mean moves to solve a 5 move problem.

Figure 24A demonstrates an improvement in spatial planning function (SOC mean moves to solve a 5 move problem score) after CT at week 10 for the immediate treatment group except user 006. This finding was not statistically significant and scores did not maintain during the follow up visit. Figure 24B reveals an improvement after the complementary treatment in the delayed treatment group. However, this change was not seen during waiting period with standard therapy only. In addition, the results were not significant (Table 3).



A B

Figure 24: SOC Mean Moves to Solve a 5 Move Problem Score. 24A and 24B denote the immediate and delayed treatment groups. Lower score illustrate better spatial planning and motor control abilities.

5.4. Analyses Combined Across All Participants

Table 5 describes the change in outcome scores from immediately prior to CT, to immediately after CT, across all participants except two drop-outs (*n* =10, i.e., participants of immediate and delayed groups).

Ten weeks of CT non-significantly improved cochlear implant users' (*n* = 10) AzBio sentence test score, β = 2.58, 95% CI [-2.84, 8.02], OTS mean choices to correct response, β = -0.03, 95% CI [-0.15, 0.08], SOC mean moves taken to solve 2 solve 2 move problems, β = -0.2, 95% CI [-0.56, 0.15]. On the other hand, it non-significantly reduced OTS number of problems solved in first choice score, β = -0.47, 95% CI [-1.60, 0.65], SOC mean moves taken to solve 4 move problems, β = 0.02, 95% CI [-0.36, 0.40].

Modest yet statistically significant enhancement of SSQ total score was seen after ten weeks of CT in cochlear implant users, *n* = 10, β = 0.60, 95% CI [0.14, 1.05]. In addition, CT significantly augmented the following cognitive test scores: SWM total errors for problems with

4 to 8 boxes, β = - 11.32, 95% CI [- 19.82, - 2.81], SWM strategy, β = - 3.08, 95% CI [- 4.36, - 1.81], VRM free recall, β = 1.25, 95% CI [0.25, 2.26], VRM recognition, β = 0.76, 95% CI [0.32, 1.20], RVP A′, β = 0.015, 95% CI [0.005, 0.026], SOC number of problems solved in minimum moves, β = 1.12, 95% CI [0.29, 1.94] and SOC mean moves taken to solve 5 move problems, β = - 0.68, 95% CI [-1.17, - 0.19].

Table 5: Treatment effect estimates for the change in outcome variables after cognitive training across all the participants

No.	Outcome Variable	Estimate [95% CI]	*p*
Hearing Outcome Measures			
1	AzBio sentence test in background noise	2.58 [-2.84, 8.02]	> .05
2	SSQ total	**0.60 [0.14, 1.05]**	**.013**
Cognitive Outcome Measures			
3	MOT mean latency	11.84 [-68.85, 92.51]	> .05
4	MOT mean error	-0.31 [-1.01, 0.40]	> .05
5	SWM total errors for problems with 4 to 8 boxes	**-11.32 [-19.82, -2.81]**	**.012**
6	SWM strategy	**-3.08 [-4.36, -1.81]**	**< .001**
7	OTS number of problems solved in first choice	-0.47 [-1.60, 0.65]	> .05
8	OTS mean choices to correct response	-0.03 [-0.15, 0.08]	> .05
9	VRM free recall	**1.25 [0.25, 2.26]**	**.017**
10	VRM recognition	**0.76 [0.32, 1.20]**	**.002**
11	RVP A′	**0.015 [0.005, 0.026]**	**.006**
12	SOC number of problems solved in minimum moves	**1.12 [0.29, 1.94]**	**.011**
13	SOC means moves taken to solve 2 move problems	-0.2 [-0.56, .15]	> .05
14	SOC mean moves taken to solve 4 move problems	0.02 [-0.36, 0.40]	> .05
15	SOC mean moves taken to solve 5 move problems	**-0.68 [-1.17, -0.19]**	**.009**

6. Discussion

6.1. Discussion of the Study Hypotheses

The discussion section of this thesis will be divided according to the hypotheses and current literature with the following main findings:

Cochlear implant users will improve on the AzBio Sentence test for speech comprehension in background noise and the Spatial Speech Qualities questionnaire for self-reported auditory ability after 10 weeks of multi-domain cognitive training, but not after the 10 week periods during which no training occurred.

These two outcome measures were included to test whether CT can enhance cochlear implant users' ability to learn new tasks beyond what they are directly trained. Here, the hypotheses regarding AzBio sentence understanding in noise score and total SSQ tests have been grouped together in discussion because of their close interface. As noted above, linguistic skills constitute localized functions (Ginsberg, 2005); however, we should not ignore the complex nature of auditory perception and possible role of the whole brain in understanding sentences in noise (Faulkner & Pisoni, 2013). The effects of generalized cognitive training via CogniFit are largely unknown in adult cochlear implant users.

The results demonstrated enhanced speech comprehension in noise by CogniFit training, $p > .05$ (Hypothesis 1). Insufficient data were available to recommend the CogniFit based CT for speech understanding in noise. Additional studies in this field are warranted.

The addition of CT into the standard therapy predicted a statistically significant improvement of functional self-reported hearing ability in the immediate treatment group, which is an untrained ability, assessed by speech spatial qualities questionnaire (Hypothesis 2). The constructive changes seen were marginal and favored CT as a complementary option for cochlear implant users' aural rehabilitation.

It seems that the speech comprehension in noise and self-reported auditory ability improvement achieved in our study supplements prior knowledge in children with cochlear implants (Ingvalson & Wong, 2013; Kronenberger et al., 2011). Future research studies targeting cognitive remediation should focus on cochlear implant users having a relatively high auditory skills and risk for developing cognitive decline or in fact who suffer from mild to moderate cognitive impairment (Ingvalson & Wong, 2013).

Cochlear implant users aged 19 or above will show an overall increased level of attention, working memory, and other basic cognitive functions after 10 weeks of multi-domain cognitive training (CT), but not after the 10 week periods during which no training occurred.

Above findings demonstrate the statistically significant, but very modest improvements in seven CANTABeclipse tests (2 OTS tasks, 2 SWM tasks, RVP A′, and 2 VRM tasks), executive functions, spatial planning ability, visuo-spatial working memory, visual verbal memory, and sustained attention. This highlights the ability of CT to improve adult cochlear implant user's cognitive skills despite a long duration of hearing loss. Here we describe the main finding regarding cognitive remediation in the immediate and delayed treatment groups:

a) Cochlear implant users showed an overall increased level of visuo-spatial working memory and executive functions (which were trained) after 10 weeks of CT in the immediate treatment group, assessed by SWM tests (Hypothesis 3).
b) Cochlear implant users showed an overall increased level of visual memory (which was trained) with CT in the immediate treatment group when assessed at week 10 by VRM Free Recall test (Hypothesis 3).
c) Cochlear implant users showed an overall increased level of sustained attention (which was trained) with CT in the immediate treatment group, assessed at week 10 by RVP A′ (Hypothesis 3).
d) Cochlear implant users showed an overall increased level of spatial planning (which was trained) with 10 weeks of CT in the immediate treatment group, assessed at week 20 by SOC mean moves taken to solve a 5 move problem. This is possibly a delayed treatment effect. In addition, cochlear implant users showed an improved performance of spatial planning, trained ability (SOC number of problems solved in minimum moves) with 10 weeks of CT, assessed at week 20 in the delayed treatment group (Hypothesis 3).
e) The administration of CT program lead to the significant improvements in sensorimotor and comprehension abilities, trained abilities (MOT screening tasks); executive function, spatial planning and WM, trained abilities (OTS tests); and visual memory, trained ability (VRM Free Recall and VRM Recognition tests) in the delayed treatment group (Hypothesis 3). However, this change was also noted after the first 10

weeks of study when the CI users in the delayed treatment group received only standard therapy.

f) Analyses combined across all the participants (Table 5) showed similar results, with CT - mediated enhancement of self-reported auditory ability (SSQ test), spatial working memory (SWM tests), verbal memory (VRM tests), sustained attention (RVP test), and spatial planning (SOC tests) skills.

The above findings lent some support to the third hypothesis and highlighted the possibility of cognitive flexibility and CT-mediated neuroplastic change in adult cochlear implant users. However, it is unclear whether post-training benefits were due to CT or practice effects. The participants in this study did not have a significant prior gaming experience which may have been counter-intuitive to evaluate the sustained attention outcome measures. Although there was a presence of huge variance between subjects, we observed the statistically significant but modest beneficial CT-mediated effects in attention, verbal memory, and visuo-spatial working memory. On the other hand, non-statistically significant deterioration of certain cognitive skills was also noted. This indicates that CT might not be equally beneficial for every cochlear implant user. Training should be tailored in accordance to patient's needs and rehabilitation outcome measures.

Even though this novel pilot study has a small sample size (N=12), it provides a substantial support to do further evidence-based research because the effects of CT in adult cochlear implant users is largely under-investigated. The current study replicates findings from several published recent reviews (Bisoglio, Michaels, Mervis, & Ashinoff, 2014; Shipstead, Redick, & Engle, 2012), which indicates improved executive functions and WM on tasks similar to training. As mentioned earlier, sustained attention is a distributed cognitive function and its enhancement after completion of CT may be secondarily due to enhancement of executive functions and WM. CT provides a unique medium to prevent and ameliorate the cognitive disorders in adult cochlear implant users. We are still uncertain about how these games drive cognitive benefit, what its mechanism of action is, what factors predict this cognitive enhancement, and whether results are transferrable to completely dissimilar training tasks. Furthermore, without imaging and surgical outcome measures, it is almost impossible to explicitly spot the CT induced structural changes in brain and/or other body organs when these changes can be due to mere presence of practice effects.

At week 20 of study, the outcome measure scores for cochlear implant users in the immediate training group will be maintained at week 10 level and outcome measure scores in the delayed training group will be improved from their baseline and week 10 levels.

Several cochlear implant users' of the immediate treatment group have sustained the constructive change of cognitive outcome measure scores in SWM, attention, and verbal recognition memory (SWM tasks, RVP A′ and VRM task) during the follow up period with only standard therapy. On the other hand, a few cochlear implant users of the delayed treatment group did not show any significant development from their pre-treatment scores, highlighting the fact that not every cochlear implant user could equally benefit from the CT. Future research should focus on identifying the drivers of the maintained effects so that we can recommend the CT to people who would benefit the most.

After 10 weeks of study, cochlear implant users in immediate training group will perform better on primary and secondary outcome measures than in the delayed treatment group.

As shown in Table 5, the adult cochlear implant users in the immediate training group (CT + Std Rx) performed better than the delayed treatment group participants (Std Rx) at week 10, in the following outcome measures: self-reported hearing ability (total speech spatial qualities score), visuo-spatial working memory and executive functions (SWM total errors for problems with 4 to 8 boxes and SWM strategy tasks), and spatial planning (SOC mean moves taken to solve a 5 move problem) (Hypothesis 5). In contrast, cochlear implant users in the immediate training group performed worse than the delayed treatment group users in the following cognitive outcome measures: motor screening task (MOT mean latency) and executive function, spatial planning and WM (OTS Tasks).

Note that significant differences were seen among the cochlear implant users of the two treatment arms (viz., the immediate and delayed treatment groups) at baseline for the five out of fifteen outcome measures. That is, cochlear implant users in the two treatment arms were not comparable in other respects for five outcome measures. Namely, AzBio Sentence test in background noise, SSQ total, two outcome measures for SWM tasks, and SOC mean moves taken to solve 5 move problems. Due to baseline differences, it was difficult to compare these two groups. The results lent limited evidence in favor or against this hypothesis.

6.2. Strengths and Weaknesses of the Present Work

Although details about the strengths and weaknesses of the present work are mentioned above, in this section we have summarized the meticulous items.

Strengths

- Randomized, prospective clinical trials are considered the gold standard study design for evidence-based assessment of an intervention (Hackshaw, 2009). Here, each participant received an intervention at random sequence over time. Randomization reduces chances of allocation and selection bias.
- RCT are known to be expensive. With due diligence and careful selection of study methodology, limited usage of resources was done for this study. Only the behavioral outcome measures had been included in this study. In addition, the trial's dependent or outcome measures are frequently used in clinical practice and research.
- This Translational NeuroTechnology project focuses on the clinically important questions and outcome measures. Although we provided insufficient evidence to implement the CT into clinical practice, it would be prudent to consider the CT for people who are having a high-risk for mild or moderate cognitive impairment.
- Researchers want the treatment effect to be retained during later non-intervention period. The follow-up evaluation at week 20 in the immediate treatment group helped us answer this question.
- Cross-over and multiple-stage sampling helped us to evaluate the effects of CT with a relatively small number of participants.
- We analyzed the data in four different ways to assess the changes seen in outcome measures. Namely, (i) After 10 weeks of CT in the analyses combined across all the participants (Table 5), (ii) Between two groups analyses (Table 4), (iii) Within/between participants analyses (Figures 10-24), and (iv) Within each group analyses (Table 2-3) over a period of 20 weeks. Each method has its own pros and cons. For example, (a) Within each group analyses was useful to figure out pre-post CT changes, ascertain pre-existing ongoing trend in the delayed treatment group and whether CT-mediated effects could be maintained in the follow-up assessment of the immediate treatment group. However, group sample size was very small. (b) Analyses combined across all the participants on our repeated-measure data

(immediately before the initiation of CT vs. immediately after the completion of CT) are known to reduce the individual differences that occur between subjects and this increases the power of the test. On the other hand, we ignored the fact that for some people (immediate treatment group) these were the week 0 and 10 visits, and for others they were the week 10 and 20 visits (delayed treatment group).

- Covariates such as age, duration of cochlear implant usage/hearing loss/profound hearing loss, education, physical activity, nutritional status, and subject effect were adjusted in LME analyses. As noted above, these variables had a strong ability to confound the generated findings.
- Both healthy physical activity and FANTASTIC lifestyle questionnaires are specifically designed for the Canadian population by the Canadian Society for Exercise Physiology. Diet, emotions, physical activity, and certain lifestyle factors are known to influence cognition. These questionnaires constitute a simple, non-invasive and easy-to-measure tool. The anthropometry, complete nutritional assessment, and thorough assessment of physical activity and lifestyle were considered beyond the scope of this study.
- There were no reported side effects with the CogniFit intervention and lab testing sessions.
- This clinical trial included independent outcome measures. There were no industry grant or potential conflicts of interest.

Weaknesses

- This study had a small sample size (*N*=12), similar with several other studies in cochlear implant users (Fu et al., 2005; Kronenberger et al., 2011; Oba et al., 2011). Furthermore, this is an interim report to evaluate the treatment effect estimates and consider the feasibility of a larger project.
- Absence of double or triple blinding and an active control can lead to biased functional outcome measure scores as opposed to objective. Self- reported auditory ability was the only functional outcome measure in this study.
- Absence of functional neuroimaging and molecular outcome measures has its own consequences. Now, we could not recognize whether CT-mediated improvements resulted from changes in the internal structure of neurons, or increased number of

synapses between neurons, or more neural pathways, or enhanced activity of certain brain regions/brain-derived neurotrophic factor, or some other reasons. However, understanding CT's mechanism of action was not our study purpose.

- Affective domains such as motivation and reward sensitivity were not explored. There were several technical glitches while the participant was playing games. Such issues can adversely affect the cochlear implant users' motivation and reward sensitivity pathways.
- Adherence data or amount of time spent playing training tasks was not available during the submission of this thesis. So, we could not demonstrate the relationship amongst CT and the amount, rate and time course of changes seen in outcome measures.
- Cochlear implant users' performance on some measures could have been improved simply due to practice, rather than an effect of treatment. We could not rule out and quantify the practice effect. On the brighter side, cochlear implant users did not report prior gaming or detailed neuropsychological testing experience.
- Interactions of ageing, environmental factors, and other medical conditions are possible. However, the speculations based on current knowledge of risk factors for cognitive decline were adjusted in linear mixed effect models. Even then, as in most clinical studies, there are always some more independent variables which could have been measured and adjusted.
- Results may not be broadly generalizable because our trial consisted of adult cochlear implant users, mostly well-educated, white Canadian adults from the Maritime Provinces with different health issues and expectations.
- Some cochlear implant users reported an improvement in their hearing after CT, but their AzBio sentence score in noise did not change. For example, user 004 and user 006 said, "I can hear better, but sentences are running fast for me". It should be noted that testing sentence understanding in background noise is challenging for people who are hard of hearing, but it mimics real life situation such as in a busy restaurant. The inclusion of additional auditory tests which probably put a less amount of cognitive load (for example, AzBio sentence test in quiet, phoneme recognition, and melodic contour identification) could have grasped this effect.

7. Conclusion

The efficacy of CT in adult cochlear implant users is an area of considerable confusion for clinicians and researchers. In the current randomized controlled trial, we proposed to compare the effects of playing CT games which involved active, experience-based, longitudinal, and safe learning in adult cochlear implant users from the Maritime Provinces. This structured CT modestly enhanced speech comprehension in noise, but this change was not significant. As well, the attention, self-reported auditory ability, spatial planning ability, visuo-spatial working memory, and verbal memory performance scores were, statistically, marginally in favor in CT + standard therapy, in adult cochlear implant users. CTs impact is questionable outside our lab data. More to the point, most participants enjoyed playing these games while some considered them rather challenging and time-consuming. In wrapping up, the present work rejects the old notion of considering brain as fixed, ended and immutable. Perhaps, novel task-specific CT may comprise a new preventive and "complementary" treatment option for adults suffering from cognitive impairment and/or hard of hearing individuals who use a cochlear implant.

8. Suggestions

Cochlear implant team should attempt to promote bilateral cochlear implantation, and arrange funding or make policy changes for candidates eligible for cochlear implantation.

The above findings should be confirmed with multicentered phase III RCTs and/or a meta-analysis. Massive variation in treatment effect size estimates was noted. It would be beneficial to plan studies highlighting the factors predicting this cognitive enhancement in the adult cochlear implant users. Thereby, CT could be tailored according to the driving factors and "unmet needs" of cochlear implant users. Only then, CT mediated good brain health, like good physical health, can yield significant contributions for public health.

Future research regarding the use of CT should focus on intensive and/or longer CT periods in people with a stable hearing loss. Interactions of lower-level sensory processes and higher-level cognitive processes in adult cochlear implant users also need further elucidation. Usage of neuroimaging/molecular neuroscience assessment tools could be fruitful in understanding the neurological bases of CT - How CT alters the brain and cognitive processes. Due consideration should be given to covariables such as duration of auditory deprivation, change in physical activity, diet, sleep, substance abuse, stress, prior gaming experience, other predictors of aural or cognitive outcome measures and long-term outcomes.

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