

Research INSIGHTS



Editor
J. D. Mendonca PhD CPsych

DECEMBER 2016 | VOL 13 No. 3

A BRIEF REVIEW AND CASE STUDY

Transcranial Magnetic Stimulation (TMS)

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ISSN 2368-6294 (Print)
ISSN 2368-6308 (Online)

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Transcranial Magnetic Stimulation (TMS): A Brief Overview



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Key words: Repetitive Transcranial Magnetic Stimulation, Major Depressive Disorder, Treatment-Resistant Depression, Treatment, Neurostimulation

ABSTRACT

The history of transcranial magnetic stimulation (TMS), a relatively non-invasive form of neurostimulation that modulates cortical activity using electromagnetic induction principles, goes back to 1771 when Galvani discovered bioelectricity. Introduced first as a neuro-diagnostic tool in 1985, and then as a clinical strategy in 1993, TMS clinical trials conducted in the 1990s and early 2000s showed that repetitive transcranial magnetic stimulation (rTMS) is a safe and effective way to treat those living with depression. As a result, TMS was approved for the treatment of depression in 2002 in Canada and the NeuroStar TMS Therapy System was approved by the United States Food and Drug Administration in 2008. A recent systematic review concluded that rTMS applied to the left prefrontal cortex (PFC) daily for 4 to 6 weeks is an effective and safe treatment for adults living with unipolar major depressive disorder who have failed one or more antidepressant trial. However, the long-term effect of rTMS on depression remains unclear. Although several mechanisms that could explain the antidepressant impact of rTMS have been proposed, the exact mechanism through which depressive symptoms are alleviated still needs to be determined. Future studies also need to verify the optimal treatment parameters for rTMS including the coil location, number of treatment sessions and ideal pulse frequency.

Background Highlights

Ever since the discovery of bioelectricity (electric potentials and currents produced by or occurring within living organisms) in 1771 by Luigi Galvani (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011), scientists and clinicians have been asking how this energy could be used to modify brain and nervous tissue activity for medical and experimental purposes. The development of electroconvulsive therapy (ECT) by Cerletti and Bini in 1937 (Endler, 1988), whereby electric currents were used to intentionally induce a seizure in those living with schizophrenia, is said to have ushered in the modern “medical device” age (Horvath et al., 2011). Since the development of ECT, a number of other medical devices, designed to alter electrical potentials within the brain, have been developed. The focus of this paper is on one specific type of electrical brain stimulation, *transcranial magnetic stimulation*.

Transcranial magnetic stimulation (TMS) is a relatively non-invasive form of neurostimulation that modulates cortical activity using electromagnetic induction principles. This technique is gaining increased attention in psychiatry and neurology. The key principles underpinning TMS were identified by Faraday in 1881 (Horvath et al., 2011). This British physicist observed that a pulse of electric current passing through a wire coil could generate a magnetic field. Further, the rate of change of this magnetic field determines the induction of a secondary current in a nearby conductor such as the nervous system.

As magnetic fields can pass through the skull with little to no resistance, unlike electrical energy, and knowing that the brain is able to conduct electrical energy, in the late 1890's there was a growing interest in the medical use of magnetic field energy. For example, in 1896, d'Arsonval placed a subject's head inside a magnetic coil to stimulate the retina, tissue that was known to be very sensitive to stimulation by induced currents (Geddes, 1991). Subjects reported seeing magnetophosphenes or sparks and some experienced vertigo and syncope (Barker, 1991). In 1902, Pollacsek and Beer,

researchers working in Vienna, Austria, treated a patient for depression using an electromagnetic coil placed over the skull (Beer, 1902). And, in 1910, Silvanus Thompson exposed the heads of volunteers, including himself, to magnetic fields of varying strength and reported “faint, flickering illumination” whether or not the persons eyes were opened or closed (Thompson, 1910).

Other researchers tried to use magnetic field energy to stimulate human muscles. For example, in 1965, Bickford and Fremming used a harmonic magnetic field and demonstrated muscular stimulation in animals and humans (Bickford & Freeming, 1965). And, in 1982 Polson, Barker and Freeston produced a magnetic stimulator capable of peripheral nerve stimulation (Polson, Barker, & Freeston, 1982). The clinical use of TMS was introduced by Barker et al. in 1985 (Barker, Jalinous, & Freeston, 1985), who demonstrated the influence of magnetic stimulation on the motor cortex. The machine that was created was developed as a neuro-diagnostic tool that could be used to study nerve fibers and create a functional map of the brain. However, the TMS machine was very slow to recharge and repetitive uses raised the coil's temperature (Noohi & Amirsalari, 2016). The era of TMS treatment began in 1993, when an Austrian group reported a beneficial effect in two profoundly depressed patients who underwent a course of repeated single-pulse TMS prior to ECT (Höflich, Hufnagel, Ruhrmann, & Müller, 1993). They followed up this study with a single-blind trial of 0.3 Hz TMS, delivered with a round coil centered at the vertex (Kolbinger, Hufnagel, Möller, Kasper, 1995), producing additional encouraging results.

Additional clinical trials of TMS efficacy were published in the 1990's. For example, in 1995, George et al. determined that the administration of daily left PFC repetitive TMS in six people with treatment-resistant depression (TRD) improved mood (George et al., 1995). Then, in 1996 Pascuale-Leone et al. conducted the first randomized sham-controlled multiple cross-over trial of daily left PFC rTMS in 17 people with TRD (Pascual-Leone, Rubio, Pallardo, &

Catala, 1996). These authors concluded that rTMS may become a safe alternative to ECT for depression. This work led to more definitive, larger, sham-controlled rTMS trials. The first large clinical trial of rTMS was conducted by O'Reardon et al. in 2007 and was sponsored by Neuronetics company, the company that made the rTMS machine (O'Reardon et al., 2007). This sham-controlled, multi-phased, multicenter trial included 301 participants recruited from 23 international sites (20 in the United States, two in Australia and one in Canada) and found that those who received rTMS had a clinically meaningful improvement in their mood when compared to the sham treatment group. Subsequently, a multi-site, industry-independent, sham-controlled, double-blind trial was conducted and confirmed the superiority of rTMS to usual treatment (George et al., 2010). This National Institutes of Health-funded study also used the NeuroStar TMS Therapy System (Neuronetics Model 2100 Clinical Research System) and applied the coil to the same area of the brain using the same type of pulse. Subsequently, the United States Food and Drug Administration (FDA) approved the use of the Neuronetics TMS machine for clinical use in treating Major Depressive Disorder (MDD) in 2008. Additional devices were approved by the FDA in 2013 and 2015 (Perera et al., 2016). The use of TMS for the treatment of depression was approved in Canada in 2002 (Dobek, Blumberger, Downar, Daskalakis, & Vila-Rodriguez, 2015).

How is TMS applied for therapeutic purposes?

Basically, during a treatment session an electric coil capable of generating a powerful magnetic field is applied on the surface of the head. The magnetic field can reach a few centimeters in to the cortex of the brain (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). The most commonly used coil is a figure-of-eight shape that generates a focal area of stimulation in the cortex. The unimpeded flow of the magnetic field creates local electric currents in the underlying cortex that travel parallel to the longitudinal axis of the coil but in the opposite direction to the electric current within the coil itself (Klomjai, Katz, & Lackmy-Valléeb,

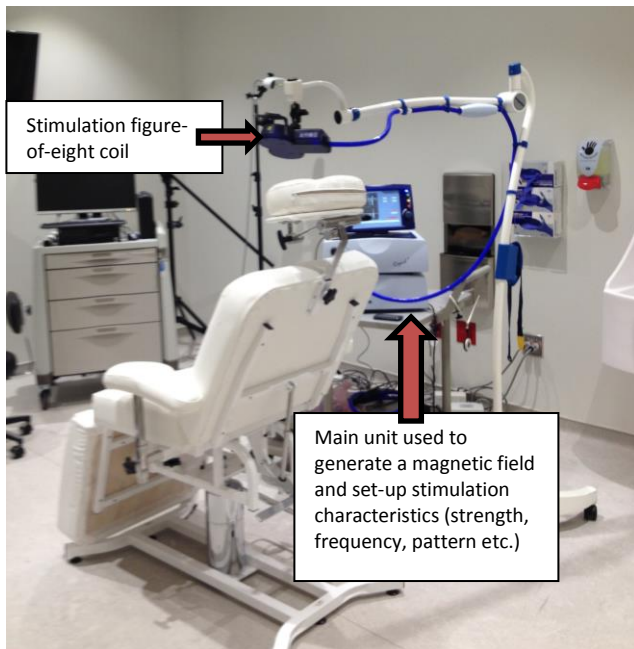
2015). This local electric current likely stimulates neuronal axons resulting in depolarization and modulates cortical interneurons activity resulting in stimulus-dependent facilitation or inhibition of the pyramidal neurons in the cortex (for review see: Brown, Ledwell, & Boyd, 2014).

TMS machines consist of a main unit and stimulating coil (Figure 1). The main unit includes a charging system (a transformer), one or more energy storage capacitors (typical energy storage is approximately 2000 Joules), a discharge switch, and circuitry that is used to control pulse shape, current intensity, and other functions. The peak discharge current needs to be several thousand amperes in order to induce currents in the brain of sufficient magnitude to depolarize neurons (about 10 mA/cm²) (Horvath et al., 2011; Rossi et al., 2009). The peak magnetic field strength achieved with each pulse is approximately 1.5 Tesla right underneath the coil, similar in strength to the magnetic field produced by a typical magnetic resonance imaging (MRI) machine (Deng, Lisanby, & Peterchev, 2013). During TMS treatments, the device's magnetic coils continually switch polarity creating a steady electromagnetic pulse. The depolarized neurons produce various physiological and behavioural effects, depending on the targeted brain area. Overall TMS is safe with few side-effects (Bewernick & Schlaepfer, 2015). Besides seizures, which are rare (Dobek et al., 2015), other possible risks associated with TMS include fainting, minor pains such as headache or local discomfort, minor cognitive changes, and discomfort or pain from the stimulation of the scalp and associated nerves and muscles on the overlying skin (Dodick, Schembri, Helmuth, & Aurora, 2010).

When administering TMS, several elements need to be considered including coil position and shape, current intensity, and frequency. All coils need to be able to produce electrical field intensity in the desired brain region that will surpass the threshold for neuronal activation with minimal side effects. As each shape produces different magnetic field patterns, coil geometric configurations impact the location and

size of the brain region(s) intended to be activated as well as the preferred direction(s) of stimulation. For example, the figure-eight coil results in a more focal pattern of activation whereas a double-cone coil is used for deeper stimulation (Deng et al., 2013).

Figure 1. TMS Machine



Prior to treatment initiation, an individual's resting motor threshold (RMT) is established so that the clinician can calibrate the TMS coil output energy. While RMT has high inter-person variation, it is relatively constant in a given individual (Herbsman et al., 2009). RMT is defined as the minimum TMS intensity needed to produce a motor-evoked potential when stimulating the motor cortex while the target muscle is at rest in at least 50% of trials (Rossini et al., 1994). The abductor pollicis brevis is usually used but other muscle groups in the hand and the leg can be targeted as well (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Once the appropriate output energy is determined, the coil is moved to the appropriate cortical region based on the target symptom or behavior.

TMS can be delivered as a single-pulse, paired-pulse or repetitive TMS. Each application has different

uses, from the mapping of motor cortical outputs and studying of brain-behavior relationship (single pulse), to the study of cortico-cortical interactions (paired pulse) (Rossi et al., 2009; Wassermann & Zimmermann, 2012). In repetitive transcranial magnetic stimulation (rTMS) the speed at which the magnetic coils change polarity is rapidly increased; positive and negative polarities are switched in just microseconds, resulting in pulses that are delivered in trains. This creates "repetitive" electromagnetic pulses and stronger electromagnetic induction with confirmed cortical effects that remain after the stimulation had ended (Pascual-Leone et al., 1994).

Pulse frequency can also be changed. Energy pulses can be delivered at either high (5-20 Hz) or low frequency (less than or equal to 1 Hz). Although there is considerable between person variability, high-frequency currents tend to increase motor cortex excitability (Pascual-Leone et al., 1994) while low-frequency currents tend to decrease motor cortex excitability (Chen et al., 1997).

TMS and Depression

Multiple studies have been conducted regarding the efficacy of TMS in the treatment of those living with depression. Depression is a complex, heterogeneous, and multi-factorial neuropsychiatric disorder. Although a reliable biomarker for depression has yet to be found, several decades of neurochemical, neurophysiological, neuropathological, and neuroimaging brain research have identified patterns of structural and functional abnormalities associated with depression. It is now accepted that patterns of activity in the neurocircuitry involved in emotional processing are part of the basic mechanism that leads to depression and impact the antidepressant treatment response. In depression, abnormally increased cerebral blood flow and metabolism have been identified in the orbital cortex, ventrolateral prefrontal cortex, sub-genual and pre-genual anterior cingulate cortex, the amygdala, ventral striatum, and medial thalamus. Some researchers took this as evidence of impaired regulation in the limbic-thalamo-cortical circuit and the limbic-striatal-

pallidal-thalamic circuit (Drevets, Ongur, & Price, 1998; Drevets, Price, & Furey, 2008; Mayberg, 1997). More recently, large-scale network dysfunction in depression has been proposed whereby the regulation of fronto-parietal (executive, action related) and default mode (resting state) network of the salient (emotional relevance) network is thought to be impaired (Y. Chen, Wang, Zhu, Tan, & Zhong, 2015; Hasler & Northoff, 2011; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Peng et al., 2015). A host of interacting structural and neurochemical factors are likely underlying large-scale network dysregulation in depression including brain atrophy, white matter lesions, glutamate/gamma-aminobutyric acid (GABA) balance, neuromodulators like monoamines, neuropeptides, and neurohormones (Drevets & Raichle, 1992; Mayberg, 2003).

Current treatment options for treatment-resistant depression include antidepressant medications, rTMS and ECT. Some studies have compared the two medical devices designed to alter electrical potentials within the brain, rTMS to ECT. A review of these studies concluded that ECT is a complementary, rather than a replaceable treatment for rTMS and standard pharmacotherapies (Fitzgerald, 2004). Although few studies have compared rTMS to usual pharmacotherapy, a recent meta-analysis conducted by two Australian researchers (Nguyen & Gordon, 2015) estimated first treatment response rate and remission rates for rTMS as 37.5% and 21.5%, respectively. Then, using data from the STAR*D trial (Rush, 2007), these authors found that the response and remission rates for antidepressant medications were 16.8 and 13.6%, respectively. Further, this study found that the Quality Adjusted Life Years (QALYs) gained with rTMS were higher than the QALYs gained with pharmacotherapy (1.25 vs. 1.18 QALYs) and that the overall treatment costs were less when using rTMS. And, although many people respond to medications specifically developed for depression (e.g., selective serotonin uptake inhibitors (SSRIs) such as Citalopram (Celexa), Fluoxetine (Prozac), or Sertraline (Zoloft)) and/or

psychotherapy, an estimated 20-40% are either unable to tolerate the medications that they have been prescribed (Ferguson, 2001) or fail to respond after repeated attempts (Greden, 2001). This again demonstrates the need for nonpharmacological approaches to care.

rTMS has been used either as a mono-therapy or in conjunction with other strategies, including medications, in the treatment of depression (Bewernick & Schlaepfer, 2015). In current depression treatment paradigms, the rTMS coil is applied to the dorsolateral PFC (targeting the middle frontal gyrus around Brodman area 46) (Bohning et al., 1997). Although the exact mechanism of the antidepressant impact of rTMS in treatment-resistant depression is still not fully understood, the therapeutic effect of PFC rTMS might be the result of the modulation of PFC excitability, which, in turn, may modulate limbic areas and their connections via cortico-thalamic-limbic pathways.

Several mechanisms that could explain the antidepressant impact of rTMS have been proposed including glutamate excitatory and GABA inhibitory modulation which likely results in a host of neurochemical and neurophysiological changes that produce the therapeutic effect (Baeken & De Raedt, 2011; Chervyakov, Chernyavsky, Sinitsyn, & Piradov, 2015; Noda et al., 2015). There is significant inconsistency in the literature regarding neurochemical and neurophysiological changes as a result of rTMS. Sources of inconsistency likely arise from multiple sources including: variability in stimulation parameters; heterogeneity of the depressive syndrome and patients treated; difficulty differentiating “state” vs. “trait” markers; and distinguishing changes induced by rTMS from changes that occur due to the remission of depression regardless of the treatment modality used.

Various approaches have been used to determine coil location, pulse frequency, and number of sessions. Regarding coil location, approaches that have been used include the “5-cm” rule (Pascual-Leone et al.,

1996), stereotaxic localization, MRI neuronavigation tools (Bradfield, Reutens, Chen, & Wood, 2012; Fitzgerald et al., 2009) or the international 10-20 electroencephalogram lead localization system (Mir-Moghtadaei et al., 2015). As discussed above, while some clinicians use high frequency (5-20 Hz) hoping to increase motor cortex excitability, others have found that using low frequency (1 Hz or below) results in lowering motor cortex excitability. There is currently no clear guidance regarding the number of pulses per session, which can vary from 600 to 3000. Clinicians are now suggesting 10 to 30 sessions as longer courses are producing more promising results (e.g. Valero-Cabre, Pascual-Leone, & Rushmore, 2008).

A recent systematic review has concluded that left PFC rTMS repeated daily for 4 to 6 weeks is an effective and safe treatment for adults living with unipolar major depressive disorder who have failed one or more antidepressant trials (Perera et al., 2016). However, the long-term effect of rTMS on depression remains unclear, as most studies only followed people for 12 weeks or less (Bewernick & Schlaepfer, 2015).

Discussion and Future Directions

While research has proven that rTMS is an effective treatment for depression with few side effects, the optimal treatment parameters, including the exact location of the coil, the frequency, number of pulses per session and the number of sessions of rTMS, remain unclear. Further studies regarding the impact of low- versus high-frequency stimulation, laterality, and the ideal rTMS pulse and train parameters are now in the field (Bewernick & Schlaepfer, 2015). As well, the short and long-term effects of a combination of rTMS and antidepressant drug therapy remain unknown (Bewernick & Schlaepfer, 2015).

While research confirms the efficacy of rTMS with depression, current research also suggests that rTMS may have valuable therapeutic potential for many other illnesses and disorders because of its unique capacity to selectively increase or decrease the

excitability of neurons in discrete brain regions. For example, some researchers have been investigating the impact of rTMS on those living with Parkinson's Disease, schizophrenia, tinnitus and Alzheimer's Disease (Wassermann & Zimmermann, 2012). The therapeutic benefit of TMS has also been examined for acute mania, bipolar disorders, catatonia, post-traumatic stress disorder, the rehabilitation of aphasia or of hand function after stroke and pain syndromes, such as neuropathic pain, visceral pain or migraines (Rossi et al., 2009).

The theta-burst paradigm is a relatively new and promising rTMS method that involves the application of 50 triplet bursts at a 5 Hz frequency. When applied continuously (continuous theta burst stimulation: cTBS), long-term depression may be induced; however intermittent application (iTBS), that is to say applying 2 seconds bursts every 10 seconds, may result in long-term potentiation and increased cortical excitability (Ni & Chen, 2008). Early studies have demonstrated some efficacy for this paradigm (Chistyakov, Rubicsek, Kaplan, Zaaroor, & Klein, 2010; Li et al., 2014; Plewnia et al., 2014).

People living with MDD and treatment-resistant depression often face a trial-and-error approach to care. The selection of the appropriate care strategy can depend on the person's home address (TMS machines tend to be available only in academic health science centres), as well as public perception (while ECT is very effective in treating treatment-resistant depression, this care strategy is still stigmatized because of its use in the past and how ECT has been depicted in the media). Further, the costs associated with TMS can vary as patients may need to drive for long distances and care delivery is not routinely covered by existing healthcare plans. Currently publically funded TMS is only available in two Canadian provinces, Saskatchewan and Quebec. While some hospitals do cover in-kind costs associated with running a TMS clinic (e.g., St. Joseph's Health Care London), sometimes through dollars made available by generous donors, accessible and equitable access to this efficacious

treatment for depression is needed. While the issue of accessibility may soon be mitigated through the availability of self-administered home TMS (George, Taylor, & Short, 2013), the impact of such an option on patient safety and treatment effectiveness has not been thoroughly investigated.

Finally, as the exact parameters of optimal rTMS delivery are developed, several clinical practice issues need to be addressed. While industry-sponsored training has a role in developing clinician skills, the role of peer-to-peer mentorship and supervision, as well as graduate medical education, should also be considered. Continuing Medical Education (CME) programs could be developed that ensure a strong foundation in TMS practice. As well, TMS clinicians may wish to establish formal standard operating procedures related to the training and ongoing evaluation of procedural skills for all involved staff.

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*Treating Chronic Tinnitus and Secondary Depressive Symptoms using Sequential Repetitive Transcranial Magnetic Stimulation (rTMS) Followed by Home-Based Transcranial Direct Current Stimulation (tDCS): A Case Study in a Tertiary Mental Health Care Setting**

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Key words: Tinnitus, Transcranial Magnetic Stimulation, Neuromodulation, Transcranial Direct Current Stimulation, Patient-Centered Care, Older Adult, Depression, Home-Based Therapy

**Written informed consent was obtained from the patient for publishing this case study and has been placed in the patient's medical file.*

ABSTRACT

Tinnitus, the perception of annoying sounds in the absence of external physical auditory stimuli, frequently presents with concomitant mood issues and can be very difficult to treat. While the pathophysiology of tinnitus remains unclear, symptoms may be related to hyperactivity in the primary or secondary sensory cortex due to changes in the balance between inhibitory and excitatory mechanisms resulting in either a lack of sensory input (reduced auditory nerve fiber firing rates) or alterations of higher cortical functions. While pharmacotherapy, counselling, and nutraceuticals work for some patients, this brief review and case study describes how neuromodulation, sequential repetitive transcranial magnetic stimulation (rTMS) followed by transcranial direct current stimulation (tDCS), were used to decrease tinnitus severity in an 80-year-old man living with long-standing tinnitus and depression. Here we describe how an older adult living with chronic tinnitus and low mood can self-administer an efficacious daily therapy from home, an approach that is more patient-centered and more cost effective.

Background Highlights

Overview of Tinnitus

Tinnitus, the perception of annoying sounds or noise in the absence of external physical auditory stimuli, is a relatively frequent health issue with an annual incidence of 1% (Hoffman & Reed, 2009). It is

estimated that approximately 150,000 Canadians experience tinnitus, while globally tinnitus affects the quality of life of 1-3% of the world's population (Dobie, 2003; Shargorodsky, Curhan, & Farwell, 2010). Those with tinnitus symptoms may hear ringing, buzzing, roaring, clicking or hissing sounds

(Jastreboff, 1990). The phantom noise can vary in pitch from a low roar to a high squeal, and may be heard in one or both ears. In some cases, the sound can be so distressing that it can interfere with a person's ability to concentrate or hear actual sound. As a result, those living with tinnitus can experience affective symptoms such as insomnia, memory problems, depression and/or anxiety, frustration, irritability and suicidal thoughts/actions (Beebe Palumbo, Joos, De Ridder, & Vanneste, 2015; Malakouti, Mahmoudian, Alifattahi, & Salehi, 2011). Concomitant mood issues are fairly common among those living with tinnitus, but estimates vary considerably depending on how the sample was generated and the size of the sample (Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011). For example, a 2008 study of those living with tinnitus showed that the overall prevalence of depression was 17.4% and that the overall prevalence of anxiety was 22.8% (Adoga, Adoga, & Obindo, 2008). Yet, another study found that 39% of the members of a tinnitus patient treatment group had a comorbid depressive disorder and that 45% had an anxiety disorder (Zoger, Svedlund, & Holgers, 2006).

Epidemiological studies have demonstrated that age, prolonged exposure to loud noises, head, and neck injuries, infections and ototoxic drugs are associated with tinnitus (Swain, Nayak, Ravan, & Sahu, 2016). It is thought that these factors can precipitate abnormal hyperactivity in the inner ear, vestibulocochlear nerve, or along the auditory pathway following deafferentation or supratentorial structural damage. However, because of the variety of triggers and possible pathways associated with tinnitus, it is likely that tinnitus is a syndrome and that more than one cause exists, precluding a single efficacious treatment. Despite this background knowledge, the full pathophysiology of tinnitus is not well understood (Beebe Palumbo et al., 2015; Kuo, Paulus, & Nitsche, 2014; Swain et al., 2016). While it was originally thought that tinnitus had a cochlear origin, severing the vestibulocochlear nerve often proved to be ineffective (House & Brackmann,

1981), showing that tinnitus is not simply a straightforward result of imbalanced firing patterns in impaired cochlea. Currently it is thought that the tinnitus signal may arise from cochlear hair cell loss, resulting in reduced auditory nerve fiber firing rates and ultimately hyperactivity caused by reduced cortical inhibition in higher brain structures, such as the auditory cortex (Norena, 2011).

Due to both the pathophysiology and the frequently seen affective component of the tinnitus, both auditory and non-auditory structures are activated among those with tinnitus. Major brain networks that have been shown to be involved in the awareness of tinnitus include the perception, distress, salience, and memory networks which, in turn, involve many areas of the brain including the prefrontal cortex, the posterior and anterior cingulate cortexes, the amygdala, the hippocampus, and the anterior insula (Beebe Palumbo et al., 2015; Shekhawat, Stinear, & Searchfield, 2015). It is thought that tinnitus may be due to hyper-excitability in any of these regions of the brain as a result of either an increase in excitation or a decrease in inhibition, thus leading to an excitatory-inhibitory imbalance.

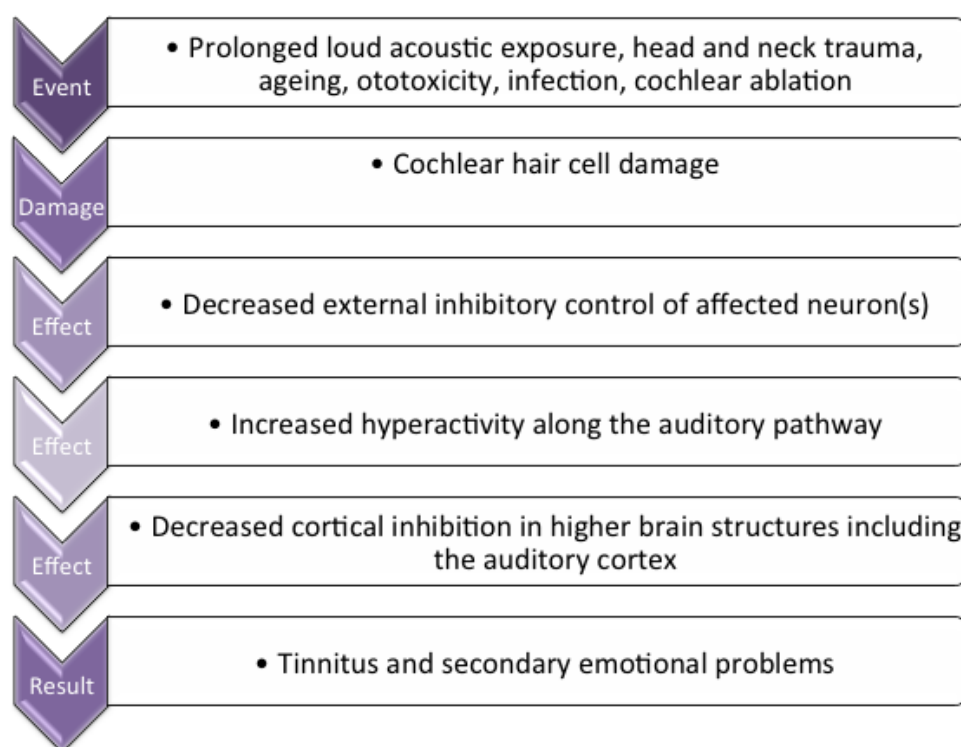
In an effort to further elucidate the pathophysiology, some investigators have focused on understanding why some drugs may lead to tinnitus. For example, a well-known side effect of aspirin/acetylsalicylic acid, the third most commonly used drug in the world (Kyle, Wang, & Shin, 2015), is hearing loss and tinnitus (Guitton et al., 2003). Studies have shown that aspirin may increase the spontaneous activity of the auditory nerve, change the average spectrum of cochleoneural activity (Cazals, 2000), and increase spontaneous firing rates in the secondary auditory cortex (Alvan et al., 2016). Another possibility, proposed by Sun et al., is that salicylate-induced tinnitus may be due to the modulation of neural processing in the central nervous system (Sun et al., 2009).

The impact of antidepressants on tinnitus also remains unclear. While some investigators have

described the induction of tinnitus following the use of tricyclic antidepressants including amitriptyline (Mendis & Johnston, 2008), others have found benefit (Bayar, Boke, Turan, & Belgin, 2001). The mechanism(s) through which tricyclics may cause or worsen tinnitus is/are unclear, but the up-regulation of glutamate leading to cochlear glutamate

excitotoxicity has been proposed as a possible mechanism (Langguth, Landgrebe, Wittmann, Kleinjung, & Hajak, 2010). These authors also suggest that tinnitus may be due to the impact of tricyclic antidepressants on neural activity in the frontal cortex. Mechanisms that may lead to tinnitus are summarized in Figure 1.

Figure 1: Proposed pathophysiology of tinnitus. Many different events can lead to cochlear hair cell loss, resulting in reduced auditory nerve fiber firing rates and ultimately hyperactivity caused by reduced cortical inhibition in higher brain structures, such as the auditory cortex. Tinnitus is commonly comorbid with emotional problems such as sleep disturbances, depression and anxiety.



In summary, tinnitus may be due to hyperactivity in the primary or secondary sensory cortex due to changes in the balance between inhibitory and excitatory mechanisms resulting in either a lack of sensory input (reduced auditory nerve fiber firing rates) or alterations of higher functions. As neurotransmitters and neuromodulators alter neuronal excitability, several treatments have been tested.

Management of Tinnitus

Pharmacotherapy can modulate neuronal activity. For example, clinical pharmacotherapeutic studies conducted in the early 80's involving intravenous lignocaine and lidocaine (sodium channel blockers that exert inhibitory effects on the central and peripheral neurons) showed promising results in reducing tinnitus when given intravenously (Melding, Goodey, & Thorne, 1978). However, the impact was not observed when given orally thereby limiting

therapeutic utility. As well in the 1980's, anticonvulsants were used to treat tinnitus. However, when the treatment was stopped, patients noticed a worsening in their symptoms (Reed et al., 1985). Drugs, such as diuretics, anticoagulants, and vasodilators, aimed at improving the microcirculation of the auditory system, have been tested without success (Baguley, McFerran, & Hall, 2013). In addition, as glutamate is the main excitatory neurotransmitter in the auditory system, studies of memantine and other glutamate antagonists have been conducted, but have failed to show benefit (Baguley et al., 2013).

Other investigators have tried to establish the efficacy of several nutraceuticals. For example, knowing that vitamin B12 deficiency is associated with axonal degeneration, demyelination, and neuronal death, Berkiten, et al. examined the impact of B12 replacements and found that among those who were B12 deficient, tinnitus severity decreased (Berkiten, Yildirim, Topaloglu, & Ugras, 2013). Coelho et al., used zinc to treat tinnitus and found that few participants saw an improvement in either loudness or annoyance (Coelho et al., 2013). In 2011, a systematic review of the impact of ginkgo biloba on tinnitus concluded that a particular extract could be effective among those with age-associated cognitive impairment or dementia in whom tinnitus was also present (von Boetticher, 2011).

Counselling approaches have also been tried and evaluated. Six studies included in a meta-analysis of the impact of Cognitive Behaviour Therapy (CBT) on tinnitus found no evidence of a significant difference in the subjective loudness of tinnitus (Martinez-Devesa, Perera, Theodoulou, & Waddell, 2010). However, quality of life increased in five studies, suggesting that CBT may have a positive effect on the management of the emotional issues associated with tinnitus. A systematic review of tinnitus retraining therapy (TRT), which includes counselling and sound-generation therapy, indicated that most studies were of poor quality, but that TRT may be more effective than tinnitus masking approaches (i.e.

providing an external sound that reduces the annoyance of the tinnitus through either disguising it, suppressing it, or making it more pleasant) (Phillips & McFerran, 2010).

Other investigators have examined the impact of reducing the severity of non-auditory symptoms or secondary complications associated with tinnitus. For example, one randomized, double-blind, placebo-controlled study examined the impact of sertraline (a selective serotonin reuptake inhibitor [SSRI] used to treat depression and anxiety disorders) among those living with concomitant tinnitus and depression. Tinnitus severity decreased more among those receiving the drug than those in the placebo group and depression and anxiety scores also improved (Zoger et al., 2006). Further, a 2011 study found that melatonin is associated with a statistically significant decrease in tinnitus intensity and improved sleep quality among those living with both tinnitus and sleep disturbances (Hurtuk et al., 2011).

Knowing that functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans have shown the involvement of various brain regions (Eichhammer, Hajak, Kleinjung, Landgrebe, & Langguth, 2007; Kang & Escott, 2008; Sajisevi, Weissman, & Kaylie, 2014), and that tinnitus is linked to high spontaneous neuronal activity due to an excitatory-inhibitory imbalance, brain stimulation has been investigated as a method to decrease neuronal activity and hence tinnitus. The remainder of this paper reviews how stimulation methods (neuromodulation methods) for tinnitus have been used. A case study where both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) is then presented for an older patient living with intractable, long-standing tinnitus to identify an effective patient-centered care approach with low cost to both the patient and the healthcare system.

Neuromodulation for Tinnitus

Repetitive Transcranial Magnetic Stimulation (rTMS)

Interest in the use of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for tinnitus has been growing, following promising results from several small-scale studies conducted 10 to 20 years ago. A well-tolerated strategy associated with few side effects, rTMS uses short, focused magnetic pulses to induce brief activity of the brain area lying underneath the treatment coil. The physiological impact of rTMS is a function of the location, intensity, frequency, duration, and time intervals between stimulations. rTMS has the potential to alter pathological plasticity and to foster physiological plasticity thereby decreasing tinnitus symptoms (Yilmaz, Yener, Turgut, Aydin, & Altug, 2014). Immediate effects are thought to be the result of direct excitation of inhibitory or excitatory interneurons. rTMS has the advantage of being non-invasive, with a relatively low side effect profile. Repeated stimulation is hypothesized to work by decreasing or increasing cortical excitability, depending on whether a low (≤ 1 Hz) or high frequency (5-20 Hz) is administered respectively (Pridmore, Kleinjung, Langguth, & Eichhammer, 2006)

Some studies have investigated the impact of a single session of rTMS on tinnitus symptoms. When high-frequency (10-20 Hz) pulse trains were applied, there were immediate but short-term impacts (Langguth et al., 2008). Another review article found that single sessions of rTMS to either the temporal or temporoparietal cortex had a transient effect on tinnitus perception in about 50% of people (Langguth, et al., 2012). Other investigators have used repeated session of rTMS on consecutive days, mainly using a low-frequency (1 Hz) current, again with mixed results (Langguth et al., 2008). This review concluded that most studies that examined the impact of rTMS over temporal or temporoparietal cortical areas found a statistically significant reduction of tinnitus complains, but that exact application parameters (e.g., location, duration)

remained unclear. Another study rTMS demonstrated a significant reduction of tinnitus symptoms when either temporal rTMS or combined frontal and temporal rTMS were used when compared to sham rTMS (Langguth et al., 2014). A possible reason for the mixed results could be that the impact of rTMS may be due to the different excitability levels at the time of rTMS use. Another, systematic review found that rTMS had little risk and showed short-term benefits, but that the long-term benefits of rTMS were questionable (Peng, Chen, & Gong, 2012).

Transcranial Direct Current Stimulation tDCS

tDCS is thought to induce glutamatergic plasticity through the application of a relatively weak current through the scalp (Kuo et al., 2014). Typically, tDCS causes changes in the resting membrane potential with anodal stimulation decreasing the resting membrane potential and cathodal stimulation leading to increased resting membrane potential (Stagg & Nitsche, 2011; Nitsche et al., 2008). Knowing that the left temporoparietal area of the brain seems to demonstrate maladaptive plasticity among those with tinnitus (Plewania, 2011), both Fregni et al. and Garin et al. demonstrated that a single session of anodal tDCS to this area of the brain resulted in short-lasting reduction of tinnitus symptoms (Fregni et al., 2006; Garin et al., 2011). Others have tried stimulating other areas of the brain. For example, based on Vanneste and De Ridder's findings that the prefrontal cortex also seems to be involved in tinnitus symptoms (Vanneste & De Ridder, 2012), Faber et al. found that bilateral prefrontal tDCS reduced perceived annoyance, but not intensity of tinnitus symptoms independent of stimulation polarity (Faber, Vanneste, Fregni, & De Ridder, 2012). Further, Shekhawat et al. explored the impact of tDCS intensity and duration on the efficacy of stimulation and found the best results for 20 minutes at 2 mA (Shekhawat, Stinear, & Searchfield, 2013). Adverse effects reported so far for tDCS are limited to mild headaches and itching of the surface to which the electrodes are applied (Been, Ngo, Miller, & Fitzgerald, 2007). Anodal and cathodal tDCS, administered for up to 20 minutes, have been

typically observed to increase and decrease excitability respectively (Been et al., 2007). While short-term benefits of tDCS have been documented, there are limited data on the effects of repetitive tDCS stimulation for tinnitus (Kuo et al., 2014). In 2012, a systematic review and meta-analysis of tDCS among tinnitus patients could not fully conclude the efficacy of the modality for the condition due to the limited number of studies, but the review did demonstrate a significant decrease in tinnitus intensity and that stimulation of the left temporal area and bifrontal tDCS resulted in comparable results (Song, Vanneste, Van de Heyning, & De Ridder, 2012).

Combining TMS & tDCS

Some studies have examined the impact of sequential rTMS and tDCS. For example, Lang et al. used tDCS preconditioning as a method of potentiating the effect of TMS on corticospinal excitability (Lang et al., 2004). These investigators found that a preconditioning session of tDCS markedly reduced the threshold for subsequent rapid-rate rTMS to provoke a lasting change in corticospinal excitability, as measured by motor evoked potential (MEP) amplitude. They found that “inhibitory preconditioning” with cathodal tDCS resulted in 5 Hz rTMS increasing corticospinal excitability above baseline levels, whereas “excitatory/facilitatory preconditioning” with anodal tDCS caused subsequent 5 Hz rTMS to reduce corticospinal excitability to below baseline levels.

Preconditioning or priming with rTMS can also maximize neuromodulation treatment impact. For example, Iyer et al. demonstrated that the inhibitory impact of low-frequency 1 Hz rTMS can be enhanced by preconditioning with 6 Hz rTMS in healthy adults (Iyer, Schleper, & Wassermann, 2003). Similarly, Langguth et al. examined the impact a 20 sessions with a combination of 20 Hz rTMS over the left frontal cortex followed by 1 Hz rTMS over the left auditory cortex (Langguth et al., 2014). These investigators concluded that this combined treatment was more efficient than either 20 treatments of PET-

based neuronavigated 1 Hz rTSM or 1 Hz rTMS over the left auditory cortex.

While these studies evaluated the impact of preconditioning, the phased care strategy described below, for an older patient with chronic tinnitus and secondary depression, uses sequential rTMS and tDCS in an effort to maintain the established short-term impact of rTMS with tDCS, a strategy that can be self-applied in a home environment.

CASE STUDY

Past medical History

An 80-year-old gentleman was referred to a tertiary care mental health facility in London, Ontario with depression associated with a 60-year history of bilateral tinnitus, worse on the left side. As a farmer and a construction worker, he was frequently exposed to loud noise sources. When seen, he had a significant hearing impairment and utilized bilateral hearing aids, which additionally served to drown out his tinnitus. An audiogram done in January 2006 demonstrated moderate sloping to profound sensorineural hearing loss, symmetrical in both ears, to a maximum loss at 4000 Hz of 65 dB, with 60% speech discrimination bilaterally. Over the last six years, his tinnitus had progressively worsened and led to secondary emotional disturbances to his life; he now fit the criteria for having both depression and anxiety. The severity of his tinnitus fluctuated and was typically worse later on in the day, occasionally waking him up from sleep at night. At times the tinnitus intensified in his ears and was experienced along with a “ringing” sensation behind his eyes and in his head. He also reported hyperacusis (increased sensitivity to everyday sounds). His past medical history revealed that he had undergone radical radiotherapy for type 2a prostate cancer and later developed radiation proctitis. He had also had a quadruple coronary artery bypass graft subsequent to a myocardial infarction. His latest MRI, performed in 2007, revealed a moderate degree of generalized cerebral and cerebellar atrophy in the absence of any

focal pathology in cerebellopontine angle of the inner ear canal.

In the past, he had undergone trials of citalopram (an SSRI) and trazodone (a tetracyclic antidepressant), which resulted in headaches and nausea. Lorazepam (a benzodiazepine), paroxetine (an SSRI), and pregabalin (an anticonvulsant) were also tried and had a deleterious effect on his tinnitus.

Approach to Care

The patient was first seen the Mood and Anxiety Clinic in May 2008. His medication list included aspirin, amlodipine, atorvastatin, zopiclone and gabapentin, in addition to clonazepam pro re nata (PRN), multivitamins, and fish oil capsules. With the exception of a postural tremor, no neurological signs were evident. Assessment also revealed depression

(Geriatric Depression Scale [GDS] (Yesavage et al., 1982): 15/30), but no anxiety (Geriatric Anxiety Inventory [GAI] (Pachana et al., 2007): 4/20), normal cognitive function (Mini Mental Status Examination [MMSE] (Folstein, Folstein, & McHugh, 1975): 29/30) and no history of alcohol abuse (Short Michigan Alcoholism Screening Test – Geriatric Version [SMAST-G] (Blow et al., 1998): 0/10).

In view of the patient's past history of limited success with pharmacotherapy, an initial trial of rTMS was undertaken in an effort to reduce the overall severity of his tinnitus. The patient first attended the Neurostimulation Clinic in London, Ontario in June, 2009. Based on the outcome of the rTMS trials, described below, the evolution of the patient's care strategy can be broken down into three phases. For a summary of the full course of treatments, see Table 1.

Table 1: Treatment Approach

Phase	Modality	Treatment Location	Stimulation Points	Total Sessions	Details
1a	rTMS	hospital	Left TPA	6 daily	1 Hz; 1200 pulses at 100% RMT
1b	rTMS	hospital	Bilateral TPA	3 daily	1 Hz; 1600 pulses at 100% RMT
2a	tDCS	hospital	Bilateral cathoidal TPA + deltoid	3 daily	CESta™ x20 min per TPA @0.5mA
2b	tDCS	hospital	Bilateral cathoidal TPA + deltoid	5 daily	CESta™ x20 min per TPA @ 2mA
3a	rTMS	hospital	Bilateral TPA	6 daily	1 Hz; 1600 pulses at 100% RMT
3b	tDCS	home	Bilateral cathoidal TPA + deltoid	7 daily	Self administered, CESta™ x20 minutes per TPA @ 2 mA

Note: rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation, TPA: temporoparietal area; Rx: treatment; Hz; hertz; RMT: resting motor threshold; mA: milliamps. CESta™: a product of Mind Alive Inc. (Mind Alive Inc. (formerly Comptronic Devices Limited) is a mental-health electronics design and manufacturing company incorporated in the province of Alberta, Canada in 1981) capable of delivering cranio-electro simulation (CES), microcurrent electrotherapy (MET) and tDCS.

Phase 1: Trial of rTMS

Based on the previously reviewed literature, the client was given a course of first unilateral and then bilateral rTMS. The temporoparietal areas (TPAs) that were to be stimulated were identified using a 10-20-20 EEG system to locate a point midway between temporal lead 3 (T3) and parietal lead 3 (P3) on the left hemisphere (LTP3) and T4 and P4 on the right hemisphere (RTP4).

Inhibitory rTMS was administered using the Magstim Super Rapid 2 machine (Magstim, UK) at a frequency of 1 Hz. The initial treatment involved stimulation with 120 trains of 10 second duration (1200 pulses) at 100% resting motor threshold (RMT), increasing to 160 trains (1600 pulses) thereafter. While rTMS was applied to the left TPA for the first six treatments, it was applied bilaterally for the remaining three treatments (see Table 1).

Using a psychometrically sound method for measuring subjectively perceived tinnitus loudness and annoyance (Adamchic, Langguth, Hauptmann, & Tass, 2012), before and after each treatment the patient was asked to draw a line across a 10 cm visual analog scale (VAS) to rate his tinnitus and mood. When asked to score tinnitus severity levels, a score of 0 indicated no tinnitus and 10 indicated the worst possible tinnitus. When scoring mood, a score of 0 indicated best mood and 10 indicated worst mood.

As seen in Figure 2, the patient started treatment with very high subjective tinnitus levels, at almost the maximum of 10. Following the first rTMS session self-rated tinnitus levels dropped from 9.7 to 6.3. Consistently, pre-treatment tinnitus scores were higher than post-treatment scores. While there was some variability in both the pre- and post-treatment scores, generally speaking, perceived tinnitus levels dropped during the rTMS sessions applied to the left TPA to just over a perceived score of 2. Although pre- and post-treatment perceived tinnitus levels were elevated during the second session of bilateral TPA stimulation with rTMS, generally speaking post-treatment scores were maintained at about 2.

The first treatment post-treatment mood score dropped substantially from 8 to 3. While this was the greatest pre- to post-treatment decrease, pre-treatment scores were always higher than post-treatment scores. Both pre-treatment self-rated tinnitus levels and mood spiked prior to the second bilateral rTMS session confirming the strong association between mood and tinnitus for this patient. Post-treatment mood scores varied from a high of 5 to a low of 1, but remained fairly steady throughout the course of phase 1, at just over 1.

Phase 2: Trial of tDCS

When contacted one week after the nine rTMS sessions, the client indicated that his tinnitus levels had again increased to just over 9. Realizing that the rTMS had decreased the patient's perceived tinnitus, but that this strategy appeared to have only short-

term effects, it was decided that cathodal tDCS, which provides a similar form of inhibition and could be eventually administered daily at home, would be tried. Initially, 0.5 mA current was tried to assess this patient's tolerance to the burning sensation often described by patients. As the patient did not experience significant burning at the lower dose, the dose was subsequently increased to 2 mA in an effort to increase the likelihood of a long-term response.

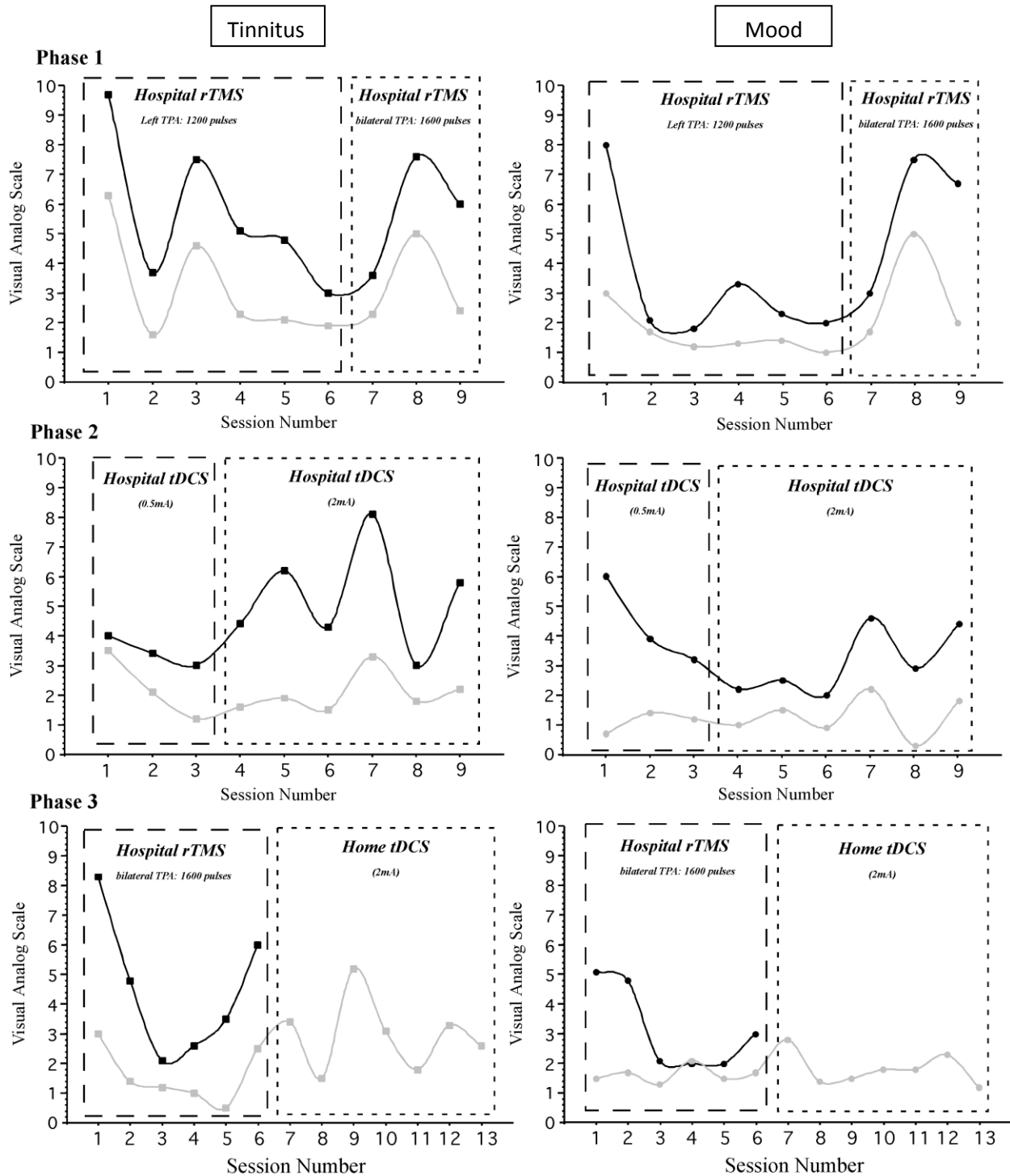
The patient was given a single session of bilateral rTMS (data not shown in Figure 2; tinnitus pre-treatment: 9.2, post-treatment: 3.6) followed by nine sessions of tDCS, 3 sessions at 0.5 mA, followed by 6 sessions at 2 mA (Figure 2). The direct current was provided by a battery powered, constant current stimulator, named the CESTa™ (a product of Mind Alive Inc. (Mind Alive Inc., formerly Comptronic Devices Limited, is a mental-health electronics design and manufacturing company incorporated in the province of Alberta, Canada in 1981), and delivered via a pair of water-soaked sponge electrodes (35 cm²). The cathodal electrodes were placed for 20 minutes over each TPA, as defined above, and the anodal electrode was placed on the deltoid muscle. Again, tinnitus and mood ratings, as scored on a VAS, were obtained before and after each treatment (Figure 2).

As seen in Figure 2, despite some variation in the perceived pre-treatment tinnitus levels, post-treatment scores were lower after the tDCS treatments and ranged from a high of 3.5 to a low of 1.2. Similarly, post tDCS treatment mood scores ranged from a high of 2.2 to a low of 0.3 suggesting a good treatment response.

Phase 3: Daily Home Treatments with tDCS

Ten days after the termination of phase 2 tDCS treatments, the patient was reassessed. Knowing that both treatment strategies had clear short-term impact on both tinnitus and mood, and that the patient would be burdened by daily in-hospital treatments, a new strategy was implemented. First, the patient received

Figure 2. Visual Analog Score (VAS) outcome measures after three phases of neurostimulation treatment for tinnitus in an 80-year old gentleman with secondary comorbid depression.. Pre (black) and post (grey) treatment measures are plotted for tinnitus (square symbols denote tinnitus measures where 0=no tinnitus, 10=worst possible tinnitus) and for mood (circular symbols where 0=best possible mood, 10=worst possible mood) against the session number. Pre-treatment measures were almost always higher (worse tinnitus or poorer mood) than post-treatment VAS scores.



six daily rTMS treatments (bilateral stimulation of TPA regions using 1 Hz; 160 trains of 10s pulses at 100% RMT) to re-establish the response.

As seen in Figure 2, perceived tinnitus levels fell from 8.3 to 3.0 with the first rTMS session. During the course of subsequent five rTMS treatments, post treatment tinnitus levels varied between 2.5 and 0.5. Similarly, the patient noted mood elevation, with post-treatment mood scores ranging from 2.1 to 1.3.

In late July, the patient received detailed instructions regarding how to self-administer bilateral TPA stimulation using tDCS. First, the patient's machine was programmed to deliver 2 mA. He was then instructed on where on his head he should place the cathodal lead and how to place the anodal lead on his deltoid muscle. He was also instructed to soak the sponge leads in normal saline and then squeeze out excess fluid before placing them on the specified locations. To assure accurate learning, the patient then self-administered the tDCS in the clinic and was given feedback on his technique. The patient then self-administered seven tDCS sessions at home and was called one week later regarding his status and the post-treatment VAS scores.

During the seven self-administered at home tDCS sessions, the post treatment tinnitus levels were lower than those seen during any other phase and ranged from a high of 5.2 to a low of 1.5. Further, during the last three sessions he was able to maintain his tinnitus levels at approximately 2.5. Similarly, this mood scores fluctuated from a low of 1.2 to a high of 2.8 indicating the ability of the tDCS to maintain both low levels of tinnitus and a better mood.

DISCUSSION

Tinnitus, a syndrome associated with perception of annoying sounds or noise in the absence of external physical auditory stimuli, can be very difficult to

treat. While factors associated with the development of tinnitus have been identified, the pathophysiological mechanisms that lead to tinnitus remain unclear. As a result, there is currently no standardized treatment for tinnitus. Drugs such as memantine, counselling strategies such as TRT, and alternate therapies such as ginkgo biloba, and neuromodulation with rTMS and tDCS have been tried, often with mixed results. As there is no one treatment for tinnitus, strategies aimed at mitigating the effects of tinnitus are an area of great interest. This paper describes how one patient whose tinnitus and depression were ineffectively treated with pharmacological agents, benefitted from neurostimulation techniques: rTMS and tDCS. Using the approach described in the paper, we were able to identify an inexpensive, patient-centered treatment option that continued to reduce longstanding tinnitus to acceptable levels and improve mood.

Despite the number of investigators who, since the 1980's, have been trying to find clear pathological mechanisms that will lead to either a cure or an effective treatment, we still do not have a clear understanding of what causes the perception of tinnitus. With the advent of better imaging techniques, it is hoped that we will soon have a better understanding of what causes tinnitus and what would be an efficacious treatment. However, it is likely that multi-centre studies will be needed to attain a large enough sample size with appropriate power to detect meaningful differences.

It appears likely that tinnitus is a syndrome with a possible myriad of pathological underpinnings. Current treatment strategies may in fact be used for screening in the future. For example, it is possible that those who respond to a particular treatment, such as lidocaine or rTMS, may make-up a unique tinnitus subtype. As well, it has been shown that those who respond to bi-frontal tDCS stimulation for tinnitus relief have a higher gamma band activity in the right primary and secondary auditory

cortex as well as the right parahippocampus prior to treatment than non-responders (Vanneste, Focquaert, Van de Heyning, & De Ridder, 2011). Findings from studies such as these may help future clinicians better match patients to treatments, leading to fewer failed treatment attempts and thereby reducing the time the patient experiences reduced quality of life.

The findings from this case report confirm a relationship between tinnitus severity and mood; both improved with treatment. However, the nature of the relationship between tinnitus and mood remains unclear. While it is possible that symptom overlap confounded both the pre- and post-treatment VAS scores, it is also possible that the combined neuromodulation strategy improved both perceived tinnitus levels and self-reported mood. While tinnitus sounds could be emotionally arousing and so lead to depression and anxiety, and some medications used to treat depression can lead to tinnitus, both tinnitus and depression could be caused by a common trigger (e.g., both health issues involve similar cortical networks and neurotransmitter systems) (Langguth et al., 2011). Although the location of the rTMS and tDCS electrodes used in the described case study was specific to the treatment of tinnitus, and was not that typically used for treating depression, there is some evidence that the inferior parietal lobule, a component of the default mode network (DMN), could have been stimulated. For example, there is evidence that the effect of prefrontal rTMS in depression extends proximally to areas in the DMN resulting in change in functional connectivity between prefrontal areas and DMN nodes (van der Werf, Sanz-Arigita, Menning, & van den Heuvel, 2010). Connectivity between prefrontal areas and areas in the DMN are thought to contribute to depressive rumination (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Although speculative, it is conceivable that direct inhibition of the temporoparietal area may have modified DMN connectivity in our patient, resulting in reduction of

rumination on tinnitus. Thus, while the goal of the treatment strategy described in the case study was to decrease tinnitus, it is possible that both mood and tinnitus were treated, resulting in both improved mood and less tinnitus. Knowing that at least 17% of those living with tinnitus also experience depression, this case study suggests that those diagnosed with depression should also be screened for tinnitus, and *visa versa*, echoing the conclusions of Hébert et al. (Hébert et al., 2012)

Although the results reported here are those of a single uncontrolled case and, as such, must be taken in context, they provide encouraging evidence that clients who need daily treatment can do so at home, by themselves, once given clear instructions. For clients who need daily treatment and who only experience short-term symptom relief from rTMS and tDCS, clinicians may need to think about self-care home-based strategies. As this care strategy does not require daily transportation to hospital, it is a more patient-centered and a less costly approach to wellness. tDCS machines are now readily available at a relatively low cost for a high quality machine that is able to deliver the right energy. However, as tinnitus is likely a syndrome with multiple causes, it is suggested that patients see a clinician/psychiatrist prior to beginning any home-based therapy.

Future studies could look at a number of issues. For example, knowing that a number of factors could precondition the impact of rTMS, Langguth et al. noted that future efficacy studies should examine the impact of the combination of patient-related and stimulation-related characteristics (Langguth et al., 2008). As well, future studies of both rTMS and tDCS need to determine the impact of coil placement, intensity, frequency and duration on both perceived tinnitus levels and concomitant disorders such as depression and insomnia in order to establish best-practice guidelines. Future clinical studies could also investigate the use of home/self-administered tDCS in a sham-controlled, double-

blind study involving a larger number of participants.

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