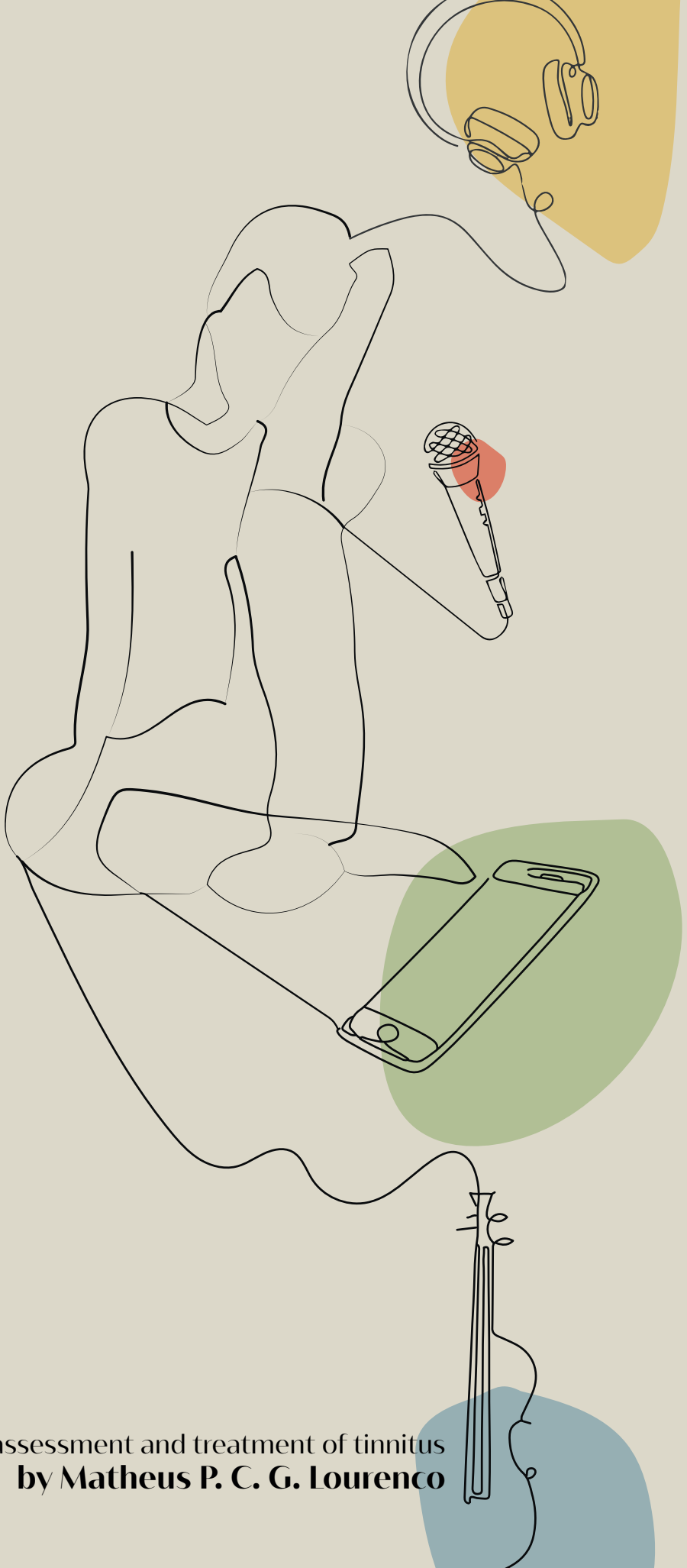
Bring the Noise!

BRING THE NOISE



Fear, assessment and treatment of tinnitus

by Matheus P. C. G. Lourenco

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DISSERTATION

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by

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CHAPTER 1

General introduction

From trees to tinnitus

> *"If a tree were to fall on an island where there were no human beings would there be any sound?"* – The Chautauquan (1883)

The answer provided to the infamous question postulated by The Chautauquan was *no*. Sound is the transformation of vibrations that travel through a medium (e.g. air) into coherent neurological signals, and consequently cannot exist outside an interpreter of sound. The corollary that may follow – "*If a human being were to hear a tree fall, would there be any tree*?" – is at the heart of this dissertation as we seek to better understand the experience of phantom sounds, specifically tinnitus.

What is tinnitus?

Current tinnitus definitions (e.g. Baguley et al., 2013; Cima, 2018; Pawel J. Jastreboff et al., 1994; Langguth, 2011; Table 1) converge in specifying a lack of an acoustic source while sound is perceived. In other words, authors agree that *tinnitus* is the perception of a sound without a corresponding acoustic origin. Different from the experience of other phantom acoustic perceptions such as voices or music, tinnitus is limited to sounds without explicit semantic meaning (e.g. tones, hissing, or chirping). Transient tinnitus experiences may subside within seconds, minutes or days (i.e. acute tinnitus), though for some its experience, whether continuous or intermittent, becomes chronic. Persistent tinnitus that does not spontaneously remit over a significant period of time (considered to be at least 3 months) may be classified as chronic tinnitus (Fuller, 2021). Chronic tinnitus may take a toll in the life of those who experience it. Sleep disturbance, concentration difficulties, suicidal thoughts, depressive symptomatology, anxiety, anger, avoidance environments perceived as too silent or loud, and decreased quality of life are some of the reported effects of tinnitus (Hall et al., 2018). Such chronic tinnitus that is associated with emotional reactivity and related disability can be further classified as Chronic Disabling Tinnitus (Fuller, 2021). The current work then utilizes the definition of Chronic Disabling Tinnitus as the unremitted perception of a sound (for at least 3 months) that is without semantic meaning nor corresponding acoustic origin, which produces significant emotional reactivity and related disability.

Table 1: Example of tinnitus definitions

Definition	Author
"A*n auditory phantom perception, and therefore cannot be associated with any sound measurement*" (p. 216)	Jastreboff et al. (1994)
"A common and distressing condition that is typically characterized by the perceived sensation of sound in the absence of an external stimulus" (p. 1635)	Langguth (2011)
"The conscious perception of an auditory sensation in the absence of a corresponding external stimulus" (p. 1600)	Baguley et al. (2013)
"The symptom itself, tinnitus aurium, can be defined as the phantom perception of continuous sound or noise in the absence of an external (or adequate) source" (p. 369)	Cima (2018)
"Tinnitus is the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source, which becomes Tinnitus Disorder 'when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioural changes and functional disability'" (p. 1)	De Ridder et al. (2021)

Epidemiology

A review of 35 tinnitus prevalence studies found that estimates for tinnitus vary widely, between 5.1 to 42.7% (McCormack et al., 2016). Variability in estimates were in part attributed to differences in the geographical location of the study, population demographics, tinnitus assessment and heterogeneous reporting (Biswas & Hall, 2020; McCormack et al., 2016). Recently, a standardized tinnitus assessment was created to be used across Europe in an attempt to provide a more accurate picture of tinnitus epidemiology. Biswas et al. (2020) included and 11 427 participants representing 11 different languages across Europe. The prevalence was estimated to be 14.7%, ranging from 8.7% (Ireland) to 28.3% (Bulgaria), without differences between genders (Biswas et al., 2020). Higher tinnitus prevalence was confirmed with increased age and worsening hearing. The authors further investigated tinnitus severity (i.e. self-reported level of annoying, worrisome or bothersome tinnitus), finding it prevalent in 1% of the participants, ranging from 0.6% (Ireland) to 1.4% (Romania), with a difference between women (1.4%) and men (1%). Moreover, the role of lifestyle risk factors (e.g. alcohol consumption, smoking, obesity) have contradictory findings and are yet to be fully understood (Biswas & Hall, 2020). As with previous reports, current epidemiological findings in the tinnitus field are restricted to the geographical location in which the study is conducted (mostly in developed countries) as well as the assessment methods of tinnitus.

Assessing tinnitus

The subjective tinnitus experience cannot be directly observed or measured, thus mostly relying on patient self-report assessments. As audiological features of the tinnitus percept (e.g. loudness, pitch, location) do not adequately explain tinnitus severity (Andersson, 2003), assessments methods evolved to include and reflect tinnitus related distress, disability, coping, attention and beliefs (Table 2).

Table 2: Tinnitus related self-report assessments

Assessment	Author	Purpose	Sub-scales	Recall Timeframe
Tinnitus Questionnaire (TQ)	Hallam (1988)	Measure psychological aspects of tinnitus complaints and distress	Emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance, somatic complaint.	One week.
Tinnitus Handicap Questionnaire (THQ)	Kuk et al. (1990)	Measure level of perceived tinnitus related handicap.	Physical, health, emotional status, social consequences hearing and communication, personal viewpoint.	No timeframe specified.
Tinnitus Handicap Inventory (THI)	Newman et al. (1996)	Measure level of perceived tinnitus severity.	Functional, emotional and catastrophic responses.	No timeframe specified.
Tinnitus Coping Style Questionnaire (TCSQ)	Budd and Pugh (1996)	Measure tinnitus related coping strategies and style.	Maladaptive coping, effective coping, and passive coping.	No time frame specified.
Tinnitus Vigilance and Awareness Questionnaire (TVAQ)	Cima et al. (2011)	Measure heightened attention towards tinnitus		No time frame specified.
Fear of Tinnitus Questionnaire (FTQ)	Cima et al. (2011)	Measure tinnitus related fear		No time frame specified.
Tinnitus Functional Index (TFI)	Meikle et al. (2012)	Measure tinnitus severity and treatment related change	Tinnitus intrusiveness, sense of control, quality of life, sleep, hearing, concentration, relaxation, and emotion.	One week.

Such a list of assessments contributes towards a comprehensive picture of those who experience tinnitus and shed light into the high heterogeneity of experience (e.g. Henry et al., 2012; Schlee et al., 2016). However, self-report assessments have limitations, which

hinder the accurate portrayal of tinnitus. High levels of reading difficulty in the tools have been reported to potentially affect tinnitus assessment (Atcherson et al., 2011). Furthermore, effects of the psychological state during assessment have been documented to influence responses (Belli et al., 2008; Brüggemann et al., 2016; Das et al., 2012; Langguth et al., 2011). More importantly, bias associated with memory reconstruction (i.e. recall bias) can be influenced by the setting of the assessment (e.g. hospital), the recency of the experience, and the averaging of experiences within longer (or unspecified) time frames (Shields et al., 2016; Stone & Shiffman, 1994).

Underlying cognitive and behavioral mechanisms of Chronic Disabling Tinnitus

Despite the limitations, a comprehensive assessment of the tinnitus experience allows for insights into the underlying cognitive and behavioral mechanisms which may explain tinnitus disability. Whereas tinnitus triggers (e.g. excess earwax, increased stress, ototoxicity) and audiological features of the tinnitus percept (e.g. loudness, pitch, location) do not adequately predict disability (Andersson, 2003; Wallhäusser-Franke et al., 2017), the role of fear, attention and avoidance have been postulated to play a major role in the development and maintenance of Chronic Disabling Tinnitus (Table 3). A brief description of each model follows.

Table 3: Overview of tinnitus models

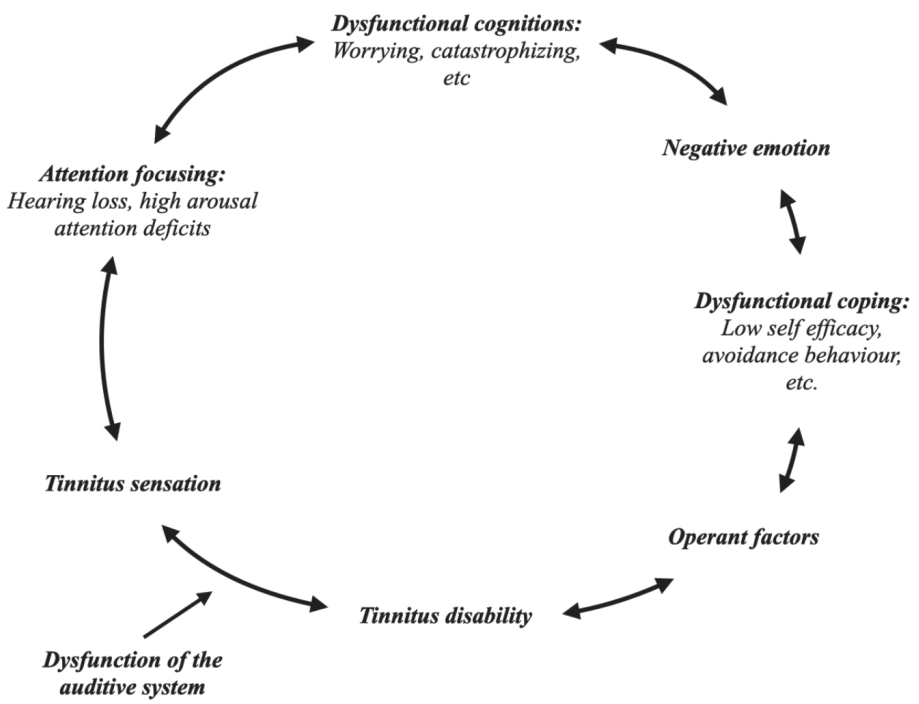
Model	Fundamental assumptions	Core prediction
Habituation model (Hallam et al., 1984)	Decrease response to the tinnitus perception (i.e. habituation) can be achieved through repeated exposure.	Habituation is disrupted due to heightened attention in moments of high physiological arousal (e.g. due to daily stressors).
Neurophysiological model (Pawel J. Jastreboff et al., 1988; Pawel J. Jastreboff, 1990)	Through classical conditioning the tinnitus perception is associated with aversive emotional responses.	Weakening the association between tinnitus perception and emotional responses is essential for habituation. Thus, extinction, the presentation of the conditioned stimulus without the unconditioned stimulus, results in decrease tinnitus disability and distress.
Cognitive Behavioural Model (McKenna et al., 2014)	Automatic evaluations of the tinnitus percept are at the core of dysfunctional responses.	Improvements in tinnitus distress and disability are achieved through altering the negative automatic thoughts on the tinnitus meaning and controllability.
Fear Avoidance model of tinnitus (Cima, Crombez, et al., 2011; Kleinstäuber et al., 2013)	Associative learning processes and catastrophic misinterpretations of the tinnitus percept are responsible for a downward spiral of emotional and behavioural reactions. Avoidance plays a pivotal role in the development and maintenance of distress and disability. Opposed to the downward spiral, a neutral or positive interpretation of the tinnitus percept is expected elicit a functional response.	Improvements are expected with the use of exposure therapy in order to facilitate extinction of the learned associations between fear and tinnitus.

The Habituation model

The model specifies that crucial to Chronic Disabling Tinnitus is the habituation process (Hallam et al., 1984), more specifically, the failure to habituate to the tinnitus percept. Habituation is defined as the decrease in responses (e.g. physiological arousal) to a repeated or continuous exposure to the stimulus (e.g. tinnitus). Thus, habituation may be hindered when attention is continuously directed towards the percept due to affective learning associations. The model assumes that tinnitus features (e.g. pitch, intensity) are constant, and thus can be classified as a repeated or continuous stimulus. In reality, tinnitus features fluctuate (Cederroth et al., 2019) and may be experienced as new stimulus whenever changes are perceived, and hence not a repeated or continuous stimulus.

Avoidant behaviours were later incorporated into the model to help explain disability and decreased quality of life (e.g. avoidance of environments perceived as too silent or loud; Figure 1; Kröner-Herwig et al., 2003). The model further elaborates on the avoidant behaviours as the result of operant learning, which refers to the change in frequency of behaviour through positive or negative reinforcement or punishment (Skinner, 1938). In the context of the Habituation model, an individual may avoid situations where heightened physiological arousal (e.g. fear) is expected or experienced. The avoidance of these experiences (i.e. removal of negative stimulus) provides immediate relief (i.e. negative reinforcement). According to the model, reduction of physiological arousal before entering such environments is a necessary part in reducing tinnitus distress by weakening the negative association (Mckenna, 2004). It should be noted that strategies to decrease physiological arousal (e.g. relaxation techniques) may act as an avoidance strategy in itself, hindering the habituation process by not challenging the originally created association between tinnitus and heightened physiological arousal (i.e. fear).

Figure 1: The Habituation model

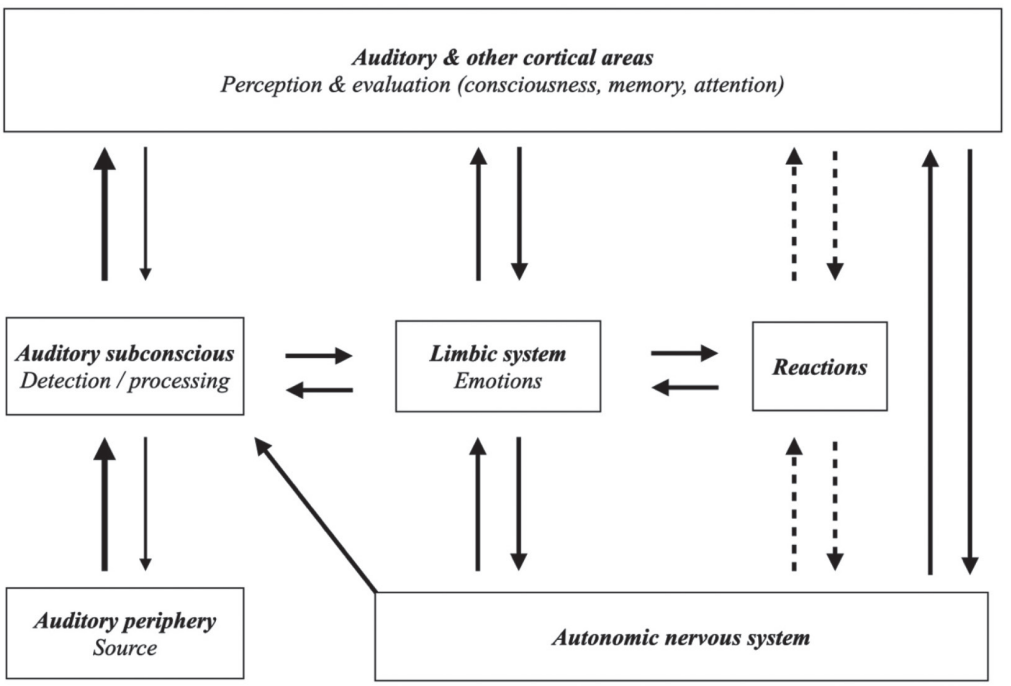


Note: adapted from Kröner-Herwig et al. (2003).

Neurophysiological model

Building upon the Habituation model, the Neurophysiological model (Figure 2) further assumes that the habituation process is hindered due to an aversive emotional state being associated (i.e. conditioned) with the tinnitus percept (Pawel J. Jastreboff et al., 1988; Pawel J. Jastreboff, 1990). Central to the model is classical (i.e. Pavlovian) conditioning, where two previously unrelated stimuli are paired (Pavlov, 1927). More specifically, a neutral stimulus (Conditioned Stimulus; CS) is paired with a biologically relevant one (Unconditioned Stimulus; US) which elicits a response (Unconditioned Response; UR). Successful pairing results in responses (Conditioned Response; CR) to the CS in the absence of the US. Despite the model's reliance on classical conditioning paradigms, there is a lack of clarity on the model's proposed associations (Baguley et al., 2013). Moreover, the research which provides the theoretical underpinnings is based on animal models and thus focused on tinnitus perception generation and limited in the explanation of tinnitus disability and distress.

Figure 2: The Neurophysiological model



Note: adapted from Jastreboff (2011; p. 579).

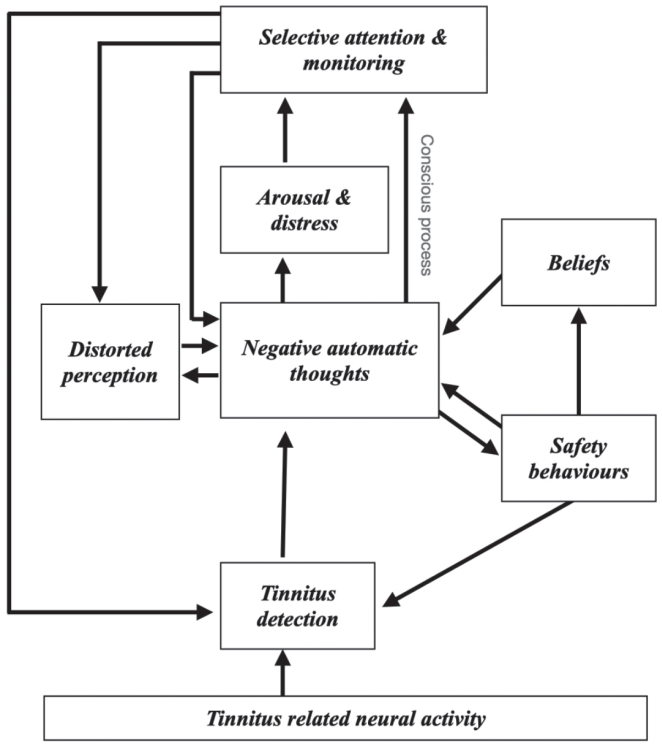
Nonetheless, treatment based on the Neurophysiological model is aimed at appeasing the patients' emotional reactions through psycho-education while utilizing sound therapy to reduce tinnitus perception (Tinnitus Retraining Therapy; Pawel J. Jastreboff & Hazell, 2004). The use of sound therapy relies on the generation of sounds that mask the characteristics of the tinnitus percept while psycho-education is used to deconstruct any tinnitus-related fears. Limited evidence for the efficacy of this particular treatment exits (Cima et al., 2019). More specifically, masking of tinnitus perception may provide short-term relief, thus avoiding the feared stimulus and working as negative reinforcement. Furthermore, distress and disability potentially increase as patients may become dependent on sound generation to avoid tinnitus perception (Mckenna & Irwin, 2008).

Cognitive Behavioural model

Contrary to the Neurophysiological model, the Cognitive Behavioural (CB) model of tinnitus aims at explaining tinnitus distress through the cognitive process of appraisal (Figure 3; McKenna et al., 2014). According to Lazarus (1991) appraisal, can be divided into primary – appraisal of the causal attributions (e.g. what causes tinnitus) – and secondary – appraisal of controllability (e.g. what can it be done to reduce tinnitus). The dual appraisal model may then explain the negative tinnitus evaluation (e.g. tinnitus as a result of irreversible hearing damage), which in turn increases physiological arousal leading to active monitoring of and selective attention towards the tinnitus percept. Safety behaviours are the direct result of such appraisals. Beliefs that loud environments may further increase tinnitus severity may lead to the avoidance of such environments or to other coping strategies (e.g. ear plugs).

Consequently, the CB model justifies treatments that focus on tinnitus appraisal (e.g. through CBT) and reducing physiological arousal (e.g. relaxation, mindfulness). Some indirect support for the model may be inferred from the efficacy of treatments, such as mindfulness based cognitive therapy (McKenna et al., 2017) in reducing tinnitus related distress. However, studies to test the model itself are lacking with only limited evidence for the separate components (McKenna et al., 2014).

Figure 3: The Cognitive Behavioural model



Note: adapted from McKenna (2014).

Fear Avoidance model

As the name suggests, fear – trough catastrophic misinterpretations of tinnitus (e.g. indication of brain damage) – is the hinge which pivots patients into a pathological spiral instead of a path to recovery (Cima, Crombez, et al., 2011; Kleinstäuber et al., 2013). The role of fear in the development and maintenance of chronic disability has been supported in the field of chronic pain (e.g. Meulders, 2020), from where the model originates (Lethem et al., 1983; Vlaeyen & Linton, 2000, 2012). Parallels between pain and tinnitus have been stipulated for decades (e.g. Møller, 1997). A starting point between similarities stems from the observation that the chronic experiences from both fields are characterized by the lack of identifiable source and (further) physical harm (D. De Ridder et al., 2011; Møller, 1997, 2007). Furthermore, severity of chronic pain and tinnitus are marked by oversensitivity to specific stimuli, such as light touch and soft sounds respectively (Møller, 1997). More interestingly, chronic experiences of pain and tinnitus are not necessarily

associated with distress and decreased quality of life. Fear, attention and avoidance contribute to the pathological expression of these experiences. Successful treatment for both chronic experiences are similar, relying on Cognitive Behavioural Therapy (CBT) with a highlighted role of exposure during treatment (e.g. Fuller et al., 2020; Vlaeyen et al., 2012). The model is further elaborated on in the next.

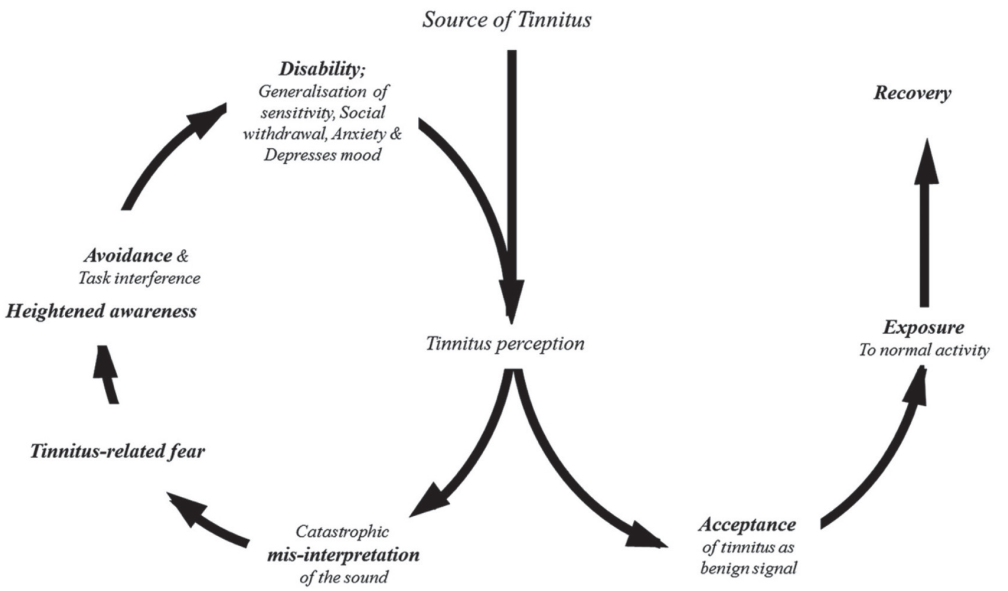
From fear to freedom

> *Or in the night, imagining some fear,*
> *How easy is a bush supposed a bear!* – Shakespeare (1605, 5.1.1)

The FA model postulates that the pathological cycle is triggered through negative misinterpretations of tinnitus. As in the name of the model, *fear* is thought to play a pivotal role in the development of Chronic Disabling Tinnitus. Tinnitus-related fear, increased attention and relentless monitoring follow. The result is defensive mechanisms, such as the avoidance of stimuli that are deemed threatening, which in turn increases disability, distress, and decreased quality of life (Figure 4). Avoidance (i.e. an adaptive behavioural response to fear; Watson & Rayner, 1920), also highlighted in previous models, takes a fundamental role in the development of disability as individuals may avoid common situations in daily life. Environments perceived to have higher levels of sound (e.g. restaurants, bars, social gatherings, movie theatres) are avoided due to the perceived threat of potential tinnitus worsening. On the other hand, moments in which the tinnitus perception may be more salient due to silence (e.g. evening and night times), are also avoided and maladaptive strategies may be employed (e.g. masking of the tinnitus percept), affecting not only the one who perceives tinnitus, but those close to them (Hall et al., 2018).

Alternatively, tinnitus may be perceived as a relatively harmless experience. In this case, no detrimental cycle is initiated, and the individual may continue with a normal, unaltered daily life. The crucial moment of tinnitus experience in which the path to recovery or pathological cycle diverge is postulated to be dependent on the learned association between tinnitus and fear.

Figure 4: Fear Avoidance model (replicated from Cima et al., 2018)



Fear is an emotional response resulting from the perception of threat to health or safety. Fear serves as an adaptive response by motivating animals to avoid harm. Examples are easily observed from mice to men: fear of heights, predators, or the dark. While some fears may be innate (e.g. fear of snakes), others may be learned (e.g. fear of flying). Learned fear holds evolutionary benefits as a harmful experience (e.g. pain resulting from a snake bite), produces anticipatory defensive behaviours (e.g. avoiding snakes). Some events may not be learned fast enough from a first-hand experience (e.g. a poisonous snake bite may end one's life). As such, indirect learning without undergoing the experience (e.g. through observation or verbal communication) provides an added benefit in the evolutionary process.

The process of creating (or re-creating) associations through observation (i.e. social learning; Bandura et al., 1967) adds yet another layer to the process of fear acquisition. Overall, humans may acquire fear from a variety of sources, such as personal experiences (i.e. classical or operant conditioning), observation and verbal instructions derived from cultural norms. Beliefs (e.g. tinnitus may signal a brain tumour vs. tinnitus as benign) can then be passed on and may become ingrained in a population. Such a rich learning environment and innate capacity to learn fear occasionally leads to maladaptive fear responses to unharmful and unthreatening events or experiences (e.g. fear of flying). Sustained maladaptive fear associations and responses may lead to the development of pathological cycles that reverberate through one's life (as illustrated in the FA model).

Biologically salient negative experiences, such as pain, are powerful motivators to seek safety and trigger avoidance behaviours. More specifically, pain may quickly create fear of stimuli which then are avoided due to potential harm. Pain is a naturally feared stimulus, and biologically imperative in the evolutionary process. The universality of pain led to comprehensive development of associate learning paradigms which robustly support the FA model. While the evidence on the relationship between fear and pain is rich in the field of chronic pain (e.g. Vlaeyen & Crombez, 2020), the development of fundamental research to support the FA model in the tinnitus field is in its infancy. Thus, the fundamental research of the FA model was based on fear of pain. Currently there is no evidence that tinnitus is as naturally as feared as pain, hampering the adaptation of the FA model. The origins of Chronic Disabling Tinnitus fear are not yet clear, though it has been suggested by the different models to rely on learned associations processes (i.e. classical conditioning, operant conditioning, social learning).

As in the Neurophysiological model, classical conditioning is postulated to be one integral mechanism in the development of Chronic Disabling Tinnitus. More specifically, fear conditioning, which relies on the pairing between a neutral (CS) and a biologically salient (US) stimulus which elicits a fear response (UR). A powerful US elicits an innate UR. In a successful association, the contingent pairings of CS and US will result in a motivational change of the CS, which activates the representation of the US, and hence starts eliciting an anticipatory conditioned response (CR) in the absence of the US. An example may be drawn from the field of chronic pain where a normally innocuous movement (proprioceptive CS; e.g. bending over) has occurred with a pain (US), leading to fear of the bending over. This type of conditioning can be and is reliability re-created in lab setting with healthy participants, where fear of movement is established, and avoidance of the movement is measured (for a review on fear conditioning in the context of pain see Meulders, 2020). Moreover, the experience of the feared CS (e.g. bending over) without the expected negative outcome (e.g. pain), provides the opportunity for the formation of new CS – no-pain-US associations, thereby challenging dysfunctional expectations and weakening the previously made association (i.e. extinction).

An unanswered question is whether we can simply substitute *tinnitus* for *pain* and establish learned fear of tinnitus sounds in a similar way. Currently, paradigms in tinnitus experimental studies are limited to animal models (e.g. Brozoski et al., 2012; Pawel J. Jastreboff et al., 1988). Animal studies have supported the correlations between hearing damage (i.e. loss of outer hair functioning) and tinnitus, as it may trigger

related hyperactivity (i.e. in the dorsal cochlear nucleus; Kaltenbach et al., 2002). Such paradigms, however, are severely limited in the understanding of tinnitus distress and disability. Moreover, even establishing that animals have acquired tinnitus perception is challenging and restricted by behaviour experiments. The clear role of tinnitus in classical conditioning models (e.g. US, CR) remains unclear and it is not known if the experience of tinnitus is as naturally feared as pain (and thus a possible US). Furthermore, the creation of tinnitus in humans within lab conditions remains a challenge as it is not known if the experience of a constant and even loud tone may lead to reliable fear conditioning.

Treating tinnitus

Currently, a common cure for tinnitus perception does not exist, and since tinnitus does not automatically translate into suffering (as the majority of individuals with chronic tinnitus do not suffer from Chronic Disabling Tinnitus), a cure, albeit desirable, may not be necessary. However, Cognitive Behaviour Therapy (CBT) is highly recommended for the treatment of tinnitus (Cima et al., 2019), with a recent Cochrane review reporting potential benefits of CBT on reducing the negative impact of tinnitus on quality of life (Fuller et al., 2020).

With a long tradition, CBT aims at the complex relationship between behaviour, cognition and emotion (Beck, 1979; Ellis & Grieger, 1977). CBT is an umbrella term that includes therapeutic approaches stemming from both behaviour, and cognitive therapies. Learned associations are challenged through behavioural techniques (e.g. exposure), while cognitive techniques modify the relationship between thought (e.g. catastrophizing) and emotion (e.g. fear). By combining cognitive and behavioural methods, CBT encompasses various psychological intervention techniques that, in the case of tinnitus, are aimed at reducing the impact of tinnitus rather than altering tinnitus features (i.e. loudness). Altering cognitions and responses by targeting different steps of the pathological cycle (i.e. catastrophizing, fear, avoidance) can be achieved through the delivery of different techniques (e.g. psychoeducation, exposure) making CBT a flexible and adaptive treatment option. The variety in techniques allows for tailored treatment approaches, resulting in unique combinations of techniques in function of the patient, therapist and setting differences. On the other hand, increased variability decreases replicability in research and treatment, with CBT treatment protocols potentially differing significantly. Thus, the role that each potential variation within treatment delivery (e.g. techniques, setting, length) plays is yet to be fully understood.

From bench to bedside to bench

Given the current state of tinnitus research and treatment we have identified three points of interest to further develop the field. They fall within the topics of (1) testing of a tinnitus fear conditioning paradigm in humans; (2) improving tinnitus assessment; and (3) the investigation of CBT components in order to better understand what works best form whom. We will subsequently expand on each point and draw the objectives of this dissertation.

1. Developing a tinnitus fear conditioning paradigm for human participants

In order to develop a comprehensive understanding of tinnitus development, maintenance and treatment, the systematic investigation of the role of tinnitus-related fear seems promising. Fundamental knowledge on the underlying learning mechanisms of tinnitus-related fear is still in its infancy. The main obstacle when adapting the FA model from pain to tinnitus is that the stimuli (pain and tinnitus) may translate differently into fundamental paradigms. Pain is considered a naturally aversive and negative experience whereas the experience of tinnitus may not as easily or universally trigger immediate alarm as pain might. Pain, when considered a representation of a serious (i.e. threatening) bodily harm (e.g. nerve damage), may act as a US, therefore creating a functional CS – US association. The implication for tinnitus research is that tinnitus itself may not be perceived as threatening nor used to consistently trigger an aversive response (US). Like pain, tinnitus threat must be associated with a perception of serious (potential) harm (e.g. damaged hearing, brain tumour). Therefore, a fear learning paradigm for tinnitus may be adapted as follows: tinnitus, conceptualized as a perception of a neutral sound (CS), acquires fear responses (CR) experienced due its association with an aversive (threatening) event (US). In other words, a neutral sound becomes a signal for a threat to well-being.

Considering fear associations in tinnitus research, an ecologically relevant US is necessary. Due to (1) the report of reduced sound tolerance on those suffering from Chronic Disabling Tinnitus (Baguley, 2003), (2) the avoidance of loud sounds due to the fear of triggering or worsening tinnitus perception (Kleinstäuber et al., 2013), and (3) the common reporting of tinnitus after experiencing of loud sounds (Gilles et al., 2013), loud sounds may be considered threatening (e.g. causing hearing damage and increased tinnitus) and thus provide a viable US. Consequently, a potentially replicable fear learning paradigm may be achieved in the tinnitus field.

Objective:

Adapt/create an associative learning model for the field of tinnitus in order to establish a replicable fear learning paradigm with healthy human participants.

2. (Re)Assessing tinnitus

Assessing tinnitus has proven a challenge, with audiological measures of tinnitus pitch, type, or intensity not translating into tinnitus distress (Andersson, 2003; Figueiredo et al., 2010; Henry, 2016; Rabau et al., 2015). Such measures do not provide insight into the toll that Chronic Disabling Tinnitus may take on one's life (e.g. social isolation, annoyance, fear). Instead, patient self-report must not be seen as the *next best thing*, but the most adequate assessment of Chronic Disabling Tinnitus. In other words, it is not specific tinnitus *features* that define the pathology but the entirety of the tinnitus *experience*, following a patient centered, rather than disease centered, approach to research and treatment.

Research in the field of chronic pain, in which a lack of direct measure has also been debated, has produced substantial arguments for the use of self-report tools as a valid technique for pain assessment (Robinson et al., 2013). We are then left with properly providing the patient with an accurate method to measure each individual's unique tinnitus experience. Hence the use of standardized self-report questionnaires to operationalize tinnitus. Many have been developed and improved upon, such as the Tinnitus Questionnaire (TQ; Hallam et al., 1988), Tinnitus Functional Inventory (TFI; Meikle et al., 2012) the Tinnitus Handicap Inventory (THI; Newman et al., 1996, 1998) and the Tinnitus Disability Index (TDI; Cima, Vlaeyen, et al., 2011). Independently from each conceptualization and objective, these tools are susceptible to the same issues of commonly used self-report questionnaires: recall bias, reading difficulty, and current psychological state.

Novel methodological approaches, namely Ecological Momentary Assessments (EMA) and End-of-Day Diaries (EDD), increase ecological validity and reduce the influence of recall bias by: (1) shortening the time between experience and assessment and (2) eliminating the artificial settings of self-report assessments (e.g. hospitals, laboratories, clinics). While EDD relies on once-a-day administration of questionnaires, EMA aims to reach information that is still in working memory by prompting participants with short and simple questions during their daily life. Previously, such methodologies were

implemented at painstakingly efforts and costs, but the development of affordable technology to a wider population (i.e. smartphones) made these methodologies more accessible for researchers and clinicians alike, providing an increasingly used alternative in the tinnitus field (e.g. Gerull et al., 2019; Goldberg et al., 2017; Schlee et al., 2016; Timmer et al., 2018).

EMA is an attractive tool in investigating tinnitus, with the added benefit to understand fluctuations during the day and further decreasing the risk of recall bias when compared to EDD. These potential benefits come at a cost since it relies on participants to remain in possession of their smartphone at all times. Participants must allow themselves to be interrupted in the midst of activities and research on the detrimental value of increased screen time is not lacking. Higher levels of stress, anxiety, depression (Elhai et al., 2017; Vahedi & Saiphoo, 2018) and lower wellbeing (Horwood & Anglim, 2019) have been associated with smartphone use. Furthermore, simply answering to an EMA prompt may elicit a cascade of events when reminders of unanswered emails, messages or tasks are readily available and highlighted by smartphones. Beyond that, increased awareness to negative experiences (i.e. tinnitus for patients suffering from Chronic Disabling Tinnitus) has been thought to negatively impact well-being as well. Conversely, EDD's minimize the burden of screen time while also potentially sacrificing recall bias and ecological validity when compared to EMA (Schneider & Stone, 2016). EDD's have been an established methodology for decades (e.g. Verbrugge, 1980), though its use in tinnitus research is scarce and a direct comparison between the tools in the field of tinnitus is lacking.

The development of technology and increased availability of smartphones has made novel assessment methods (EDD and EMA) viable alternatives to questionnaire and interview methods of measuring tinnitus. Nevertheless, these methodologies are yet to be fully tested within the field of tinnitus and must be better understood before being applied to wider use. We identified two main areas of focus in regard to this area. First, following one of the main principals of healthcare – *Primum non nocere* (*first, do no harm*) – we seek to explore the possible negative effects that EMA may have on well-being and tinnitus experience by filling the gap of previous studies on the matter. Second, we seek to compare EMA and EDD methodologies in the hope of making a substantiated recommendation for the use of either methodology.

Objectives:

Investigate whether EMA negatively affects tinnitus experience.

&

Investigate whether EMA provides a more accurate measure of tinnitus experience when compared to diary assessments.

3. CBT for tinnitus: what works for whom?

Finding a cure for tinnitus has challenged the field, with a lack of consensus on tinnitus definition, treatment and resource allocation (McFerran et al., 2019). Despite lack of consensus, the literature has repeatedly shown that, even without a common cure, meaningful improvement in tinnitus distress and quality of life can be achieved through the use of CBT (Fuller et al., 2020). In tinnitus, CBT aims at breaking, altering or recreating learned associations between tinnitus and maladaptive responses (e.g. avoidance) as well as identifying and modifying cognitive interpretations in the tinnitus experience (e.g. fear).

The variety of CBT techniques and combinations is an issue that does not only pertain to the tinnitus field. In an attempt to increase reproducibility of interventions, Michie et al. (2013) established a taxonomy that expands to 93 possible behavioural change techniques. Even with such detailed framework, authors of the recent Cochrane review (Fuller et al., 2020) point to the lack of availability of detailed protocols used in CBT interventions. Furthermore, mode of delivery (e.g. face-to-face, videocall), length and frequency of sessions, setting (e.g. hospital, clinic), delivery agent (e.g. therapist, chat-robot) and unit of delivery (i.e. group or individual) create an infinite number of possible CBT protocols that preclude the consideration of equivalent treatment. Thus, whereas CBT has been shown to be an added value in tinnitus treatment, lack of replicable protocols hinders the capacity for research to understand what works best and for whom, preventing more tailored approaches to be designed.

Tailoring of treatments can be accomplished in different degrees, such as the stepped care in the CBT approach used by Cima et al. (2012), which delivers care as needed (by steps) according to severity (increasing in treatment complexity). More tailored approaches can be reached through stratification or matching (Linton et al., 2018). Stratification, different from stepped care, classifies patients according to severity levels from the first visit. This approach curbs the assumption made by stepped care, in which most patients

will recover with little to no treatment (i.e. filtering out the less severe cases at each step). Further tailoring can be achieved through matched care. Expanding on the severity-based stratification, matched care includes individual risk factors which are then the focus of treatment.

It must be clarified that *tailored* treatment does not necessarily translate to *individual* treatment. Individual treatment simply refers to receiving a treatment in an individual setting (i.e. alone). Therefore, an individual treatment is not, by definition, tailored and vice versa, with tailored treatment sometimes being delivered in group settings. Beyond potentially reducing the costs of treatment delivery, group treatment may allow for social learning processes to be used as a powerful agent of change, particularly within CBT. Group-based CBT has the added benefit of changing behaviour, cognitions and emotions through increased availability of social learning cues (Bandura et al., 1967). These cues, such as observing another patient being exposed to the feared stimulus (e.g. loud noise, tinnitus) without the expected negative outcome (e.g. anxiety, loss of control) challenges previously learned pathological associations. Moreover, observing someone else expose themselves to a feared stimulus (i.e. vicarious extinction of fear; Rachman, 1977) may lead to superior fear reduction when compared to the standard extinction of undergoing the experience themselves (Golkar et al., 2013, 2016). Hence, beyond the behaviour and cognitive techniques employed in CBT, the additional layer of yet another learning mechanism, may prove beneficial.

Group-based CBT has had some positive results in the tinnitus literature (e.g. Cima et al., 2012), but it is not yet known if the group-based treatment is a contributing part of CBT for tinnitus or for whom it may be more beneficial. Group and individual CBT methods applied to tinnitus were previously compared by Fuller et al. (2020) in the context of a meta-analysis. Both individual and group-based CBT were more effective than wait list control or "active comparison" conditions and no difference between individual or group-based treatment was found. These comparisons were made on the results from separate studies, using either individual or group-based CBT and no study has compared one specific treatment protocol under each condition.

Objective:

Contrast and compare individual to group-based CBT in the treatment of tinnitus

Summary

With a brief account of the current state of the tinnitus field we have identified three areas of interest in which a novel contribution to the field would more likely result in direct progress in tinnitus research and treatment. From each area of interest specific objectives were derived as follows:

The first objective of the current work relies on the adaptation/creation of an associative learning model for the field of tinnitus in order to establish a replicable fear learning paradigm with healthy human participants (Chapter 2).

Two objectives were drawn from the area of tinnitus assessment. They were to (1) investigate whether EMA negatively affects tinnitus experience and to (2) investigate whether EMA provides a more accurate measure of tinnitus experience when compared to EDD assessments. These objectives are respectively reflected in the studies reported on Chapters 3 and 4 of the current PhD dissertation.

In the area of tinnitus treatment, the current CBT approach and desire to tailor treatment inspired the investigation of contrasting and comparing individual to group-based CBT for tinnitus (Chapter 5).

With the results reported in each study, Chapter 6 offers a synthesis and general discussion on the overall findings of the current body of work. Future research perspectives are drawn and a statement on the impact of this dissertation is made.

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CHAPTER 2

Fear in the ear: the role of fear conditioning in the acquisition and extinction of fear of sounds

CHAPTER 3

Effects of Ecological Momentary Assessment (EMA) induced monitoring on tinnitus experience: a multiple-baseline single-case experiment

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Abstract

Introduction: Ecological momentary assessment (EMA) is a method capable of assessing tinnitus experience throughout the day, enabling the exploration of daily dynamic changes of tinnitus expression. However, the effects on patients' tinnitus experience itself are still largely unknown. This study seeks to test the hypothesis that the use of EMA negatively influences tinnitus experience in participants with severe tinnitus. **Method**: A multiple-baseline single-case experimental design included four severely affected tinnitus volunteers who were recruited online and randomized into different phasing schedules. Baseline phase (A) ranged from 11-24 days, followed by an EMA phase (B) for the remainder of the 33-day schedule. End-of-day diary assessments of tinnitus experience (e.g. annoyance, intrusiveness, mood) were visually inspected, and complemented with inferential statistics (randomization tests and Tau-U). **Results**: End-of-day diary data revealed no change in broadened median between phases. Nevertheless, tinnitus experience scores improved as variability decreased and a significant improvement in stress was observed through weighted Tau-U statistics. **Conclusion**: Findings of this study corroborate that EMA assessment does not negatively affect tinnitus experience. On the contrary, participants may have improved. The underlying mechanism of improvements are still to be uncovered. Findings are limited to severely affected tinnitus sufferers at present.

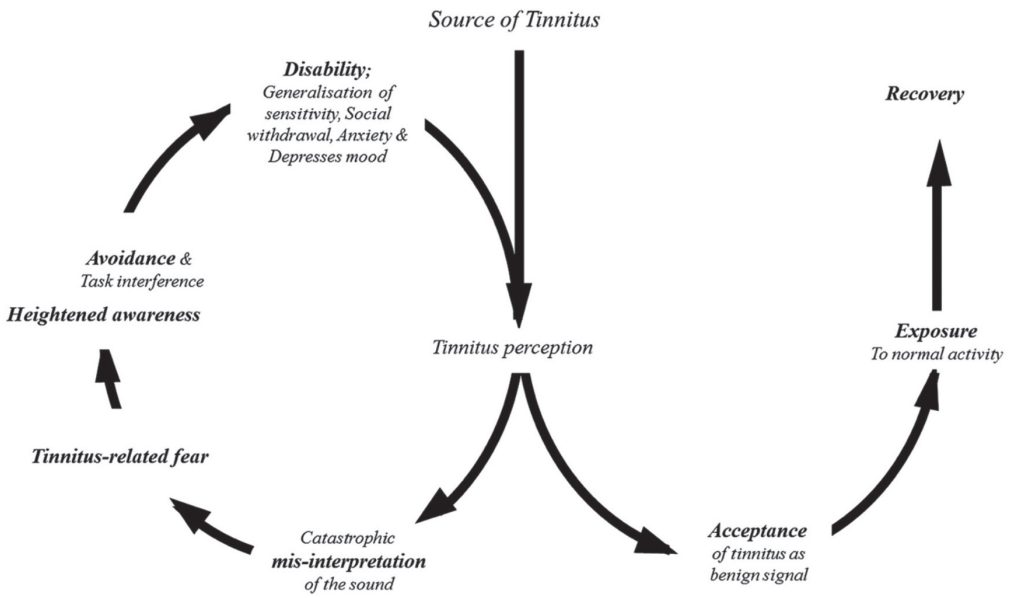
1. Introduction

Tinnitus is defined as the perception of sound(s) (e.g. ringing or buzzing) in the ear or head without a detectable corresponding physical source. While nearly 20% of the adult population reports tinnitus, it is only a small subset (1-6%) who suffer from it, experiencing severe distress and disturbances in numerous aspects of daily life (Davis and Refaie, 2000; Cima, Crombez and Vlaeyen, 2011; Kim *et al.*, 2015; Bhatt, Lin and Bhattacharyya, 2016; McCormack *et al.*, 2016; Hall *et al.*, 2018). There is currently no cure for chronic tinnitus and, while treatment options are varied, Cognitive Behavioural Therapy (CBT) approaches are strongly recommended for treatment (Cima *et al.*, 2019) with a recent Cochrane review emphasizing the positive effect it has on quality of life (Fuller *et al.*, 2020).

The Fear Avoidance (FA) model of chronic pain (Lethem *et al.*, 1983; Vlaeyen and Linton, 2000, 2012) provides the underpinnings for CBT by predicting the development, maintenance and increase of chronic pain disability, and has successfully been applied to tinnitus as well (Cima, Crombez and Vlaeyen, 2011; Kleinstäuber *et al.*, 2013). The model states that a pathological cycle may start with catastrophic misinterpretations about the tinnitus perception that feed into tinnitus-specific fear, heightened attention and constant monitoring, avoidance of stimuli that are expected to increase tinnitus, which in turn increases disability, distress, and decreased quality of life (Figure 1). In an alternative to the detrimental spiral, tinnitus may be perceived as a common and harmless sensation, leading to continuation of valued activities, thereby confronting stimuli that may increase tinnitus (e.g. exposure) and eventual recovery. Research has supported the negative role of tinnitus catastrophizing, fear and attention in regards to quality of life (i.e. disability; Cima, Crombez and Vlaeyen, 2011). Beyond the tinnitus field, exposure techniques have been long supported in literature and are considered the golden standard for their effectiveness in reducing psychological distress associated with other chronic conditions, such as pain (Vlaeyen *et al.*, 2001; Woods and Asmundson, 2008; e.g. Hedman-Lagerlöf *et al.*, 2018) and anxiety disorders (Meuret *et al.*, 2012; e.g. Carpenter *et al.*, 2018). Exposure techniques may take different forms but rely on the repeated confrontation with the fear-provoking stimuli. Simply put, fear and catastrophic thoughts are reduced by confronting the patient with the distressing experience (e.g. tinnitus) without the anticipated negative outcome (e.g. loss of control), thus violating the expected prediction (Craske *et al.*, 2014; for a detailed review on underlying mechanism of inhibitory learning and exposure see Craske, Hermans and Vervliet, 2018). Despite

empirical support, mechanisms behind these exposure components of CBT and, more specifically, the role of attention to tinnitus are still debated, with competing techniques and therapies recommended in standard practice (e.g. masking, sound enrichment therapy, TRT). Controversies also exist about the rise of novel assessment methodologies (e.g. Ecological Momentary Assessment) and technologies (e.g. TrackYourTinnitus app, Schlee *et al.*, 2016) that aim to capture tinnitus fluctuations by repeatedly assessing participants throughout the day.

Figure 1: Fear Avoidance model (replicated from Cima, van Breukelen and Vlaeyen, 2018)



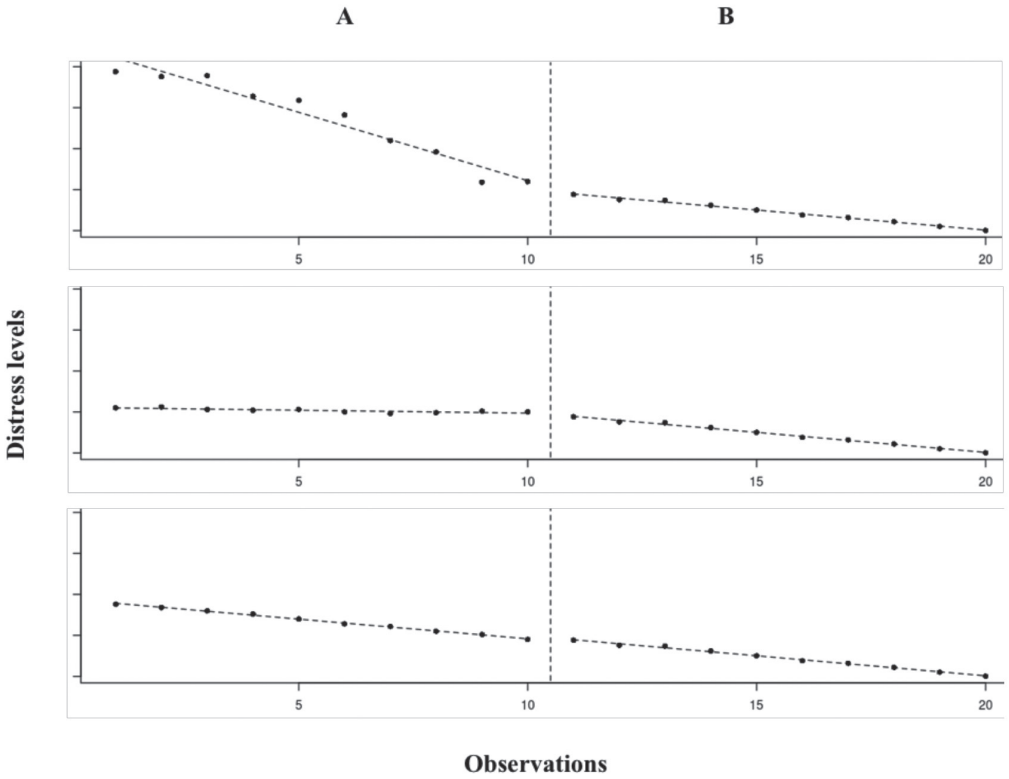
Ecological Momentary Assessment (EMA) has been under scrutiny for potentially increasing attention to tinnitus (e.g. Henry *et al.*, 2012; Schlee *et al.*, 2016). Worries exist that the repeated daily measurements will lead to increase in awareness of tinnitus with detrimental effects on patients and their disability due to tinnitus. EMA attempts to capture in-the-moment experiences in real-life situations by randomly delivering questions throughout the day, thereby avoiding common limitations of standardized self-report questionnaires such as possible fallacies of recalling and reconstructing experiences (Stone and Shiffman, 1994). EMA questionnaires are designed to be rapidly answered and items may focus on different dimensions of an individual's life, including well-being (e.g. happiness, stress, sleep), daily activities (e.g. current location, social contact, environmental noise), and tinnitus experience (e.g. annoyance, anger, distraction). Technological advances and the rising use of smartphones has enabled EMA to be

commonly delivered through purpose-built apps, increasing its research applications. Despite the growing use of EMA the effects of it on tinnitus experience are still widely unknown.

1.1. Previous research

Henry et al. (2012), the first to look into the potential effects of EMA on tinnitus subjects, used personal digital assistants (PDAs) and 24 participants who underwent a 2-week long EMA phase. Reactivity to EMA was analysed through pre- and post-EMA group mean measurements of the Tinnitus Handicap Inventory (THI; Newman, Jacobson and Spitzer, 1996; Newman, Sandridge and Jacobson, 1998), where an observed worsening was not statistically significant. Moreover, the researchers evaluated the individual trajectories of participants' EMA responses by plotting and visually inspecting the daily scores over time. The authors observed a high degree of intra- and inter-individual differences and nearly half of the participants (54.2%) were classified as "consistent" where no clear trend could be visually fitted. Six (25.0%) participants were observed to have an "improving trend" while the remaining five participants (20.8%) were found to "worsen" during the EMA phase. The lack of statistical support prevents a more accurate trend fitting. Furthermore, the absence of a control condition (i.e. baseline phase) hinders the interpretability of the data. For instance, an "improving trend" may be deceiving, as baseline data could have revealed a steeper improvement trend before the introduction of EMA (Figure 2). Beyond these limitations, the interpretation of the individual data sheds light into the group level analysis. The stipulated improvement and worsening of individual participants within the group may cancel each other out when analysing group means, and true effects might therefore remain undetected. In other words, EMA may have significant negative or positive effect on a particular subset of participants.

Figure 2: Example of possible baseline trends (A) prior to intervention phase (B) with higher distress levels reflected through higher scores on *y*-axis. From top to bottom graphs respectively indicate worsening, improving and no change after intervention onset.



More recently, Schlee et al. (2016) investigated the potential effects of EMA on tinnitus loudness and distress. Data gathered online through an EMA delivery app for smartphones was analysed. From 857 volunteers who participated in data collection, linear regression was applied with participants who used the app for at least one month (n=66). No significant association between EMA use and tinnitus loudness or distress was observed. The lack of reactivity was further supported by a different group-level analysis in which the average first and last five assessments were compared through a t-test. The same test was conducted for the remainder of participants who had completed the EMA from anywhere between 5 and 30 days. While no significant change was found using group level analysis, the authors observed high intra- and inter-individual differences, congruent with findings from Henry et al. (2012). While linear regression analysis is a methodological improvement to visual inspection of trend, the reliance on group level analysis continues to limit the interpretability of data as participants high variability in scores at the individual level may offset each other's when combining the data.

1.2. Single-Case Experimental Design (SCED)

As group studies fail to acknowledge the idiosyncratic nature of tinnitus, individualized research designs offer an alternative that thrives on such variability. Previous group-based research has supported lack of reactivity in scores of tinnitus handicap, distress and loudness to EMA, but it has also emphasized the high degree of divergence in tinnitus experience. Such individual variability remains hidden when interpreting results from group level analysis, possibly omitting significant individual effects, thereby limiting the generalizability of group-findings to a specific patient's profile. As such, the conclusion that tinnitus sufferers may lack EMA reactivity excludes subgroups (e.g. severe tinnitus sufferers) who could potentially benefit or worsen from its utilization.

In order to bridge the gap in knowledge about the effects of employing EMA, the current study uses a Single-Case Experimental Design (SCED) to investigate whether EMA influences tinnitus experience. Different from non-experimental designs (e.g. case-studies), SCED relies on repeated measurements of the dependent variable (e.g. tinnitus experience) over time during at least two different levels of the independent variable (e.g. with/without EMA) (Morley, 2018). Recent guidelines (i.e. Tate *et al.*, 2016) have emerged as the result of a growing interest in SCEDs. Alternatively to group-based designs and congruent with the push for individualized treatment and research (Schork, 2015), SCEDs can equally investigate causal relationships between variables (i.e. EMA and tinnitus experience). By repeatedly assessing individuals before (baseline phase: A) and after the introduction of an intervention or manipulation (phase: B), usually at a random starting point within a predefined time window, changes between phases' level, trend and variability are inspected for each participant and statistically analysed (i.e. randomization tests, Tau-U). Furthermore, the multiple observations at baseline create robust control conditions, despite the high intra- and inter-individual variance, which allows for addressing the limitations of previous research.

Building on previous findings, a specific subgroup is analysed in this study. The FA model illustrates the role of constant monitoring and unwarranted attention to the tinnitus percept and its pathological progression. As higher levels of attention towards tinnitus haven been associated with higher degrees of tinnitus severity (e.g. lower quality of life; Cima, Crombez and Vlaeyen, 2011), it is hypothesized that severe tinnitus sufferers respond negatively to the use of EMA (e.g. increased tinnitus annoyance, increased stress levels, decreased sleep quality).

2. Method

2.1. Study design

An AB multiple-baseline SCED where baseline phase (A) always precedes an experimental phase (B) was employed. Within the different SCED possibilities, the utilization of a multiple-baseline design across participants limits confounding factors by requiring different individuals to undergo an AB schedule with randomized B phase onset.

End-of-day diary assessments were continuously gathered throughout both phases, while during phase B, EMA was added, which included real-time assessment, equivalent to those assessed in the diary. Data was gathered through a purpose-built app (TinNotes) developed in-house by Maastricht University's Instrumentation Engineering department. TinNotes ran on iOS devices and notified participants daily (at 8pm) for the completion of the diary assessment and, during phase B, also delivered daily EMA at 7-random time points with at least 30-minutes in-between prompts. The participant was able to set a sleeping schedule and to snooze EMA prompts twice for 5-minutes each time, after which the assessment was cancelled. Data was sent directly to Maastricht University's servers when the device was connected to the internet. Six different AB schedules were randomly determined through a Single Case Data Analysis app (SCDA; https://tamalkd.shinyapps.io/scda/). Five consecutive observation points were considered minimally necessary per phase, and 23 potential phase B (EMA introduction) onset points were available, totaling 33 potential diary assessments per participant. According to the regulated randomization principle (Koehler and Levin, 1998), after the six randomized schedules were created, each participant was randomly assigned to a schedule and unaware of phase B onset day. The study was pre-registered (Lourenco, Cima and Vlaeyen, 2019) and approved by Maastricht University's Ethical Review Committee Psychology and Neuroscience (ERCPN-204_23_02_2019). Reporting of the study follows the guidelines established at SCRIBE (Tate *et al.*, 2016).

2.2. Participants

Recruitment took place through an advertisement published in the newsletter of the Dutch national tinnitus patient association (Stichting Hoormij). The research was also announced at the annual symposium of the association. Compensation for participants who completed the study was 75€ (seventy-five euros). Inclusion criteria included: (1) own and use an iPhone; (2) self-reported tinnitus; (3) not currently undergoing treatment for tinnitus or psychological, psychiatric or any other kind of therapy

addressing psychological, social, emotional, and or behavioral problems; (4) absence of severe anxiety or depression; (5) able to read and write in Dutch. Participants were excluded if: (1) the criteria for severe tinnitus was not met, as measured by the Tinnitus Questionnaire (TQ > 59; Hallam, Jakes and Hinchcliffe, 1988), or (2) met the criteria for severe Anxiety or Depression, assessed through the Hospital Anxiety and Depression Scale (HADS-A > 14 or HADS-D >14; Zigmond and Snaith, 1983). Participants were blinded to the study's objective and were invited to test a new tinnitus tracking app. After data collection ended participants were debriefed to the true objective of the study.

Participants who completed the screening online and met inclusion criteria (n=175) were systematically contacted to participate. The first six participants who filled out the survey at T0 were randomly allocated to an AB schedule (Table 1). Participants were instructed to download the app and login via a unique code that allowed the app to deliver the specific AB schedule. Participants' codes were encrypted, and the key was maintained in a secure server.

Table 1: Six randomly created schedules where baseline (A) and EMA phase (B) required a minimum of five consecutive observations per phase. PP = participant.

	Observation																		
	1	**…**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**…**	**33**
PP 1	A	…	A	A	A	A	A	A	A	A	A	A	A	A	A	A	**B**	…	**B**
PP 6	A	…	A	A	A	A	A	A	A	A	A	A	A	**B**	**B**	**B**	**B**	…	**B**
PP 2	A	…	A	A	A	A	A	A	A	A	A	**B**	**B**	**B**	**B**	**B**	**B**	…	**B**
PP 3	A	…	A	A	A	A	A	A	A	A	**B**	**B**	**B**	**B**	**B**	**B**	**B**	…	**B**
PP 4	A	…	A	A	A	A	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	…	**B**
PP 5	A	…	A	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**	…	**B**

2.3. Measurements

2.3.1. Primary outcomes

The end-of-day diary assessments were the primary study endpoints gathered by the TinNotes app. Compiled of 15 questions on a 7-point Likert scale and one qualitative question, the diary items were extracted and adapted from existing questionnaires (e.g. TFI, TQ) by a group of four specialists which included researchers and therapists. The questions were delivered in a different order every day of the week. Each question assessed a different aspect of tinnitus experience, including avoidance, annoyance, intrusiveness, invasiveness, fear, sadness, pleasantness, distraction, masking and anger. It also included questions about overall well-being, assessing happiness, feeling stressed, sleep quality,

activity level, anxiousness and social interaction (qualitative). Treatment fidelity was assessed through the completion rate of EMA, with at least a 75% completion rate required.

2.3.2. Secondary outcomes

Standardized questionnaires were collected before baseline (T0) and after EMA (T1) phases.

Tinnitus Functional Inventory (TFI; Meikle et al., 2012): The TFI is a 25-item self-report measure of impairment in daily functioning. Respondents use 10-point Likert scales to indicate what tinnitus related experiences they have had over the previous week. The TFI has subscales on intrusiveness; reduced sense of control; cognitive interference; sleep disturbance; auditory difficulties attributed to tinnitus; interference with relaxation; reduced quality of life; and emotional distress. A total score, with a maximum of 100 can be calculated with higher scores reflecting greater levels of interference in daily activities. The TFI has excellent psychometric properties and was specifically designed to be used as an outcome measure in clinical trials with a 13 point change deemed as clinically significant (Meikle *et al.*, 2012). A Dutch version of the TFI was recently developed and validated for use with Dutch speaking patients (Rabau, Wouters and Van de Heyning, 2014).

Tinnitus Questionnaire (TQ; Hallam, Jakes and Hinchcliffe, 1988; Meeus, Blaivie and Van de Heyning, 2007): The TQ is a 52-item measure of tinnitus-severity. Each question is rated on a three-point scale and assesses psychological distress associated with tinnitus. The TQ is widely used in tinnitus research (Hall *et al.*, 2016) and has good psychometric properties (Fackrell *et al.*, 2014). A Dutch version has been developed and validated for use (Meeus, Blaivie and Van de Heyning, 2007).

Fear of Tinnitus Questionnaire (FTQ; Cima, Crombez and Vlaeyen, 2011): The FTQ is a 17-item self-report measure of a person's feared outcomes of living with subjective tinnitus. A higher total score on the FTQ is associated with higher levels of interference in daily activities of living. A recent analysis of the psychometric properties reported that it is a reliable and valid measure (Fuller *et al.*, 2019) and has demonstrated that it is responsive to clinical change (Cima *et al.*, 2012).

Tinnitus Catastrophizing Scale (TCS; Cima, Crombez and Vlaeyen, 2011): adapted from the 13-item Pain Catastrophizing Scale (Sullivan, Bishop and Pivik, 1995) for use with

tinnitus patients – the word "pain" being replaced by the word "tinnitus". Participants are asked to respond on a five-point Likert-type scale (0 = Not at all; 1= to a small extent; 2 = to some extent; 3 = to a large extent; 4 = always) to statements describing thoughts and feelings that might be related to their tinnitus. Higher levels of catastrophizing as measured by the TCS has been found to be closely related to poorer quality of life (Cima, Crombez and Vlaeyen, 2011).

Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983): The HADS is a widely used scale to screen for depression and anxiety. There is a total of 14-items with a 4-point Likert scale. Each subscale has a possible score of 21, with higher scores indicating higher levels of anxiety (HADS-A) and depression (HADS-D). The scale was used for screening with scores over 14 for any of the subscales indicating the presence of severe depression and/or anxiety.

Demographic and tinnitus characteristics data were gathered through the ESIT-SQ (Genitsaridi *et al.*, 2019): developed by the Tinnitus Research Initiative (TRI) and the European School for Interdisciplinary Tinnitus research (ESIT), the Screening Questionnaire (ESIT-SQ) is a comprehensive self-report tool for healthy individuals and tinnitus patients that provide demographic and multidisciplinary information on tinnitus relevant variables. Translated into six languages, this tool offers a standardized assessment for tinnitus research across Europe.

2.3.3. Analysis

Each item of the end-of-day diary was analysed per participant. For the purpose of this study the end-of-day diary items on social interaction and activity level were removed from analysis as they are treatment specific goals of CBT and do not pertain to this study's main hypothesis. Visual inspection of annoyance and stress items were selected to illustrate findings with the remaining individual visual analysis presented as supplemental material.

The end-of-day diary scores were plotted over time. Visual inspection of the data was carried out in order to determine changes in level and variability. The broadened median (Rosenberger and Gasko, 1983) was utilized due to its resistance to outliers and plotted for change in level inspection. Visual inspection of variability was aided by including range lines per phase. Randomization tests were calculated for each participant with a combined p-value calculated (Onghena and Edgington, 2005). Monte Carlo sampling

(1000) was used with the test statistic defined as $\overline{A}$-$\overline{B}$ due to the dependent variables' projected increase (worsening) after EMA introduction, while inverted items' (happiness, tinnitus pleasantness and sleep quality) test statistics was defined as $\overline{B}$ -$\overline{A}$. Visual analysis and randomization tests were carried out through a purpose-built web-application which provides an interface for the shiny SCDA software, which utilizes the R packages SCRT, SCVA and SCM (https://tamalkd.shinyapps.io/scda/; Bulté and Onghena, 2013). Tau-U, a more conservative analysis of non-overlap statistics, was utilized to detect and correct for baseline trend when comparing phases. Tau-U enables confidence intervals and p-values to be calculated by following the "S" sampling distribution (Parker *et al.*, 2011). The web-application 'Single Case Research: web based calculators for SCR analysis (Version 2.0)' (Vannest *et al.*, 2016) was utilized for Tau-U calculations.

3. Results

Data was retrieved from the server after the completion of the study. An unknown error caused the app to malfunction for two participants, from whom the data was not included for analysis. One participant completed less than half of the EMA delivered (44.8%) compromising treatment fidelity and thus the data was not included for analysis. Three participants completed the study with over 83.3% and 91.7% compliance rate on end-of-day diary and EMA respectively. Participants who completed the study had been allocated to schedules 1 (PP 1), 2 (PP 6) and 4 (PP 3). Participants' demographic and tinnitus characteristics are presented in Table 2.

Table 2: Demographic and tinnitus characteristics

	Age	**Sex**	**HADS**		**Tinnitus**			
			A	**D**	**Duration**	**Location**	**Daily fluctuation**	**Type**
PP 1	55	Female	10	8	5 months	Both ears, worse in left	Stable	High pitch tone
PP 6	49	Female	12	9	10 years	Both ears, worse in left	Sometimes fluctuates	High pitch tone
PP 3	66	Male	7	4	12 years	Right ear	Stable	High pitch tone

3.1. Diary assessments

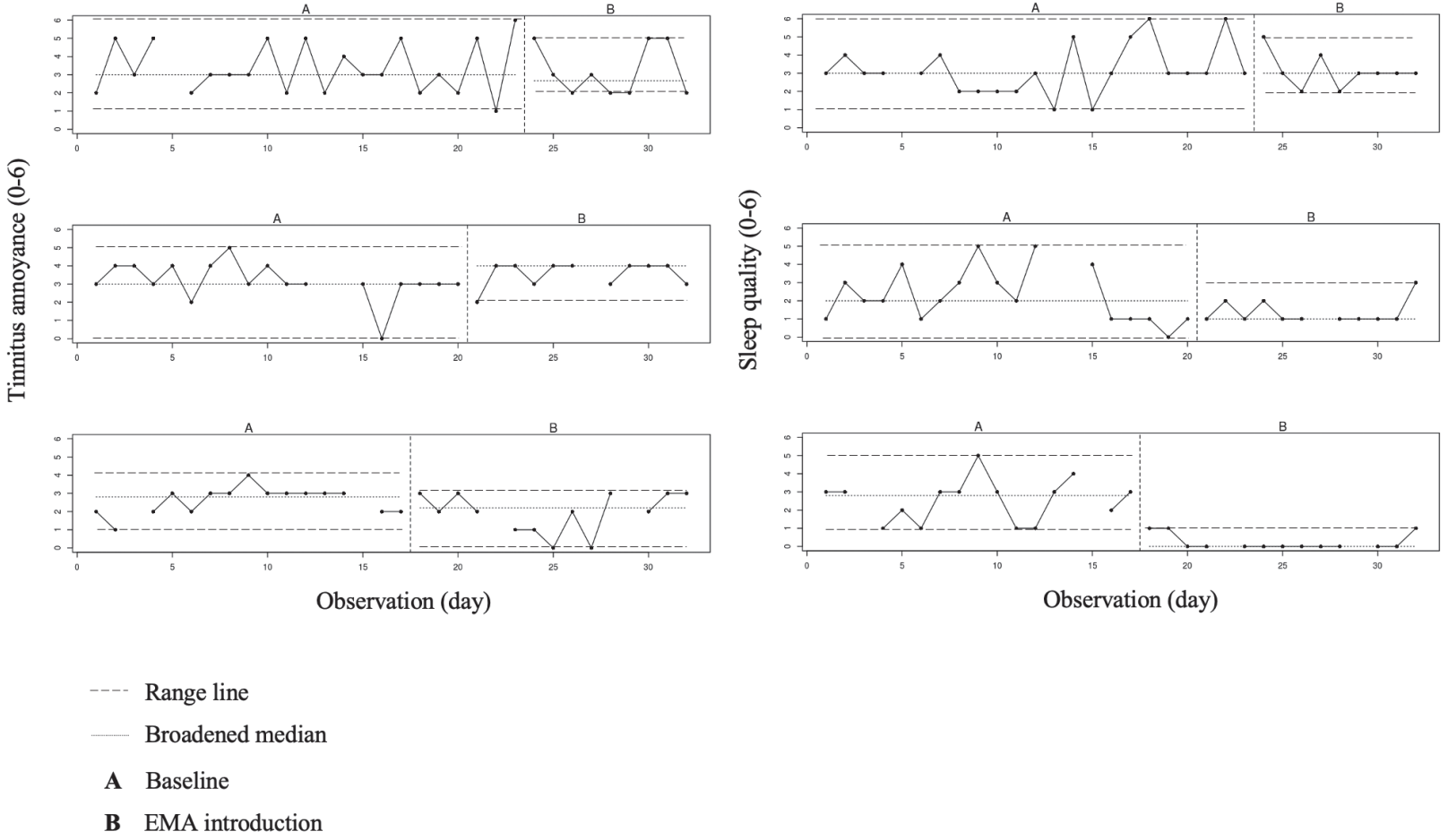
Visual inspection of the end-of-day diary scores for items on tinnitus annoyance and stress levels are presented in figure 3. P-values for the combined randomization tests and weighted Tau-U analysis are presented in Table 3 (individual Tau-U tables are presented as supplemental material). No statistically significant worsening was found by randomization tests, while Tau-U analysis revealed a statistically significant improvement in stress levels.

Table 3: P-values for combined Randomization Tests (RT) and weighted Tau-U analysis per item.

Item	RT	Tau-U
Anger	.767	.588
Annoyance	.521	.677
Anxiety	.603	.297
Avoidance	.486	.262
Distraction	.541	.792
Fear	.496	.435
Happiness†	.228	.549
Interference	.640	.683
Invasiveness	.514	.533
Pleasantness†	.220	.282
Sadness	.534	.335
Sleep quality†	.147	.644
Stress	.112	< .001**

†inverted items (test statistic = $\overline{B}$ -$\overline{A}$)
*p-value < .05
**p-value < .001

Figure 3: Visual analysis of multiple-baseline AB-design of end-of-day diary for participants PP 1, PP 6 and PP 3 respectively showing level of each phase using broadened median scores and variability of each phase using range lines. Range lines are omitted when concur with broadened median.



3.2. Standardized assessments

Change in standardized questionnaires were calculated for each participant (Table 4). No participant had clinically meaningful improvement or worsening according to the TFI. Analyses of the TFI sub-scales (Table 5) revealed that in participant 6 (PP 6) overall worsening was mainly associated with decreased sleep quality (Sl), though visual inspection of diary data for sleep quality revealed no shift in level and variability.

Table 4: Scores before baseline (T0), after EMA phase (T1) and change (Δ) of the Tinnitus Questionnaire (TQ), Tinnitus Functional Index (TFI), Tinnitus Catastrophizing Scale (TCS), and the Fear of Tinnitus Questionnaire (FTQ).

	TQ			**TFI**			**TCS**			**FTQ**		
	T0	**T1**	**Δ**	**T0**	**T1**	**Δ**	**T0**	**T1**	**Δ**	**T0**	**T1**	**Δ**
PP 1	68	60	-8	48.8	40	-8.8	37	20	-8	12	10	-2
PP 6	78	72	-6	67.6	80	12.4	31	20	-11	14	11	-3
PP 3	66	71	5	58	63.6	5.6	37	42	5	10	10	0

Table 5: Score change (Δ) of the Tinnitus Functional Index (TFI) sub-scales: Intrusive (I), Sense of Control (Sc), Cognitive (C), Sleep (Sl), Auditory (Au), Relaxation (R), Quality of Life (Q), and Emotional (E).

	TFI							
	Δ I	**Δ Sc**	**Δ C**	**Δ Sl**	**Δ Au**	**Δ R**	**Δ Q**	**Δ E**
PP 1	13.33	-10	-13.33	-20	10	-3.33	-25	-16.66
PP 6	-10	-3.33	-6.66	60	20	16.66	17.5	3.33
PP 3	33.33	16.66	-20	-10	10	-13.33	15	10

4. Discussion

The aim of this study was to investigate whether tinnitus monitoring induced by the use of EMA negatively affects overall tinnitus experience. In order to mitigate previous research limitations (e.g. lack of control condition), the present study employed a SCED with participants suffering from severe tinnitus.

Change in tinnitus experience was primary assessed through visual inspection of end-of-day diary data, showing no meaningful and consistent shift in level in any variable. Visual inspection also revealed that while one participant's (PP 1) scores at baseline presented a floor effect on the item regarding tinnitus pleasantness, all other items and participants presented adequate variation of scores and patterns that did not show floor

and ceiling effects. This lack of negative reactivity of tinnitus experience to EMA was further confirmed through randomization tests, which rendered no significant change for each variable. While level remained similar between phases, improvement was observed through variability decrease in all variables for at least two participants with the exception of tinnitus invasiveness and pleasantness. Decrease in variability of answers has been previously reported in literature and it is not attributed to instrumental effects (Vachon *et al.*, 2016). Surprisingly, Tau-U analysis indicated a significant decreased stress-levels after EMA introduction. Overall, EMA may have had a positive effect on participants' experience by increasing awareness of their current state during the day and allowing them to rate it on a scale. Such a monitoring exercise may lead to a more accurate reflection of overall daily experiences, which is then reported on the end-of-day dairy. Furthermore, in the parallel field of chronic pain, monitoring of pain sensations have previously demonstrated potential long-term benefits when compared to distraction techniques for patients (Nouwen *et al.*, 2006) and highly fearful individuals (Roelofs *et al.*, 2004). These findings also fit the clinical benefits of exposure, in which increased tinnitus awareness is evoked to change threat-expectancies, leading to decreased safety-seeking and fear-responding.

Closer analysis of Tau-U calculations revealed that one participant's (PP 3) stress improvement outweighed other participants' lack of changes. More specifically, the change found may have been heavily influenced by changes in level and variability across most items of that participant observed in the one week. Due to the number of observations and the robust baseline established, caution in interpretation of the effects is warranted in that improvements reported during observations 23-27 of PP 3 might be due to external influences.

Standardized outcomes (TQ and TFI) revealed no clinically significant changes. Moreover, one participant's (PP 6) TFI score increase was mainly attributed to worsened quality of sleep, though diary data showed that there was no change in level or variability when comparing phases. Consequently, sleep quality worsening is not likely due to EMA. The remaining assessments (TQ, TCS and FTQ) of the participant indicated marginal improvements, which may also be observed in most items of the end-of-day diary.

Despite the dissonant result on the TFI, special consideration must be given to its interpretation. The TFI was developed to assess clinical change and is thus favoured over the TQ (Jacquemin *et al.*, 2019). Nevertheless, as with other self-report measures of subjective experiences, the TFI is susceptible to fallacies such as memory recall and

reconstruction. Retrospective self-reports may be influenced by biases in reconstruction of events according to the individual's own beliefs, behaviours or knowledge acquired after the event, as well as the current emotional state and physical location at the time of assessment (Stone and Shiffman, 1994; Kahneman *et al.*, 2004). Highly variable experiences such as tinnitus, further increase the burden of assessment, challenging individuals to quantify (e.g. average) it over a longer time period. The lack of convergence between the TFI and other assessments – for PP 6 – highlights the possible discrepancies that can result from retrospective self-reports of highly variable and subjective experiences (i.e. tinnitus). Novel approaches were developed to tackle these limitations, and as such this study favours end-of-day diary use, which decreases the timeframe of recall, therefore, reducing the risk of bias.

Tinnitus fear and catastrophizing, as measured by the FTQ and TCS respectively, revealed no meaningful negative change. According to the FA model, increase at any point of the pathological cycle strengthens the negative experience of tinnitus. A hypothetical monitoring effect induced by EMA must not exceed the current monitoring level of severely affected tinnitus sufferers. Interestingly, two participants demonstrated a decrease in tinnitus fear and catastrophizing. Exposure techniques reduce fear and catastrophic thoughts by repeatedly confronting the individual with the distressing experience without the expected negative outcome. Although speculative, the EMA-induced monitoring may have increased the number of instances where violation of expectations occurred (i.e. exposure). While the reported changes in fear and catastrophic misinterpretations may not be considered meaningful at this point, findings may pave the way for future research on the underlying mechanism of potential EMA-induced improvements.

At the time of the study, the app was limited to iOS devices only. Research on the differences between Android and iOS users in a tinnitus population have been previously conducted. Pryss et al. (2018) found small but significant differences in age and tinnitus duration. Android users were found to be slightly older and perceived tinnitus for longer when compared to iOS users. However, meaningfulness of previous findings is based on group-level analysis and therefore limited for the current study. Although different operational systems for smartphones are not expected to have an effect on the findings, future research which includes Android users is warranted.

The multiple-baseline SCED employed in the current study made it possible to create control conditions (i.e. baseline), which was lacking in previous research. Moreover, the minimum number of participants recommended for a multiple-baseline AB design was

reached (Kratochwill *et al.*, 2013). Only a subset of tinnitus sufferers was selected, and the focus on severe tinnitus is considered a strength of this research, which aims at untangling previous findings in the field by following novel standards for individualized medicine and research (Schork, 2015).

5. Conclusion

The present study corroborates and expands on previous findings regarding EMA reactivity in tinnitus sufferers (Henry *et al.*, 2012; Schlee *et al.*, 2016). Inter- and intra-individual tinnitus experience variability is narrowed in the present study by including only severe tinnitus sufferers using single-case methodology. These participants were not observed to have meaningful negative reactions to EMA utilization. Contrary to expectations, slight improvements after EMA onset were observed. The underlying mechanism of the EMA-induced improvements are still to be uncovered.

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CHAPTER 4

The daily experience of subjective tinnitus: Ecological Momentary Assessment (EMA) vs End-of-Day Diary (EDD)

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Abstract

Objective Traditional methods of self-report assessments are susceptible to bias (i.e. memory, recall, recency). Ecological Momentary Assessment (EMA) may curb these biases by repeated momentary assessment of the participant throughout the day. High costs and participant burden may however impede the use of EMA. End-of-Day Diary (EDD) provides an attractive alternative to EMA, though no direct comparison has been carried-out in the tinnitus field. **Design** 4,732 data entries were collected from nine participants undergoing Cognitive Behavioural Treatment (CBT) for tinnitus. Eleven equivalent EMA and EDD items were collected for approximately 3-months. Tinnitus experience (i.e. anger, annoyance, avoidance, distraction, fear, invasiveness, pleasantness and sadness) and wellbeing (i.e. anxiety, happiness and stress) were correlated and means compared (t-tests). **Results** All variables presented adequate correlation ($r > .68$) between the EMA and EDD counterparts. Small (< 3.9%) significant daily mean differences between EMA and EDD were found for six variables (tinnitus anger, invasiveness, pleasantness, sadness, as well as anxiety and stress) with worse results reported in EDD. **Conclusion** The small significant effects found may be attributed to the large number of data points. When EMA is not possible or recommended, EDD provides a viable alternative to assess tinnitus experience daily. Further research on the underlying mechanisms of tinnitus experience and recollection is warranted.

1. Introduction

The use of Ecological Momentary Assessment (EMA) has risen with the development of technology and growing availability of smartphones. The increased use of EMA has been reflected in a variety of research fields, including suicidal ideation (e.g. Kleiman et al., 2017), substance use (e.g. Jones et al., 2019) and chronic pain (e.g. May et al., 2018), to name but a few (for a comprehensive review on EMA we guide the interested reader to Shiffman et al., 2008). EMA aims at capturing experiences during real-life activities and situations by assessing individuals at several random times during the day. The advantages of these in-the-moment assessments are threefold: (1) reduced recall bias, (2) increased ecological validity, and (3) the exploration of symptom fluctuation (Schneider & Stone, 2016). Recall bias refers to any unwanted bias associated with the cognitive processes of memory reconstruction (e.g. mood, setting, recency) and summation (i.e. average) of these experiences (Shields et al., 2016; Stone & Shiffman, 1994). Reducing the time between events and assessment reduces recall bias and focuses on reaching information that can be accessed in working memory. Increased ecological validity is achieved by assessing the participant during real daily-life situations, and thus outside a setting that may unduly influence responses (e.g. hospital, clinic, lab). Fluctuation patterns of experiences (e.g. stress, tinnitus annoyance) during the individual's daily life may provide insights in the relationship of those variables with specific (e.g. social) or cyclical (e.g. sleep/awake) patterns. In order to capture such data, EMA is deployed several times during each day, requiring participants to remain in possession of their smartphone at all times, and allow interruption of activities in order to respond to the assessments. Such intrusiveness has been suggested to potentially produce negative outcomes in participants. Smartphone use has been associated with increased stress, anxiety, depression (Elhai et al., 2017; Vahedi & Saiphoo, 2018) and lower wellbeing (Horwood & Anglim, 2019). While symptom fluctuation during the day may be of importance to researchers and clinicians, daily average EMA scores can provide a broader daily picture.

Similarly, to EMA, End-of-Day Diary (EDD) minimizes the effects of recall bias by being deployed once a day. An established methodology for decades (e.g. Verbrugge, 1980), EDD has been used in a variety of fields, including chronic pain (e.g. Rost et al., 2016), eating behaviour (e.g. Debeuf et al., 2018), and emotionality during the COVID-19 pandemic (Moroń & Biolik-Moroń, 2021). EDD's benefit of reduced burden to the participant potentially sacrifices ecological validity when compared to EMA (Schneider & Stone, 2016). In order to make an informed choice between EMA and EDD a direct

comparison is warranted. Broderick et al. (2009) found little differences between both assessment methods after one week, however the findings are limited to the field of chronic pain and fatigue as well as to the period of one week. Moreover, results diverged according to the experience being assessed (i.e. pain, fatigue), specifically when comparing the daily equivalence between EMA and EDD. Research on different experiences (i.e. tinnitus) and over longer time periods that usually comprise existent intervention protocols are warranted.

The assessment of tinnitus, the experience of phantom sounds (e.g. high-pitched tone, chirping), relies on self-report only, and a precise evaluation of the experience is paramount for the development of research and symptom management. EMA use within tinnitus is in its infancy, with studies exploring possibilities and limitations of its use (e.g. Gerull et al., 2019; Lourenco et al., 2019; Pryss et al., 2018; Schlee et al., 2016). However, its superiority to retrospective self-reports has been confirmed (Goldberg et al., 2017). On the other hand, use of EDD, while common for decades, it is rarely utilized as an outcome measure within the tinnitus field. The current study aims at comparing results from EMA and EDD assessments in tinnitus patients undergoing treatment, in order to provide recommendations for future research. More specifically, EDD mean values are compared to EMA means. Moreover, EMA gathered close (late in the day) to the EDD completion are compared with earlier-in-the-day EMA and EDD. These analyses elucidate if EDD accurately reflects the overall daily picture, as illustrated by EMA.

2. Methodology

2.1. Participants

As part of a larger project on the effects of Cognitive Behavioural Therapy (CBT) on chronic tinnitus, we collected data from two subsequent clinical studies (duration of 3-months each) in which both assessment methods were used: EMA and EDD. Studies within the project applied a Single-Case Experimental Design (SCED) approach. In such a design, a small number of participants are repeatedly and consistently assessed to establish an individual and unique control condition (baseline phase). Afterwards, each participant undergoes a manipulation phase (e.g. treatment onset), while maintaining the continuous assessment (for an in depth review of SCED we guide the interested reader to Kazdin, 2018; Morley, 2018). As such, these powerful designs rely on large amount of data from a small number of participants. Each study included six tinnitus patients undergoing specialised CBT for tinnitus which contained a variety of treatment

components (e.g. exposure, relaxation, psychoeducation) delivered twice a week in 2-hour treatment sessions for a total of 20 sessions (for detailed treatment protocol see Cima et al., 2012). Patients on the waiting list for CBT treatment from the Adelante Department of Audiology and Communication (Hoensbroek, The Netherlands) were sequentially invited to participate in the project. Exclusion criteria comprised: (1) undergoing other tinnitus-related or psychological treatment during the time of the study; (2) commenced the use of hearing aid within three months of the start of treatment; (3) commenced or ceased the use of antidepressants, antipsychotics, anxiolytics, Ritalin, hormone replacement therapy, or medication to lower high blood pressure within three months of treatment; (4) unable to read and write in Dutch; (5) disclosed current suicidal intent or (6) had more than 40dB of uncorrected hearing loss in one or both ears as measured by calculating a Pure Tone Average (on the frequencies of 500, 1000 and 2000 Hz).

Patients' tinnitus severity was measured at baseline by the validated Dutch version (Meeus et al., 2007) of the Tinnitus Questionnaire (TQ; Hallam et al., 1988), which utilizes 52 items on a three-point scale for a total score ranging from 0 (low severity) to 104 (high severity). Further characterization of the sample is provided through the Dutch (de Beurs et al., 2001) version of the Depression Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995). Consistent of 21-items on a 4-point Likert scale, each sub-scale indicates levels of depression, anxiety and stress on a score from 0 (low) to 21 (high).

Each of the two studies included were conducted consecutively starting in May 2019 and registered at the Nederlands Trial Register (trial numbers NL7826 and NL8056). Ethical approval was obtained from the Medical Ethical Committee at Maxima Medical Centre, Veldhoven, The Netherlands (METC; NL63262.016.18).

2.2. Ecological Momentary Assessments (EMA) and End-of-Day Diary (EDD)

EMA and EDD data were collected continuously throughout the duration of treatment (3 months). EMA and EDD were collected through purpose-built apps installed on participants' smartphones. One study utilized an in-house developed app (TinNotes) by Maastricht University's Instrumentation Engineering department, while the subsequent study utilized an equivalent third-party app (mEMA; ilumivu, Inc., Cambridge, MA, USA; www.ilumivu.com). EDD assessments were delivered at 8-pm with a 4-hour time limit for completion. EMA questions were prompted seven times during the day, at random points with at least 2-hours in between prompts. Participants had the option

to snooze the prompt twice for 5-mins each time, after which the questionnaire would not be available any longer and result in a missing EMA measure for that time-point. Individualized sleeping hours were set so that prompts would not be delivered during those hours. Participants had to complete at least 50% of EDD assessments to be included for analysis. Assessments comprised of 16 (EDD) and 17 (EMA) items, presented in random order, of which 12 had content-equivalence. Eleven of the equivalent items (Table 1) were rated on a 7-point Likert scale (0-6) and related to either tinnitus experience (i.e. anger, annoyance, avoidance, distraction, fear, invasiveness, pleasantness and sadness) or overall wellbeing (i.e. anxiety, happiness and stress). One item (Social Interaction; EMA - "*Who are you with?*"; Diary - "*Who did you spend time with today?*") was descriptive and not included for analysis.

Table 1: Equivalent items of both assessment types: End-of-Day Diary (EDD) and Ecological Momentary Assessment (EMA).

EDD	EMA
How angry did your tinnitus make you today?	My tinnitus makes me angry
How annoying was your tinnitus today?	My tinnitus is annoying
How anxious were you today?	I feel anxious
How hard did you try to avoid your tinnitus today?	I try to avoid the tinnitus
How distracting was your tinnitus today?	My tinnitus is distracting
How afraid of hearing your tinnitus were you today?	I am afraid of hearing my tinnitus
How happy were you today?	I feel happy
How invasive was your tinnitus today?	My tinnitus is invasive
How pleasant was your tinnitus today?	How pleasant is your tinnitus?
How sad did your tinnitus make you today?	My tinnitus makes me sad
How stressful has your day been?	I feel stressed

2.3. Analysis

Pairwise comparisons using Spearman Rank Correlation between EMA and EDD were carried out between all equivalent items. EMA data of each item was plotted through time and a daily mean calculated. In order to compare EMA gathered proximally to EDD (delivered at 8-pm) and given the minimum 2-hour gap between EMA prompts, EMA delivered from 6-pm (2-hours before EDD delivery) was separated. Two new EMA means were calculated: (1) early EMA (before 6-pm), and (2) late EMA (after 6-pm). Paired t-tests between EMA means and EDD were conducted and corrected for multiple comparison (Holm, 1979). The Holm method controls for family-wise Type I error, with corrections decreasing the threshold of significance for each hypothesis tested. Following

convention, we considered p-values below 0.05 "statistically significant". Pairwise deletions were used to account for missing values. Effect sized were calculated through Cohen's D (Cohen, 1988).

Statistical analyses were performed with R version 4.0.1 (R Core Team, 2020) with supporting packages (Grolemund & Wickham, 2011; Tiedemann, 2020; Tierney, 2017; Wei & Simko, 2017; Wickham, 2019; Wickham et al., 2018, 2019).

3. Results

Nine participants (88.9% Men; Mean age = 58.11, SD = 9.98) were included for analysis for a total of 4,732 data entries (Table 2). From the original pool of 12 participants, 1 participant dropped out due to personal reasons unrelated to the treatment. An unknown error with the TinNotes app deemed data for two other participants to be unreliable. Data for one participant, who had recently commenced the use hearing aid, was included for analysis as the use of the hearing aid was not continued during treatment.

EMA fluctuations (Figure 1) show the difference between experience variability according to the time of day (e.g. decrease of tinnitus fear after 7-pm). Strong correlations (r > .70) were found for all but one (i.e. stress) EMA and EDD items (Figure 2). Paired t-tests (Table 3) indicated significant differences between EMA and EDD daily means on six variables (i.e. tinnitus anger, anxiety, tinnitus invasiveness, tinnitus pleasantness, tinnitus sadness, stress). EDD reports for these variables were significantly worse with the exception of tinnitus avoidance, which indicated no differences (Figure 3). Comparisons between EDD and early EMA (before 6-pm) indicate similar results of worse EDD scores for five variables (i.e. tinnitus anger, anxiety, tinnitus invasiveness, tinnitus sadness, stress). Moreover, EDD comparisons with late EMA (after 6-pm) indicated worse EDD scores for four variables (i.e. tinnitus anger, anxiety, tinnitus pleasantness, tinnitus sadness, stress) and improved scores for tinnitus avoidance.

Figure 1: Mean Ecological Momentary Assessment (EMA) recording per hour.

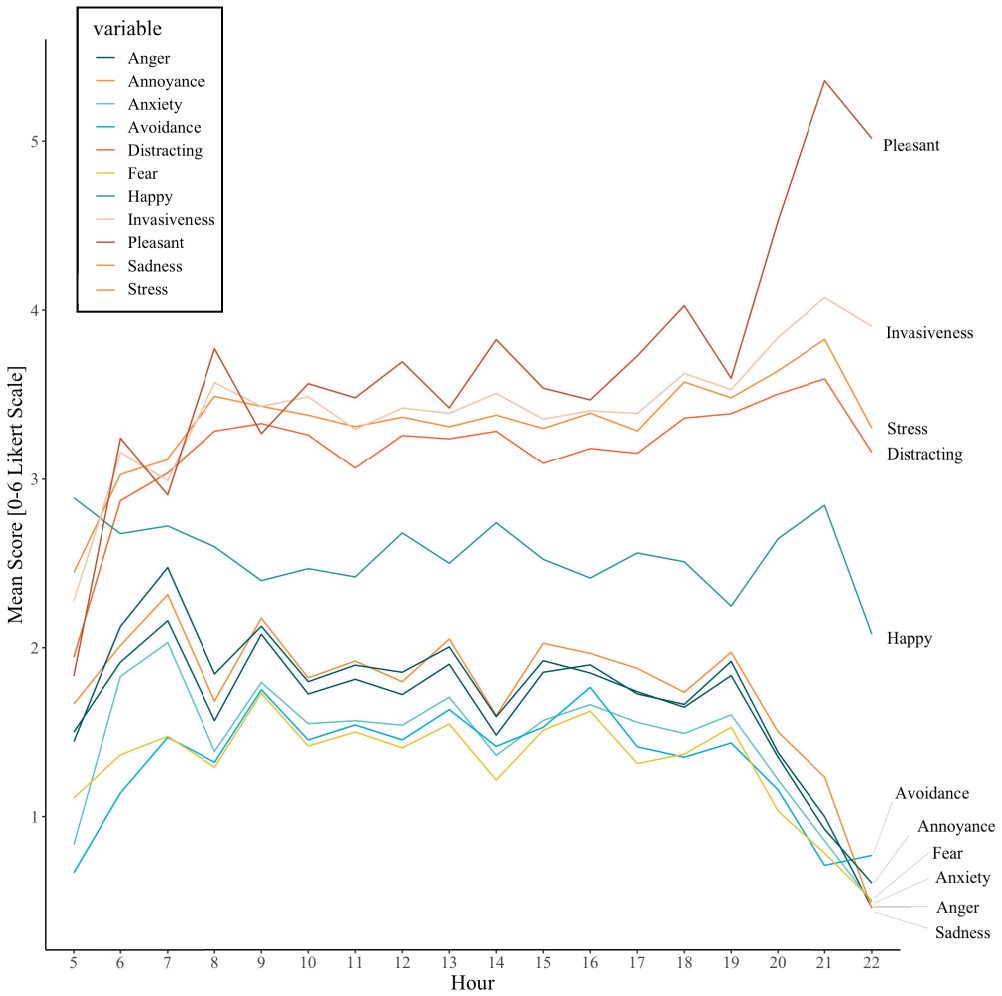


Figure 2: Correlation coefficient strengths.

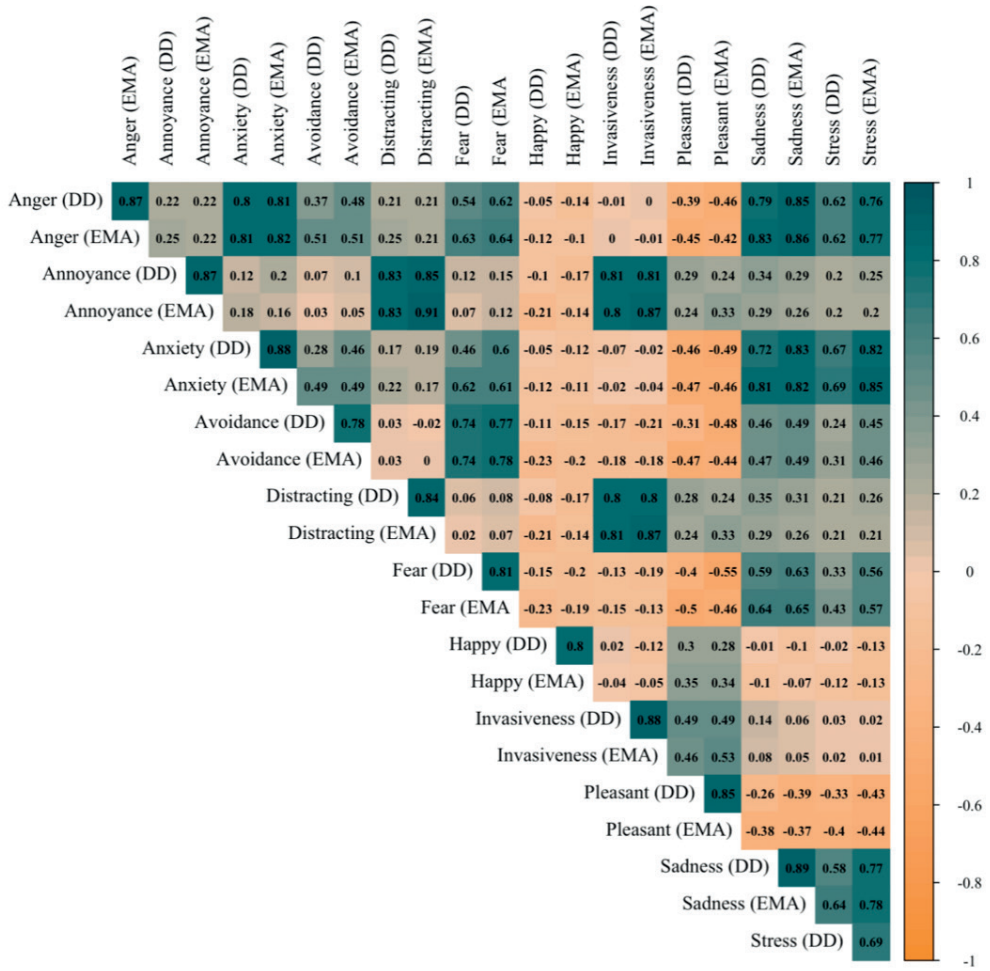


Table 2: Demographic characteristics

P	Age	Gender	Hearing aid (time)	DASS-21			Compliance (%)		Tinnitus			
				D	A	S	EMA	EDD	Duration	Location	Type	Severity
1	67	Men	10 years	4	0	2	15.8	77.5	2 years	Both ears	High pitch	81
2	62	Men	> 30 years	8	4	6	51.3	73.6	12 years	Both sides of head	High pitch	48
3	59	Men	No hearing aid	2	0	6	70.6	98.8	9 months	Both ears	High pitch	61
4	65	Men	No hearing aid	0	0	0	89.8	83.8	15 years	In the head	Middle pitch	68
5	66	Men	1 week	12	6	16	64.8	87.5	12 years	Right ear	High pitch	57
6	57	Women	No hearing aid	6	10	11	72.9	90.9	35 years	Both ears	Buzzing	54
7	64	Men	No hearing aid	1	1	3	90.5	98.5	2 years	Right side on the back of the head	High pitch	38
8	43	Men	No hearing aid	13	9	11	76.8	100	11 months	Whole head	High pitch	80
9	40	Men	No hearing aid	2	0	6	70.6	89.4	6 years	Both ears	High and middle pitch	77

Note: Tinnitus severity measured by Tinnitus Questionnaire (TQ); Depression (D), Anxiety (A) and Stress (S) measured by the Depression Anxiety and Stress Scale (DASS-21).

Table 3: Paired sample t-tests with adjusted p-values for equivalent variables of Ecological Momentary Assessment (EMA) and End-of-Day Diary (EDD) on a Likert scale (0-6).

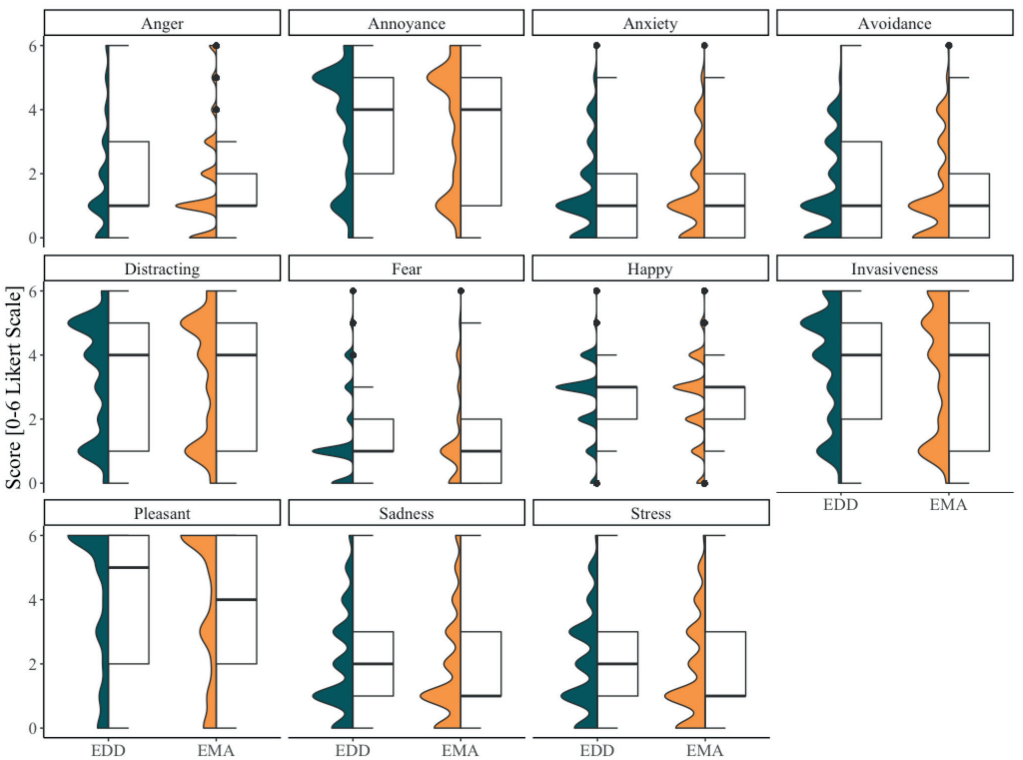
	Mean EMA (SD)	Mean EDD (SD)	p	Cohen's D
Anger	1.756 (1.723)	1.870 (1.748)	< .001**	.065
Annoyance	3.382 (1.931)	3.414 (1.932)	.156	.017
Anxiety	1.575 (1.42)	1.648 (1.44)	< .001**	.050
Avoidance	1.454 (1.477)	1.422 (1.451)	.156	-.022
Distracting	3.242 (1.891)	3.202 (1.855)	.11**0**	.065
Fear	1.403 (1.399)	1.425 (1.431)	.17**0**	.016
Happy†	2.503 (1.308)	2.507 (1.247)	.815	.003
Invasiveness	3.461 (1.895)	3.522 (1.805)	< .001**	.033
Pleasant†	3.649 (2.271)	3.587 (2.28)	.03**0***	-.027
Sadness	1.869 (1.679)	1.956 (1.697)	< .001**	.051
Stress	1.831 (1.576)	2.102 (1.587)	< .001**	10.172
	Mean early EMA (SD)	**Mean EDD (SD)**	**p**	**Cohen's D**
Anger	1.885 (1.777)	1.997 (1.791)	< .001**	.063
Annoyance	3.337 (1.954)	3.372 (1.939)	.348	.018
Anxiety	1.690 (1.447)	1.750 (1.452)	< .001**	.042
Avoidance	1.563 (1.514)	1.550 (1.485)	.974	-.009
Distracting	3.199 (1.912)	3.175 (1.858)	.920	.063
Fear	1.507 (1.43)	1.532 (1.463)	.580	.017
Happy†	2.52 (1.354)	2.527 (1.283)	.974	.006
Invasiveness	3.374 (1.893)	3.438 (1.792)	.007*	.034
Pleasant†	3.408 (2.294)	3.377 (2.3)	.920	-.013
Sadness	2.007 (1.711)	2.066 (1.726)	< .001**	.035
Stress	1.988 (1.605)	2.211 (1.594)	< .001**	10.140
	Mean late EMA (SD)	**Mean EDD (SD)**	**p**	**Cohen's D**
Anger	1.386 (1.5)	1.503 (1.564)	< .001**	.076
Annoyance	3.511 (1.857)	3.534 (1.906)	1	.013
Anxiety	1.248 (1.285)	1.353 (1.361)	< .001**	.079
Avoidance	1.142 (1.317)	1.053 (1.28)	.012*	-.068
Distracting	3.365 (1.826)	3.276 (1.847)	.080	.076
Fear	1.101 (1.259)	1.119 (1.287)	1	.014
Happy†	2.456 (1.164)	2.448 (1.134)	1	-.006
Invasiveness	3.709 (1.881)	3.762 (1.82)	.296	.029
Pleasant†	4.339 (2.054)	4.19 (2.11)	< .001**	-.072
Sadness	1.475 (1.517)	1.639 (1.572)	< .001**	.106
Stress	1.379 (1.397)	1.789 (1.523)	< .001**	10.279

	Mean early EMA (SD)	Mean late EMA (SD)	p	Cohen's D
Anger	1.87 (1.748)	1.756 (1.723)	< .001**	Paired Cohen's D could not be computed due to unequal number of measures
Annoyance	3.414 (1.932)	3.382 (1.931)	.003*	
Anxiety	1.648 (1.44)	1.575 (1.42)	< .001**	
Avoidance	1.422 (1.451)	1.454 (1.477)	< .001**	
Distracting	3.202 (1.855)	3.242 (1.891)	.004*	
Fear	1.425 (1.431)	1.403 (1.399)	< .001**	
Happy†	2.507 (1.247)	2.503 (1.308)	.163	
Invasiveness	3.522 (1.805)	3.461 (1.895)	< .001**	
Pleasant†	3.587 (2.28)	3.649 (2.271)	< .001**	
Sadness	1.956 (1.697)	1.869 (1.679)	< .001**	
Stress	2.102 (1.587)	1.831 (1.576)	< .001**	

*p < .05; **p < .001; †inverted item

Comparison of early and late EMA indicated significant differences in all but one (i.e. happiness) variables. Items on tinnitus anger, annoyance, fear, invasiveness, pleasantness, and sadness as well as levels of anxiety and stress improved after 6-pm, while tinnitus avoidance and distraction worsened.

Figure 3: Ecological Momentary Assessment (EMA) and End-of-Day Diary (EDD) distribution and box plot per variable.



4. Discussion

This study sets out to compare two similar but different daily measurement methods, namely EMA and EDD in chronic tinnitus patients during a 12-week treatment. Generally, both methods provide quite similar results. All but one item (stress, r = .69) showed strong correlations between EMA and its EDD counterparts (r > .77). Nevertheless, EDD stress reports are significantly higher than early-in-the-day EMA measures (where mean stress levels were at their highest). EDD painted a worse picture for another five variables when compared to EMA (i.e. tinnitus anger, anxiety, tinnitus invasiveness, tinnitus pleasantness, tinnitus sadness). EDD reports favoured negative experiences rather than recent experiences (i.e. EMA after 6-pm). Broderick et al. (2009) found similar results when comparing EMA and EDD of pain and fatigue experiences. Such occurrence is akin to the "experience memory gap" (Miron-Shatz et al., 2009), where recalled symptoms are reported as worse when compared to real-time in the moment assessments (i.e. EMA). Such memory biases were studied in a recent review (Van Den Bergh & Walentynowicz, 2016), indicating that pain and fatigue experiences are overreported when assessments rely on longer recall periods. While these findings are significant in the field of self-report assessments, no study with tinnitus complaints was included in the review and parallels must be drawn with caution.

The large sample of data provided by novel methodological approaches (e.g. EMA, EDD, SCED) present both statistical opportunities and issues not commonly encountered. Despite correcting for multiple comparisons (i.e. Holm, 1979), which decreased the threshold for significant results, the findings are still affected by the large number of data and traditional p-value selected (i.e. 0.05). As such, more conservative approaches that are beyond multiple comparison corrections may provide a more accurate picture of the results (i.e. lower p-value thresholds). In the current study, the largest significant mean difference found in tinnitus related variables was tinnitus anger (1.63%), with stress levels (3.87%) holding the largest, although small, difference in wellbeing variables. Whether these statistical differences are clinically relevant are therefore questionable. Furthermore, while EDD results may have differed from early or late EMA, the daily EMA mean accurately reflected the remaining variables (i.e. tinnitus annoyance, tinnitus avoidance, tinnitus distraction, tinnitus fear, and happiness).

An exception was found in happiness levels, which did not significantly differ between EMA and EDD measures at any point. EMA and EDD measures of happiness strongly correlated (r = .80) even though both measures correlated weakly (r < .24) with other

variables. Despite this seemingly independent level of happiness from other experiences (e.g. tinnitus anger, tinnitus annoyance, anxiety, stress), accurate assessment of happiness remains a challenge, with the very definition of happiness still debated (Ludwigs et al., 2019). As such, interpretations of happiness stability and independence are limited.

The choice of variables to be measured, while theoretically driven and based on specialist consensus, lacked the insight from other key stakeholders and may further benefit from initiatives acknowledging patient preferred outcomes (i.e. Hall et al., 2018). An added benefit of EMA and EDD measures is that it may conform with the push for individualized medicine (Schork, 2015; Senn, 2018) due to its flexibility in incorporating different items. Therefore, while the outcomes used in the current research are relevant within its theoretical framework, they are limited by the pool of specialist used to create the items. Further research utilizing a broader consensus of outcome variables, as suggested by Hall et al. (2018) may increase the relevance and use of EMA and EDD. Moreover, the choice of a 7-point Likert scale, while not directly inspired by standardized tinnitus self-report assessments, was made due to technical limitations of the TinNotes app. Further research incorporating other scales, specifically Visual Analog Scales (VAS), are recommended.

Additional limitations include the high proportion of men 40 years or older (88.89%) in the sample, limiting the generalizability of the findings. The homogeneous sample follows epidemiological trends in tinnitus, with 80% of tinnitus diagnosed after the age of 40 (Stohler et al., 2019) and higher incidence detected in men (Fujii et al., 2011; McCormack et al., 2014, 2016). Despite the limitations, the current results add important knowledge on long-term EMA versus EDD comparisons and provide insights into using these methods in tinnitus patients (in addition to chronic pain and fatigue)

5.Conclusion

Generally, EDD and EMA provide similar data. EDD measures significantly differed from EMA daily averages for six out of eleven variables: tinnitus anger, anxiety, tinnitus invasiveness, tinnitus pleasantness, tinnitus sadness, and stress. The differences support previous literature which found that longer recall periods associate with worse symptom/experience recollection. Despite their statistical significance, the effects were small and may be attributed to the large number of data entries. As such, the minor differences may not justify EMA as the measurement of choice as the added burden to participants may be of ethical or theoretical concern. When these arise, EDD provides a viable alternative

since it accurately and closely reflects daily life experiences as measured by EMA daily mean. Nonetheless, when the use of EMA is necessary the minor differences found in the current study do not justify a correction of the data collected. EMA may better suit the need of closely investigating cyclical tinnitus patterns (e.g. sleep/awake) or possible daily correlates (e.g. work environment, presence of triggers). The knowledge of specific correlates allows for the recognition of maladaptive patterns and emotional reactions which may be addressed during treatment. Moreover, the use of repeated assessments (i.e. EMA and EDD) is vital in the application of SCEDs which are tailored to the push for individualized research and treatment (Schork, 2015).

The continuous development and understanding of tinnitus assessment must be prioritized as the lack of an objective measure of tinnitus entails an over-reliance on patient self-reports for research and treatment. Future research on accurate measurements of the underlying mechanisms of the tinnitus experience may pave the way for a broader understanding about the onset, maintenance and recovery of tinnitus disability.

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CHAPTER 5

Better together. Group vs individual Cognitive Behavioural Therapy (CBT) for tinnitus: A multiple-baseline Single-Case Experimental Design

Under revision:

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Better together. Group vs individual Cognitive Behavioural Therapy (CBT) for tinnitus: A multiple-baseline Single-Case Experimental Design. *Ear and Hearing*

CHAPTER 6

General Discussion

To see the forest from the trees

Three main areas of interest for closer investigation were identified from the current state of the tinnitus field in Chapter 1: (1) the testing of a tinnitus fear conditioning paradigm in humans; (2) improving tinnitus assessment; and (3) the investigation of CBT components in order to better understand what works best form whom. From these, 4 specific research questions were drawn, and each question was addressed in a dedicated chapter. They were: (1) the adaptation/creation of an associative learning model for the field of tinnitus in order to establish a replicable fear learning paradigm with healthy human participants; (2) the investigation of whether Ecological Momentary Assessment (EMA) negatively affects tinnitus experience; (3) the comparison between EMA and End-of-Day Diary (EDD) in measuring tinnitus experience; and, relating to tinnitus treatment, (4) contrasting and comparing individual to group-based Cognitive Behavioural Therapy (CBT) for tinnitus. Next, we provide an overview of the research findings followed by a critical discussion and future directions.

Tinnitus fear conditioning

The tinnitus Fear Avoidance (FA) model explains the role of fear in the development and maintenance of Chronic Disabling Tinnitus. Clinical studies have shown the model to be valid, nonetheless, replicable experimental paradigms to investigate underlying associative learning processes in with human participants were lacking. A novel differential fear conditioning paradigm was introduced (Chapter 2). We repeatedly presented a neutral sound (CS+), conceptualized to be tinnitus-like, followed by a short delay and the same sound at higher intensity (US) to healthy human participants. The CS+ produced fear responses (seen in self-reported expectancy ratings) in participants in absence of the US. A different, but perceptually equivalent auditory stimulus that was not paired with the US (CS-) did not elicit these fear responses. In other words, during the first phase (i.e. acquisition phase), fear of a neutral sound was acquired, after pairing it with the same louder sound. The finding provides support that classical conditioning, increased fear responding towards a neutral sound can be acquired, which may provide support for the key role of fear in triggering the pathological cycle of the FA model. Classical conditioning has been previously proposed as the underlying mechanism of the Neurophysiological model, although definition of the learning components (e.g. CS definition) have been vague and unspecific (Baguley et al., 2013). Moreover, conditioning research focused solely on animal paradigms to study tinnitus generation (Jastreboff, 1990; Jastreboff et al., 1988, 1994).

At a second phase (i.e. extinction phase) of the paradigm, the acquired fear responses decreased with repeated presentation of CS+ without US. Surprisingly, CS- evoked fear responses at the beginning of this phase also decreased. This lack of differentiation between CS+ and CS- was also observed in the third phase of the experiment (i.e. reinstatement phase), where reinstatement was tested through a single non-contingent presentation of the US. The unexpected lack of differentiation was postulated to be a consequence of conducting Acoustic Stapedial Reflex Threshold (ASRT) and Loudness Discomfort Level (LDL) tests between experiment phases for assessment purposes. These tests include presentation of acoustic probes that were similar to the CS+/- and US, potentially interfering with the CS-US associations and thereby diminishing the fear responses to the US. Moreover, the change in context, necessary to conduct the tests between phases, potentially decreased the strength of the association formed at acquisition. Beyond reconsidering the use of ASRT and LDL tests between the experimental phases, improvement of the paradigm in future studies can be achieved through limiting change of context (i.e. moving between rooms) and augmenting the number of trials during the acquisition phase, thereby increasing opportunities for a more robust and enduring fear-learning.

Findings, while not robustly establishing a fear learning paradigm, are promising and do not rule out the role of classical conditioning as a possible origin for Chronic Disabling Tinnitus. Despite the several limitations of the study, fear learning was observed in the fear expectancy ratings. On the other hand, physiological responses were inconsistent, indicating a quick habituation and indiscriminate fear learning to CS+ and CS-. Again, the limitations presented by the ASRT and LDL measurements as well as the change in context may have unduly influenced responses, specifically those after the acquisition phase (where change of context happened more often). Nevertheless, physiological measurements, including the ones used in the current study (Skin Conductance Response and Heart Rate acceleration) may be limited in explaining tinnitus disability. Given a threatening US, self-report measures of fear have stronger diagnostic, predictive and construct validity when compared to physiological measurements (Boddez et al., 2013). Therefore, an updated paradigm might take a step back in order to create a simpler approach with a lower number of outcome measures (i.e. threat expectancy only) and increased power through increased assessment points, number of trials and participants.

(Re)assessing tinnitus

Self-report tools that are widely used to assess tinnitus experience may be susceptible to bias (i.e. recall bias, reading difficulty, and current psychological state). Ecological Momentary Assessments (EMA) increase ecological validity and reduce the influence of bias. However, the unwarranted attention towards the tinnitus experience has been thought to be detrimental to the patients. Increased awareness of the tinnitus percept has been shown to be associated with increased Chronic Disabling Tinnitus (e.g. lower quality of life; Cima et al., 2011). The use of EMA may exacerbate awareness of tinnitus in severe tinnitus sufferers by increasing attention to tinnitus, since it requires responding and reflecting on disability intensively on a daily basis. Chapter 3 investigated these potential negative effects through a Single-Case Experimental Design (SCED).

Our findings supported and expanded on previous findings regarding EMA reactivity in tinnitus sufferers (Henry et al., 2012; Schlee et al., 2016) as participants did not show meaningful negative reactions to EMA. Interestingly, slight improvements in tinnitus experience (i.e. decreased tinnitus avoidance, annoyance, interference, fear, sadness, distraction, masking and anger), and overall well-being (i.e. happiness, stress, sleep quality, activity level, anxiety) were observed after EMA introduction. Important to note is that EMA reactivity was only tested in participants with severe tinnitus distress. It remains to be explored if such findings are replicable in individuals with varying levels of tinnitus distress. Furthermore, attentional processes which could have further helped explain the findings, were not measured. More importantly, the surprising potential benefits of EMA remain to be explored. As research into internet and app delivered interventions is growing exponentially (e.g. Beukes et al., 2017, 2018; Hesser et al., 2012), and given the impact of the COVID-19 crisis for tinnitus patients (Beukes et al., 2020), the potential of EMA to become part of a treatment is worth exploring.

Replication studies including participants with different levels of tinnitus-severity should include whether there is an added burden on participants while using EMA, posing ethical and theoretical concerns (e.g. increased screen time). End-of-Day Diaries (EDD) could be a promising alternative to EMA by providing equivalent assessments at a lesser cost, specifically in cases where EMA data is aggregated in the form of daily scores (e.g. means).

As direct comparisons between EMA and EDD assessments in tinnitus patients had not been carried out, Chapter 4 compared EDD mean values to EMA means. Furthermore,

EMA gathered close in time to EDD was compared with earlier-in-the-day EMA and EDD. The study focused on testing if EDD accurately reflected the overall daily picture, as illustrated by EMA. Our results indicated that EDD and EMA provide similar data, though some significant differences were found. EDD measures significantly differed from EMA daily averages for six out of eleven variables: tinnitus anger, anxiety, tinnitus invasiveness, tinnitus pleasantness, tinnitus sadness, and stress. The differences indicated worse scores (e.g. lower tinnitus pleasantness, higher anxiety) on EDD. This is in line with previous literature revealing that longer recall periods are associated with worse symptom/experience recollection (Miron-Shatz et al., 2009). Despite statistical significances, the effects were small and may be attributed to the large number of data entries (4,732). Such minor differences may not justify EMA as the measurement of choice given the added burden to participants.

These findings are limited by the homogeneity of the population and external validity would be strengthened by successful replications in different age groups and in participants with varying levels of tinnitus distress. Furthermore, a more extensie set of tinnitus experiences, beyond the ones utilized in the chapter (e.g. perceived tinnitus control) can potentially produce different results due to the heterogeneity of experiences. While a preference for EDD is stated, EMA use is not to be dismissed. EMA remains a powerful tool that may be of specific benefit in understanding daily cyclical patterns in tinnitus experience (e.g. fluctuations from morning to night). Beyond these patterns, EMA may further elucidate the dynamic relationship between emotions (e.g. fear), individuals, and their environment (Shiffman et al., 2008). Reactions to specific situations and granular level insight into temporal chain reactions have the power to pinpoint clinically relevant triggers. Future research must focus on the relevant use of EMA or EDD pending research objectives and associated costs.

Beyond replicating the study with a different and wider population, other limitations of the original research may be further addressed. The use of questions developed with the patient and potentially tailored to a patient's individual need and acknowledging patient preferred outcomes is possible through the flexibility of EMA and EDD methodologies (i.e. Hall et al., 2018). Such tailoring may, for example, provide answers on how to accurately measure overt avoidance behaviour. Such as GPS location (e.g. avoidance of known restaurants, bars, concert halls), as well as the use of smartphone microphones to measure noise exposure. The use of an adapted EMA delivery, that is prompted by the participant when he/she recognizes a trigger or catastrophic thought, has potential

when integrating EMA in ongoing interventions. Naturally, while promising and exciting methodological possibilities are theoretically possible, technological and budgetary constraints may limit the adequate deployment of such tools. The use of smartphone microphones, for example, is limited to the quality of each individual smartphone used and dependent on the quality of the hardware (e.g. sensitivity of the microphone, battery life) and software (e.g. operating system) employed by the manufacturer, making it difficult to standardize and compare.

Chapters 3 and 4 highlight the potential of alternative assessment methods to standardized questionnaires, namely individualized EMA and EDD. Findings highlight that EMA can be used with severe tinnitus sufferers without negative consequences and, when EMA concerns are present, EDD is an adequate alternative for tinnitus assessment. Both represent more ecologically valid methods of assessment. Beyond a reduction in bias, these methods facilitate the use of SCEDs. As observed in this dissertation (Chapters 3 and 5), SCED relies on the frequent and repeated assessment of participants to establish a robust baseline condition. These designs are particularly useful in the field of tinnitus as they account for the high heterogeneity of tinnitus experiences. Coupling EMA or EDD with designs that focus on within-subject change and fluctuation, specifically SCED, provide promising avenues in tailored treatment research.

CBT for tinnitus

Tinnitus can be treated successfully with CBT. While positive outcomes have been reported in both group and individual settings, no direct comparison with the same treatment protocol has been carried out (Fuller et al., 2020). Group treatment may provide added benefits, such as decreased treatment delivery costs and higher speed of recovery due to increased social learning opportunities. Chapter 5 aimed at comparing a successful CBT for tinnitus treatment protocol (Cima et al., 2012) between group and individual delivery setting. This chapter revealed that participants experienced increased benefits when treated in group, compared to when treated on an individual basis, as measured on over half of the variables (tinnitus anger, annoyance, fear, interference, invasiveness and sadness, as well as happiness and anxiety). Moreover, participants who switched from group to individual treatment were less happy and had lower activity levels when compared to those who went the opposite direction (from individual to group treatment).

Overall, CBT proved an effective treatment for tinnitus up to nearly six-month follow up, supporting previous findings (Cima et al., 2012, 2019; Fuller et al., 2020). Nonetheless, one single participant did not record clinically significant improvements – on neither the Tinnitus Questionnaire (TQ; Hallam et al., 1988), the Tinnitus Functional Index (TFI; Meikle et al., 2012) or self-reported goals. The participant uniquely registered higher fear levels and variability as well as self-reported nonadherence to the treatment component, namely exposure (i.e. interoceptive avoidance of exposure sessions). These observations are consistent with the FA model and appear to underscore the beneficial role of decreased fear by exposure on treatment outcomes. Conversely, the lack of treatment response also highlights the importance of individualized medicine. Studying specific effects of each individual treatment component (e.g. exposure, relaxation, psychoeducation) as well as possible combinations, contributes to achieving the most efficacious treatment geared to specific groups and tailored to the individual needs of each patient.

Cognitive Behavioural Treatments for tinnitus should continue to be explored, as we strive to understand what component works best for whom. Chapter 5 focused on only one treatment variant (i.e. delivery setting) and results were limited to men in the sixth decade of their lives. Replicability of findings in samples including women and other age groups must be carried out.

Planting seeds

Despite growing evidence of the prominent role of fear in the acquisition, development and maintenance of Chronic Disabling Tinnitus, research within this perspective is scarce. A quick search of the literature (in March 1st, 2021) reveals that 4 articles have been published with the terms "fear" and "tinnitus" in the title, compared to over 950 in a similar search with the terms "fear" and "pain" (dating back to 1975). The earliest of the articles within the tinnitus field was published in a peer reviewed journal 10 years ago (Cima et al., 2011). During the same period 412 (of the 950) articles were published in the field of pain. Resistance to adopting a psychological tinnitus model may be encountered as patients and healthcare providers call for cures and hope for relief through sophisticated technology (McFerran et al., 2019). Yet, the majority of individuals who perceive tinnitus do not suffer from it (Davis & Refaie, 2000; Gallus et al., 2015; Kim et al., 2015). Therefore, the elimination of the tinnitus percept solely, may not directly translate to diminished suffering. Interestingly, reduction of tinnitus-related fear may be a path to diminished tinnitus perception. In the field of chronic pain, reduction in pain perception has been observed after diminished pain-related fear (de Jong et al., 2012). Growing literature on CBT for tinnitus is robust and consistent in diminishing tinnitus suffering (Fuller et al., 2020). This dissertation has highlighted the role of cognitions, behaviour and emotional reactions in Chronic Disabling Tinnitus. Current findings point towards a better understanding through the role of fear in its development (Chapter 2) and recovery (Chapter 5).

Hair of the dog

It has been long believed that "like cures like" (Latin: *similia similibus curantur*). Development of vaccines, for example, lie within a concept not too far from the one in the times of Hippocrates. Exposure techniques may be used in CBT protocols, and resonate strongly with this line of thought by using the feared stimuli as treatment to the fear responses. Following the FA model, the alternative to the pathological cycle (i.e. perceiving tinnitus as a threat to health and functioning) is the recovery path (i.e. perceiving tinnitus as a harmless experience). On the path to recovery, the continuation of valued activities follows, and with it, confronting stimuli that would otherwise be avoided due to the fear of increasing in tinnitus (e.g. silent or loud environments, or avoiding it by distraction). In other words, fear can be reduced by confronting the patient with the fearful experience (e.g. silent environment evoking tinnitus experience without the

option of distraction) without the expected negative outcome (e.g. increased tinnitus). However, since exposure takes the form of confrontation with the fear-provoking stimuli, and *fear* is the catalyst of the pathology, confronting patients with the fearful stimuli can be a challenge (as highlighted in Chapter 5). The violation of the expected threatening prediction, which allows for the creation of a new and more adaptive association with tinnitus. This process however can unintentionally be interrupted and avoided (for a detailed review on underlying mechanism of inhibitory learning and exposure see Craske et al., 2014, 2018). Adding to this, despite support for exposure techniques and the strong recommendation for CBT (Cima et al., 2019), competing techniques and therapies are often recommended instead (e.g. masking, sound enrichment therapy, TRT). These require less therapeutic effort, less initial patient discomfort by confrontation with fear and less agency from the patient, with a higher perceived sense of comfort. Similar to some CBT protocols, TRT utilizes psycho-education (e.g. deconstructing tinnitus threat misconceptions), yet, contrary to CBT-Exposure, avoidance of the tinnitus experience is favoured through masking and sound enrichment therapy (Jastreboff & Hazell, 2004).

While exposure techniques have gathered support beyond the field of tinnitus, and especially in the field of chronic pain (e.g. Craske et al., 2018), findings on the detrimental effect of the utilization of safety-seeking behaviours during exposure (e.g. avoidance) are inconclusive (Meulders et al., 2016). Fundamental research in the field of tinnitus, which would provide a way into examining such effects, are lacking in part due to the absence of replicable human paradigms. Recent review findings, slightly, favour CBT over TRT (i.e. Fuller et al., 2020), however, the inconsistency, variability and availability of protocols utilized limit the interpretability of findings.

From whole to unit

One for all, all for one – Dumas (1844)

Studies with broad inclusion criteria fail to acknowledge the idiosyncratic characteristics of tinnitus. The high inter- and intra-individual variability may not be properly acknowledged when interpreting results from group-based analysis. Strong individual effects are lost in the search for a one-size-fits-all solution. Given such limitations, there is a push for individualized medicine (Schork, 2015), warranting tailored designs for treatment and research. Following the call, half of the four studies here presented employed SCED to achieve meaningful results that would otherwise be impossible (Chapters

3 and 5). Unlike observational/non-experimental designs (e.g. case studies), SCED investigates causal relationships between variables through repeated measurements of a dependent variable over at least two different conditions of a manipulated variable (e.g. treatment onset; Morley, 2018). Practically speaking, SCED usually works by repeatedly assessing individuals before (baseline phase: A) and after the random introduction of an intervention or manipulation (phase: B). Effects are mainly examined through differences between phases in level (e.g. mean, median, broadened median), trend (e.g. Least Square Regression) and variability (e.g. range lines, trended range; Kratochwill et al., 2010). Robust statistical methods have been developed to further support the power of analyses on results from SCED (e.g. Randomization Test, NAP, Tau-U). Participants (or units) may be added to further increase power through multiple (i.e. simultaneous start) or sequential (i.e. different start) baselines. The growing use of SCED is reflected in the emergence of published guidelines, such as the Risk of Bias in N-of-1 Trials (RoBiNT; Tate et al., 2013) and The Single-Case Reporting Guideline In BEhavioural Interventions (SCRIBE; Tate et al., 2016).

As we have seen in Chapter 5, SCED may prove an adequate and powerful solution to further study the individual components of CBT for tinnitus. Beyond the capacity to isolate components (e.g. exposure, relaxation, psychoeducation), SCED allows for an intimate exploration of potential pivoting moments in treatment phases within the participant (e.g. identifying triggers of cascading events, emotions, and reactions), as well as a better understanding of current treatment options (e.g. pinpointing when change happens and potential sequence of events/treatment components) while potentially creating new research questions. Perhaps, more importantly, is the capacity for SCED to robustly investigate treatment effectiveness in small samples and single individuals. Due to the wide variety of tinnitus aetiology, longevity and experiences, SCED rises as a promising method due to the capacity to isolate and investigate identified cohorts of tinnitus patients, however small, and the possibility to perform meta-analyses over aggregated data of multiple studies with SCED. These analyses may strengthen external validity of treatment components, without losing individual case results. Creative and interesting investigations using SCEDs are continuously emerging, from analysing patterns of change within a chronic lower back pain intervention (Caneiro et al., 2019) to the efficacy of supervision in increasing CBT competencies (Alfonsson et al., 2020). Future research within tinnitus may integrate the promising research from similar fields (e.g. Caneiro et al., 2019), as well as deepen already existing findings within the field,

such as the benefits of Tinnitus Retraining Therapy (TRT; Jastreboff & Hazell, 2004) or transcranial direct current stimulation (tDCS; Jacquemin et al., 2018). Thus, SCED brings a new perspective within the field that may lead to new knowledge and the re-assessment of existing theories, while also allowing for flexible study designs without compromising the quality of findings.

Naturally, some limitations are noticeable. SCED is not adequate when time periods for phases (i.e. baseline, treatment, follow-up) are not appropriate (Vlaeyen et al., 2020), such as acute care (e.g. emergency care) or longer follow-up periods (e.g. 1 year). More importantly, the generalizability of findings provided through SCED is often questioned. While group-designs seek to increase the generalizability of findings through a larger number of participants, statistical analysis of group averages (means) may not directly translate to treatment effects at the individual level (Kazdin, 2018) and may not even translate to the individuals within that group. Such may also be due to the less idiosyncratic measures utilized in group studies when compared to SCED. By placing the patient in the center of research and treatment, as it is done in SCED, generalizability is created through the replication of treatment protocols with idiosyncratic outcome measures. In other words, it is not the use of standardized questionnaire scores which defines the outcome of an intervention, but the robust individual differences between phases of each unit studied. Replicability, a long standing issue in social sciences (e.g. "Estimating the Reproducibility of Psychological Science," 2015; Lilienfeld, 2017), is as always, the key to the future. SCED allows for health care providers, and not only researchers, to produce robust findings which in itself may be replicable. In SCED, the feasibility of small-scale research that is rich in information may contribute to a larger set of aggregate data which can provide important insights needed into future research and treatment.

From tinnitus to trees

> "The objects of sense exist only when they are perceived; the trees therefore are in the garden... no longer than while there is somebody by to perceive them." – Berkeley (1710)

The original thought of Berkeley has inspired the question posed by The Chautauquan which opens this PhD dissertation. The corollary: "*If a human being were to hear a tree fall, would there be any tree?*" was presented and the original thought by Berkeley may provide insight into the answer. The philosopher insisted that existence requires perception, creating the branch of idealism where *to be is to be perceived* (Latin: esse is percipi). While avoiding the philosophical debate that endured centuries and which is beyond the scope of this thesis, it is still possible to enrich ourselves from such a point of view. Thus, the existence of tinnitus, as the trees for Berkeley, can only exist as long as there is one to perceive it. Applying this knowledge to the postulated corollary, one might only ascertain that if a human being were to hear a tree fall, the *sound would exist*, whilst the tree remains to be perceived.

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CHAPTER 7

Impact statement

Impact statement

The current body of work sought to develop three different, but related, areas in the tinnitus field. First, we focused on new tools for assessing the tinnitus more accurately. Second, we investigated tinnitus treatment, more specifically, Cognitive Behavioural Therapy (CBT) for tinnitus and whether a group delivery would be better than individually delivered CBT. Lastly, we tackled the development of research into the role of fear in tinnitus.

The investigation of new tools for assessing tinnitus was deemed necessary due to the limitations of assessing tinnitus. Due to the lack of a "definitive" measure of tinnitus, such as the results of blood sample analysis for certain conditions (e.g. hepatitis, HIV, etc), tinnitus relies solely on self-report measures. Traditional self-report measures (i.e. questionnaires) have limitations that can strongly influence results. One such limitation is that these questionnaires are subjected to biases. In other words, participants are influenced by their memory (e.g. remembering only negative experiences), mood (happy vs foul), and location (hospital vs home) when filling out these questionnaires. Newer methods that are delivered through smartphone apps allow for assessing tinnitus in daily life, where it matters most, through small questionnaires and during longer periods of time (e.g. months). Although the possible negative side-effects of such strategies (e.g. extended screen time, excessive smartphone use) were yet to be investigated within the tinnitus field.

Tinnitus treatment delivery (group vs individual) has not been directly tested within the tinnitus field before. Previous literature has demonstrated the power of group treatment, specifically the use of learning through others (i.e. observational learning). Whether if group treatment has added benefits to the participants provides guidance for future treatment design and a better understanding of the tinnitus recovery process.

It is postulated that the role of fear in the development and maintenance of tinnitus is of vital importance. Inspired in research of other fields (i.e. chronic pain), fear of tinnitus is believed to trigger a detrimental cycle where misinterpretations of the tinnitus experience (e.g. fear that tinnitus is a symptom of a tumour; i.e. catastrophic thoughts of the meaning of tinnitus), excessive and constant tinnitus monitoring, and maladaptive behavioural responses (e.g. avoiding silence or social situations; i.e. avoidance of non-harmful activities) lead to a significant decrease in quality of life. Some research on fear and tinnitus has been conducted, though research is still in its infancy.

Our findings were promising. New tools to measure the tinnitus experience were proven safe for use with those suffering from severe tinnitus. Also, given the personal or financial burden of some of those tools for the researcher (i.e. Ecological Momentary Assessment, EMA), a different method (i.e. end-of-day diary, EDD) has proven an adequate alternative. Regarding tinnitus treatment, group CBT was observed to be more beneficial when compared to individual treatment. Finally, the challenge to investigate the role of fear in tinnitus was met with a novel experimental paradigm, which provides insights into learning fear of tinnitus, and by extension the development of chronic tinnitus.

Scientific advances from these findings are considerable. We have paved the way for the safe use of new tools and methodologies within the tinnitus field. The use of EMA and EDD provides a different perspective to the understanding of the tinnitus experience that is closer to the *lived experience* of those who suffer from it. These methods also make it possible for researcher and healthcare providers to pinpoint pivoting moments in the patient's illness trajectory (e.g. trigger of emotional and behavioural cascades). This approach is congruent with personalized medicine, where treatments are tailored to the individual in question. Benefiting from the individualized treatment was the finding that group CBT provides better care when compared to individual CBT. This finding is particularly relevant for at least two reasons: (1) *tailored* treatment does not necessarily mean *individual* treatment, and as such, group treatment may be part of a tailored treatment path; and (2) healthcare resources may be optimized in order to provide the best care under the least cost.

Within the field of tinnitus, fundamental research is mainly conducted with animal samples. Animal models provide insight into the possible workings within a physical model, it cannot account for the disability and distress that tinnitus has on human beings. Perhaps more difficult to directly translate into direct patient outcome is the development of experimental research into the role of fear in tinnitus. While investigation in treatment outcomes are of paramount importance, the understanding of the underlying cognitive and behavioural mechanisms of change provide the pillars upon which such treatments stand. The understanding of the development of chronic from acute tinnitus, as well as tinnitus distress and disability all hinge in the advance of theoretical models. The contribution on this front may be the most substantial yet. While not without its limitations, our research may improve tinnitus research in human participants.

Those who suffer from tinnitus directly benefit from the research presented. All studies conducted may directly influence the treatment approaches to tinnitus patients. Beyond tinnitus, the findings of this body of work may be adapted and inspire similar fields. The growing incidence of chronic conditions may yet benefit from models adapted from parallel fields (as tinnitus has from chronic pain research). A culmination of a body of work from different fields may create a broader framework that could potentially help better understand similar disorders under a similar context. Currently and perhaps more importantly, the financial burden of such conditions (as tinnitus) to the healthcare system and the personal burden on the patients and their families may be reduced through the development of research and more efficacious treatments.

With that in mind, all the findings are (or will be) available to the public. Initiatives by the funding agencies and the author are taken to spread the knowledge produced. It is our hope to inspire future tinnitus research and push for newer ways of research which puts the individual in the center of care.

CHAPTER 8

Acknowledgments

> *No man is an Iland, intire of itselfe; every man is a peece of the Continent, a part of the maine; if a Clod bee washed away by the Sea, Europe is the lesse, as well as if a Promontorie were, as well as if a Manor of thy friends or of thine owne were; any mans death diminishes me, because I am involved in Mankinde; And therefore never send to know for whom the bell tolls; It tolls for thee.*
>
> —John Donne, Meditation XVII

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