Sound-Based Tinnitus Management Approaches

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Part 1: Sound Therapy Options

The first part of my presentation today follows primarily from a 2014 review of practical options for sound therapy for tinnitus management authored by Derek Hoare, Grant Searchfield, Amr El Refaie, and Jim Henry, which appeared in the Journal of American Academy of Audiology 25: 62-75.

Part 2: NIH-Sponsored Phase III Tinnitus Retraining Therapy Trial (TRTT)

The second part of my presentation will review the TRTT, a multi-site randomized controlled trial of Tinnitus Retraining Therapy (TRT) in which we evaluated TRT efficacy in relation to a rigorous standard of care protocol, and parsed the contributions of the sound therapy and counseling components of the treatment.

Part 1: Review of Sound Therapy Options

Sound Therapy (ST)

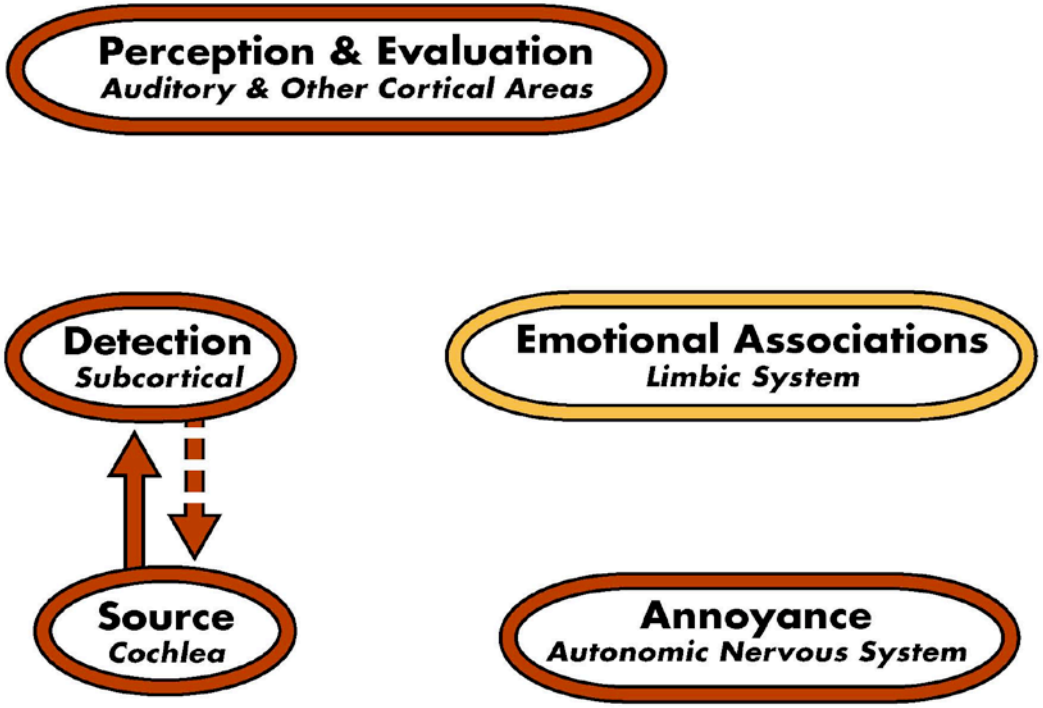
As defined by Hoare et al (2014):

"ST represents any use of sound where the intention is to alter the tinnitus *perception* and/or the *reactions* to tinnitus in a clinically meaningful way."

Mechanisms of Tinnitus Amendable to ST

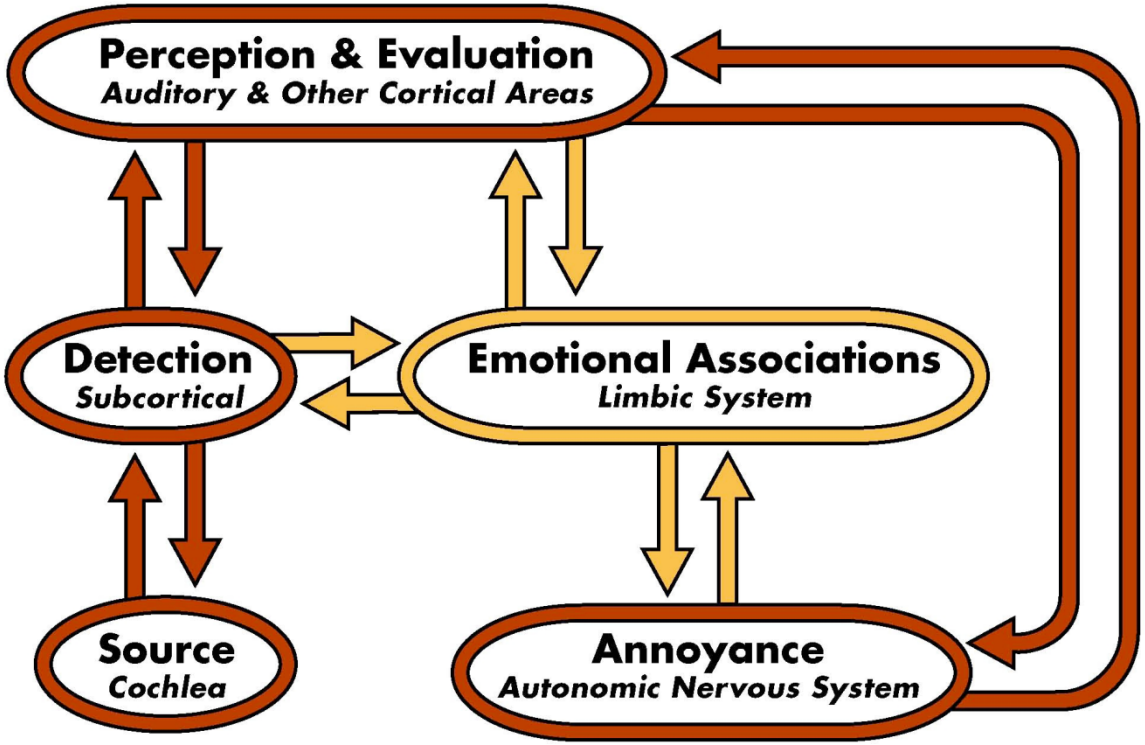
- In theory, peripheral auditory damage, often associated with measurable hearing loss, initiates plastic changes in the central auditory pathways that give rise to cortical / tonotopic reorganization
- This plasticity, in turn, may manifest in the form of increased neuronal hyperactivity, neural synchrony, and/or central auditory gain
- It is this enhanced neural activity that is believed to account for tinnitus *perception* (awareness), but not for tinnitus *reactions* or annoyance (i.e., untoward emotional, psychological, and physiological responses to the tinnitus)

Tinnitus Without Awareness & Annoyance: Subcortical Filtering



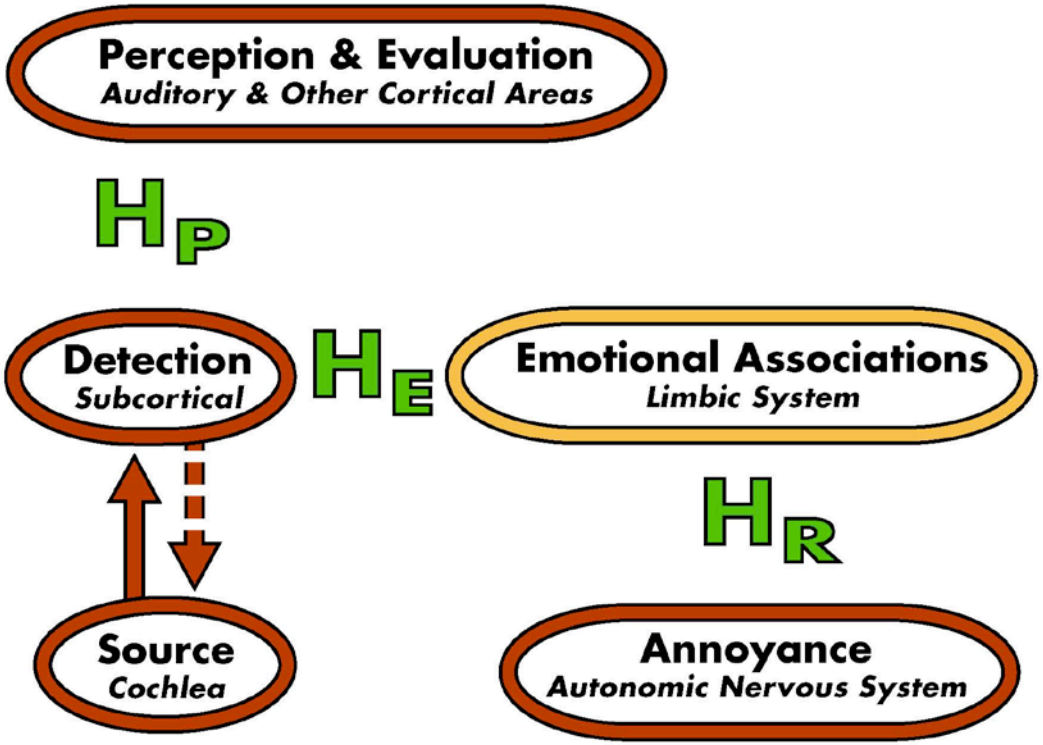
TRTT (after Jastreboff, 1995)

Conscious & Subconscious Neuronal Circuits Activated by Distressing Tinnitus



TRTT (after Jastreboff, 1995)

Habituation of Reactions, Emotional Associations & Perception to Tinnitus



TRTT (after Jastreboff, 1995)

Sound Therapy Reduces Tinnitus Perception

- Most, if not all, forms of ST used in treatment of tinnitus focus on reducing the *perception* or awareness of tinnitus
- Counseling, which is often combined with ST, is the primary tool for reducing negative *reactions* to tinnitus, leading to reclassification of the tinnitus signal as a neutral stimulus

Sound Therapy May Facilitate a Reduction in Reactions to Tinnitus

- To the extent that ST may reduce the patient's awareness of tinnitus and his/her attention to it, associated activation of those central processes that give rise to untoward emotional, psychological, and physiological responses to the tinnitus should be reduced
- ST offered in the form of a relaxing musical stimulus may also contribute to a reduction in the stress response and, in turn, to a reduction in other associated negative responses to the tinnitus (e.g., anxiety, distress, depression, insomnia)

Proposed ST Actions on Tinnitus

ST may exert its benefits through:

- Total or partial masking to cover or reduce tinnitus audibility, which may contribute to a sense of relief
- Habituation of tinnitus *reactions* and *perception*
- Reversal of abnormal cortical reorganization that gives rise to increased neuronal hyperactivity, synchrony, and/or central auditory gain contributing to tinnitus *perception*
- Promotion of relaxation to reduce stress to tinnitus

Enriched Environmental Sound in Masking of Tinnitus

- Alexander of Tralles (ca. 525-605 AD) noted that tinnitus sufferers obtain relief when taking a walk in “sondry places”
- Pseudo-Aristotle from the School of Salerno (ca. 13th century) questioned “Why is it that the buzzing in the ears ceases if one makes a sound? Is it because a greater sound drives out the less?”
- The French physician J.M.G. Itard in 1821 described judicious selection of appropriately matched bedroom noises to relieve tinnitus of different pitch and sound qualities, thus leading to improved sleep. This was the first practical description of a comprehensive approach to tinnitus masking

Modern Day Tinnitus Masking

- In 1976, Vernon proposed total masking of tinnitus with white noise to make tinnitus inaudible with a more acceptable sound
- In 1981, Vernon advocated for partial masking or suppression of tinnitus, touting its utility for relief among tinnitus patients using ear-level maskers and/or hearing aids in combination with maskers

Modern Day Tinnitus Masking (continued)

- Subsequent Cochrane reviews (Hobson et al, 2010, 2012) of three RCTs of tinnitus masking, conducted between 1984-2006, concluded these masking studies failed to show strong evidence of efficacy of ST (masking) in tinnitus management
- However, Hobson et al noted a lack of quality research, confounded by combined approaches of ST with counseling, limited their conclusions

Tinnitus Retraining Therapy (TRT)

- Hobson et al (2010/2012) also considered TRT in their inconclusive review of six RCTs using ST
- TRT, which was introduced in the 1990s by Jastreboff and Hazell, used ST in a way that represented a significant departure from the traditional masking approach of Vernon
- TRT combined Hazell's low-level broadband noise ST, set below the mixing point of the ST noise with tinnitus, with counseling principles based on Jastreboff's neurophysiological model to promote tinnitus habituation

ST Used in TRT

- In theory, ST used in TRT can be achieved with enriched environmental sound, aided environmental sound, ear-level sound generators, and/or a combination hearing aid with a sound generator
- In each case, ST is intended to facilitate counseling, which initiates habituation of tinnitus *reactions*, while facilitating habituation of tinnitus *perception* by decreasing the strength of the tinnitus

ST Mechanisms in TRT

Specifically, the mechanisms of ST per Jastreboff and Hazell (2004) are to:

1) reduce the contrast between the tinnitus and the neuronal background activity, which, in turn, reduces the strength and awareness of the tinnitus; and
2) reset central auditory gain contributing to tinnitus *perception*, thereby also decreasing the strength of the tinnitus while facilitating the habituation process.

TRT Controversy

- Subsequent to the ST reviews reported by Hobson et al, the outcomes of three new TRT clinical trials have yielded mixed results for TRT efficacy: one positive (Bauer & Brozoski, 2011); another indicating total masking yields the same TRT outcome as that achieved when setting ST at or below the mixing point (Tyler et al, 2012); and a third trial indicating a modified CBT approach is superior to TRT (Westin et al, 2011)
- An independent Cochrane review of the TRT literature (Phillips & McFerran, 2011) also questioned the efficacy of TRT based on analysis of a single qualifying RCT (Henry et al, 2006) with quality concerns

Neuromonics

- Also considered in the Hobson et al Cochrane review of ST were trials of Neuromonics
- Neuromonics is a staged 6-month desensitization protocol for tinnitus management using modified music, compensated for hearing loss, initially delivered in stage 1 for about 2 hours daily in combination with broadband masking noise and then presented in stage 2 at a lower level with the noise removed

Neuromonics (continued)

- Neuromonics, a commercial protocol that includes counseling, has been shown in several studies to yield improved tinnitus questionnaire scores over time, albeit the rigor and quality of these studies has been questioned
- The physiological mechanisms underlying Neuromonics are unknown, but ostensibly involve relaxation and stress reduction

Aided ST

- The most widely advocated tinnitus management approach for persons with tinnitus and hearing loss is the use of hearing aids for ST
- Despite widespread recognition that hearing aids may be beneficial for managing tinnitus for many hearing-impaired persons, numerous open trials and cohort studies have yielded inconclusive evidence of efficacy
- In question is whether ST affects a change in *reactions* to tinnitus versus an improvement in aided hearing function and associated reduced listening effort

Aided ST (continued)

- Amplified environmental sound, however, does reduce the contrast between tinnitus and the aided background, thus, contributing to a reduction in tinnitus *perception*
- ST from hearing aids also may decrease neuroplastic changes within the central auditory system, which may contribute further to reduced tinnitus *perception*

Aided ST Conclusions

Despite the low quality of aided ST research, the general consensus from a recent Cochrane review (Hoare et al, 2014) and an independent analysis of treatment options for tinnitus (Tunkel et al, 2014) is that:

> appropriately fitted hearing aids* are a safe and harmless option for ST for persons with hearing loss, yielding a tinnitus treatment effect similar to ear-level sound generators (Parazzini et al, 2011).

*Excellent coverage of this topic has been provided by Searchfield (2006), who recommends fitting strategies for tinnitus and hearing loss that contrast with those in fitting hearing aids for hearing loss alone.

Combination Devices for ST

- Combination hearing aid plus sound generator/noise masker devices have been available commercially since the 1980s
- A recently reported RCT (Henry et al, 2016) revealed:

Tinnitus treatment efficacy, as measured by the TFI, was similar for combination hearing aids, receiver-in-the-canal hearing aids, and deep-fit extended-wear hearing aids, all yielding clinically significant improvements in reaction to tinnitus over a 4-5 month treatment period. There were no statistical differences among the three treatments.

Combination Devices for ST: Conclusion

Although the data are not definitive at this time, the addition of noise or other sounds to hearing aids may be beneficial for some hearing-impaired persons with tinnitus, with the primary effect likely being on tinnitus *perception*.

Other ST Options

An emerging class of sound therapies are aimed at desynchronizing pathological, highly synchronized, cortical neural activity associated with tinnitus:

1) Acoustic Coordinated Reset (CR) Neuromodulation
2) Serenade (S tones)
3) Dichonics

Other ST Options (continued)

- These emerging STs target reduction of tinnitus *perception* and may also contribute to reduction of the tinnitus-related stress response
- The most promising of these STs appears to be Acoustic CR neuromodulation, which has been shown to affect EEG activity thought to contribute to tinnitus *perception*

Other ST Options (continued)

Notched Music:

- A modified music listening protocol with a one-octave notch set around the tinnitus pitch frequency
- The goals of this ST are to achieve lateral inhibition and reverse maladaptive synchronous activity contributing to the tinnitus
- Reduced MEG responses, believed to be associated with the tinnitus generation, provide some support for notched music ST

Miscellaneous ST Options

- Noise Cancellation (Phase Out/Phase Shift)
- Extended Residual Inhibition (Tipa)
- Table top ST devices, sound pillow, web-based apps via personal listening devices

None of these ST options has quality evidence of efficacy at this time.

Conclusions in the Use of ST

- Per Tunkel et al (2014): Clinicians may recommend ST to patients with persistent, bothersome tinnitus
- ST should be considered an option based on RCTs with methodological concerns, with a balance between benefit and harm

Recommendations

- ST should be part of an individualized, multidisciplinary approach to management of tinnitus, usually including counseling (i.e., “one size may not fit all”)
- ST for tinnitus should be considered along with management of co-morbid conditions that may exacerbate the tinnitus problem (e.g., hearing loss, hyperacusis, depression, etc.)
- The patient’s motivation and willingness to use ST is an important consideration to assess (e.g., Cleveland Clinic Sound Therapy Option Profile)

Research Needed

- Studies are needed to identify types of STs appropriate for subgroups of tinnitus sufferers
- Studies are needed to establish specific benefits and modes of action for STs with appropriate behavioral and physiological measures
- RCTs are needed to establish definitive efficacy for promising STs, with and without counseling, and the respective contributions to Tx success

Part 2: Tinnitus Retraining Therapy Trial (TRTT)

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The TRTT was designed as a definitive randomized, placebo-controlled, multi-center trial with the aim of testing the efficacy of TRT versus standard of care treatment in individuals with self-perceived debilitating tinnitus who qualified for treatment in US military medical centers.

The TRTT

- Hallmarks of the TRTT include:
  - First Phase III Clinical Trial of TRT Efficacy
  - Independent and Impartial Study Chair & DCC Offices
  - Multi-Center (6 military treatment centers)
  - Multiple Treatment Groups (3)
  - Randomized Treatment Assignment
  - Placebo-Controlled Treatment (sound therapy)
  - Fixed Sample Size (n=151, ~50/group)
  - Blinding
  - Baseline Data Collection with Follow-Up Data Collection at 3, 6, 12, and 18 months.

TRTT Resource Centers

- Study Chair's Office; University of Alabama,
  - *Craig Formby, PhD, Study Chair*
- Data Coordinating Center, Johns Hopkins Bloomberg School of Public Health,
  - *Roberta W. Scherer, PhD, Director*
- National Institute on Deafness & Other Communication Disorders
  - *Steven Hirschfeld, MD, Project Officer*
  - *Gordon Hughes, MD, Project Officer (in memoriam)*

NIDCD

TRTT Clinical Sites

- Wilford Hall Ambulatory Surgical Center (TX)
- David Grant Medical Center (CA)

- Walter Reed National Military Medical Center Bethesda (MD)

- Naval Medical Center Portsmouth (VA)
- Naval Medical Center San Diego (CA)
- Naval Medical Center Camp Pendleton (CA)

Key Eligibility Criteria

Non- medical

- Active and retired military personnel and dependents
- Age 18 or older
- Able to understand counseling and complete English-language questionnaires
- Willing and able to participate in a research study

Medical

- Continuous, chronic, subjective tinnitus of $\geq$ 1 year
- Tinnitus Questionnaire (TQ) score $\geq$ 40 (moderate impact of tinnitus)
- Unaided hearing sensitivity bilaterally within the audiometric range from normal to mild limits

TRTT Study Hypotheses

- TRT is an efficacious therapeutic intervention for severe disabling tinnitus, resulting in habituation of the sensation, awareness, annoyance, and impact of tinnitus
- Both directive counseling (DC) and sound therapy (ST) are essential for treatment efficacy

TRTT Treatment Groups

TRT

Directive Counseling

Sound Generator

Partial TRT

Directive Counseling

Placebo Sound Generator

Standard of Care

Standard of Care

Environmental sound

Primary Treatment Comparisons

TRT

Directive Counseling | Sound Generator | versus | Standard of Care

Sound Therapy

Directive Counseling | Sound Generator | versus | Directive Counseling | Placebo Sound Generator

Directive Counseling

Directive Counseling | Placebo Sound Generator | versus | Standard of Care

TRTT Directive Counseling Protocol

- Didactic educational approach to Tx of the tinnitus problem
- Review results of the ATH evaluation
- Describe anatomy and physiology of auditory system
- Describe how the brain handles auditory input
- Describe how the anatomy, physiology and brain function relate to tinnitus
- Present Jastreboff Neurophysiological Model of Tinnitus
- Encourage use of environmental sound, the assigned ST, and avoidance of silence
- Describe habituation goals of treatment

TRTT Sound Therapy

Sound generators provided by General Hearing Instruments

- Conventional Sound Therapy
  - Initially began trial with BTE instruments and later converted participants to in-the-ear non-occluding devices
  - Generates low-level broadband (seashell-like) noise
  - Volume set at/ just below “mixing point”
  - Unique data-logging features to monitor protocol compliance and sound environment
- Placebo Sound Therapy
  - Similar to above, but…
  - Noise begins to fade after ~40 minutes
  - Noise undetectable after additional 30 minutes
  - Resets upon removal from ear
  - Operation enables double-blind ST

Development and Implementation of the TRTT Standard of Care Control Protocol

- Survey of military audiologists' for tinnitus practice patterns (2003, 2009)
- Establish practice quality: followed ASHA Preferred Practices for tinnitus Tx
- Embed content in patient-centered care scripted format
- Training/Credentialing: Review/approval of recorded practice sessions conducted by study clinicians
- Check list to monitor protocol coverage by clinicians
- Follow-up with protocol monitor for quality control of recorded counseling sessions

TRTT Standard of Care Protocol

- Patient-centered Tx approach based on the patient's needs
- Goal is to facilitate patient’s motivation, progress, and engagement in managing the tinnitus problem
- Elicit patient narrative, summarizing key points
- Discuss hearing mechanism and ATH evaluation
- Describe strategies to deal with problems related to:
  - Sleep
  - Stress
  - Concentration
- Encourage use of environmental sound at all times
- Set goals based on assessment of patient's needs

Directive Counseling vs Standard of Care

Directive counseling	Standard of Care
Based on Jastreboff's neuro-physiological model	Based on existing military practices and ASHA guidelines
Theory-driven	Patient-driven
Didactic	Interactive
Directive	Facilitative
Top-down	Horizontal

Adherence Measures Used During Counseling

- **Directive counseling**

Script and handouts

3-D ear model

Flip chart

Voice recorder

- **Standard of care**

Script and handouts

3-D ear model

Voice recorder

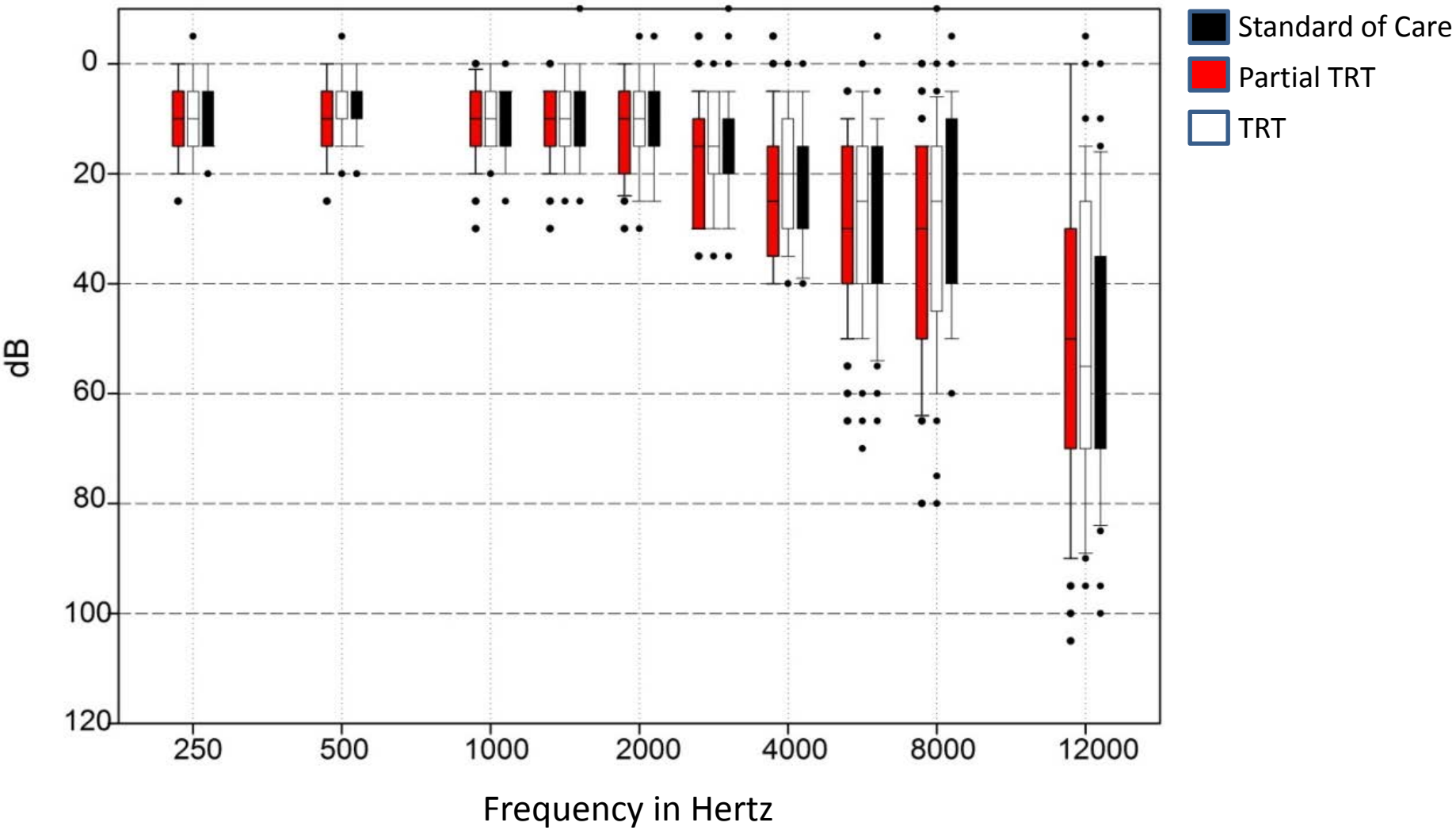
TRTT Outcomes

- **Primary Outcome**
  - Change in the Tinnitus Questionnaire (TQ) score evaluated longitudinally between the baseline visit and the 18-month follow-up visit
- **Secondary Outcomes**
  - Change evaluated longitudinally in:
    - TQ subscales
    - Tinnitus Functional Index (TFI) and subscales
    - Tinnitus Handicap Inventory (THI) and subscales
    - Visual analog scales of TRT Interview
    - Digit Symbol Substitution Task
    - EuroQoL
    - Audiometric measures

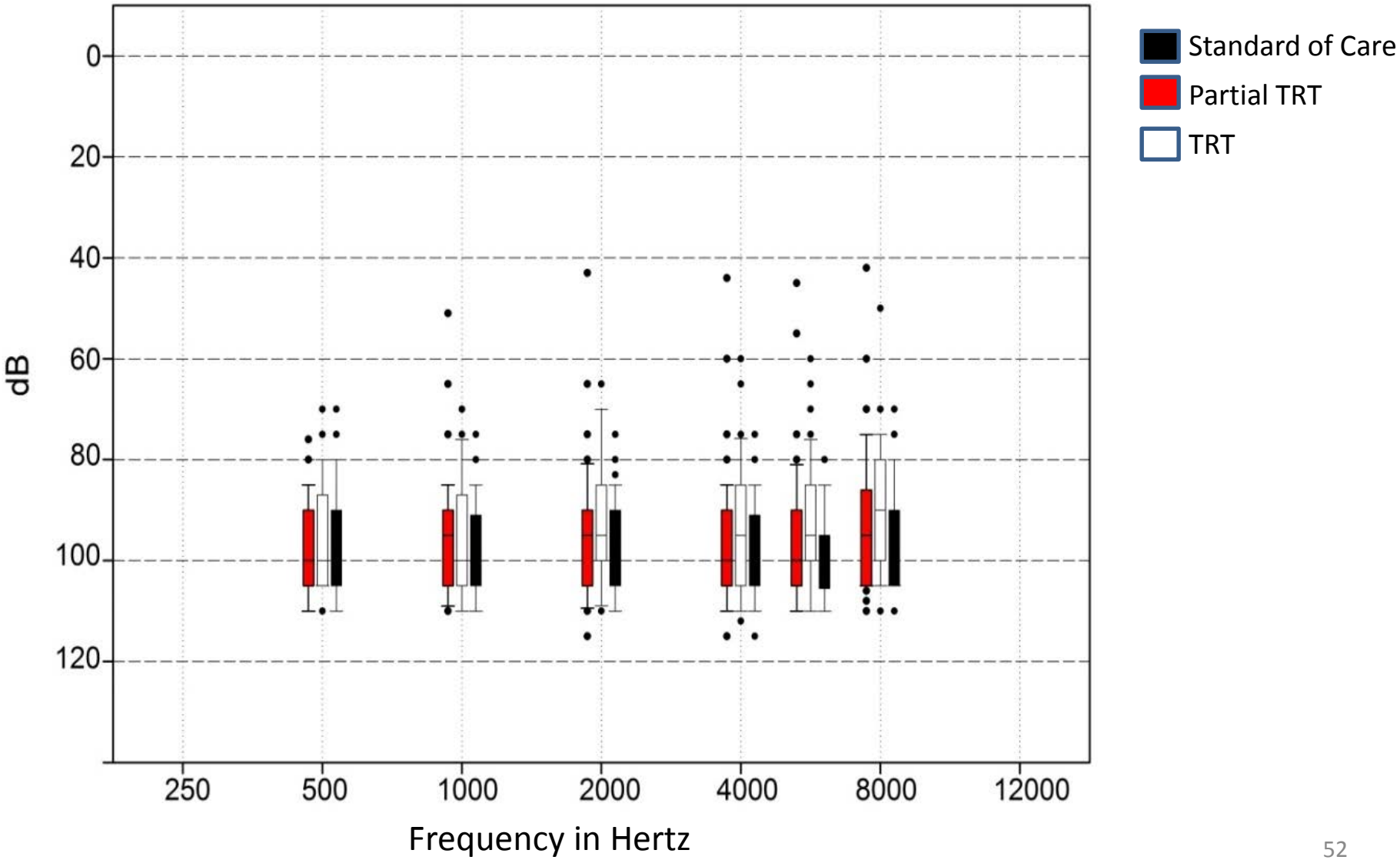
TRTT Study Visits

- Baseline Eligibility Visit
- Randomization visit
- 2 treatment visits
  - Within one month of randomization
  - One month after first treatment visit
- Follow-up visits (3, 6, 12, and 18 months after first treatment visit)

Baseline Audiograms



Loudness Discomfort Levels



Demographic Characteristics

Characteristic	Standard of Care	Partial TRT	TRT
N	49	51	51
Age, mean (S.D.)	49.9 (10.0)	50.9 (11.2)	51.1 (12.6)
Male sex,%	73.5	72.6	66.7
Race/ethnicity,%			
White	71.4	76.5	70.6
Black/African-American	14.3	11.8	9.8
Other	4.1	7.8	5.9
Hispanic/Latino	10.2	9.8	13.7
Marital status,%			
Married/with partner	83.7	80.4	76.5
Without partner	16.3	19.6	21.6

Baseline Tinnitus Characteristics

Characteristic	Standard of care	Partial TRT	TRT
N	49	51	51
Tinnitus duration	%	%	%
Tinnitus a problem < 2 years	12.2	21.6	23.6
Tinnitus a problem 2 to 5 years	40.8	33.3	29.4
Tinnitus a problem > 5 years	44.9	43.1	47.1
Sudden onset	24.5	33.3	25.5
Gradual onset	65.3	54.9	58.8
Event associated with onset	53.1	43.1	45.1
Tonal	95.9	92.2	92.2
Low frequency noise	2.0	3.9	7.8
High frequency noise	0	2.0	0
Other (crickets, clicking, other)	0	2.0	0

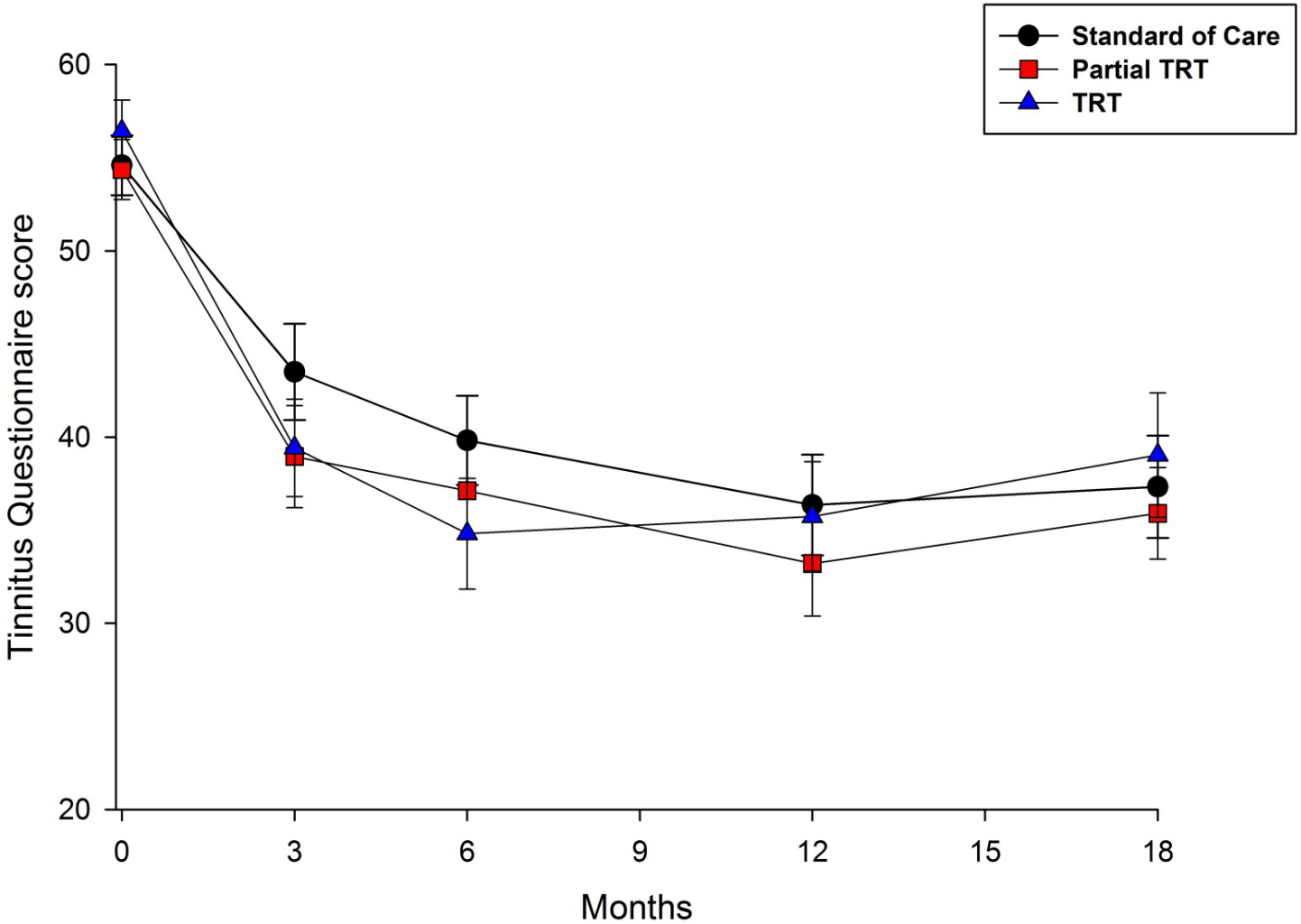
Baseline Tinnitus Properties

Characteristic	Standard of care	Partial TRT	TRT
N	49	51	51
Location	%	%	%
One ear	16.4	11.8	19.6
Both ears	32.7	45.1	45.1
In the head	22.5	23.5	11.8
In the head and one or both ears	28.5	19.6	23.6
Most 'troublesome' tinnitus:			
Left ear, n	30	27	24
Loudness match, dB, median (IQR)	38 (28 to 44)	40 (27 to 57)	46 (34 to 60)
Frequency match, KHz, median (IQR)	8 (4.9 to 11.8)	8 (6.0 to 9.25)	6 (3.6 to 8.0)

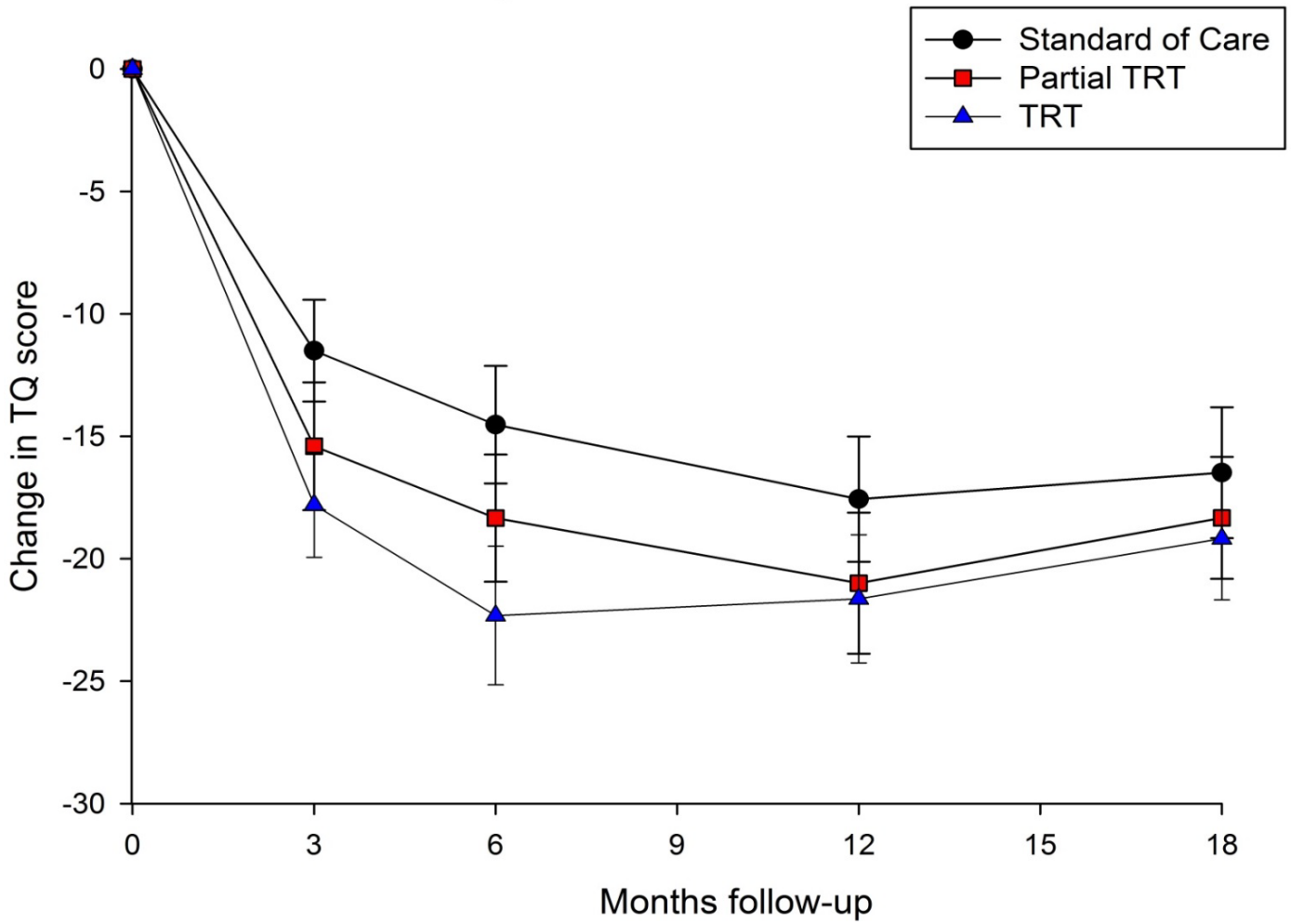
Baseline Tinnitus Distress

Instrument	Standard of care	Partial TRT	TRT
N	49	51	51
Tinnitus Questionnaire			
median (IQR)	53(46, 61)	51 (45, 62)	55 (46, 64)
mean (S.D.)	54.6 (11.2)	54.4 (11.5)	56.4 (11.9)
Tinnitus Functional Index			
median (IQR)	55 (45, 65)	50 (36, 63)	47 (34, 60)
mean (S.D.)	53.5 (17.3)	50.3 (17.1)	48.1 (17.6)
Tinnitus Handicap Inventory			
median (IQR)	36 (28, 48)	40 (28, 58)	38 (28, 44)
mean (S.D.)	38.6 (16.7)	42.3 (20.7)	37.8 (13.0)
VAS scale from TRT Interview			
median (IQR)	7 (5, 8)	7 (5, 8)	6 (5, 8)
mean (S.D.)	6.7 (1.9)	6.5 (1.8)	6.4 (1.8)

TQ scores by visit and treatment group



Change in TQ Scores by Visit and Treatment Group



Intention to Treat Analysis

- The intention to treat analysis assumes all participants enrolled in the study will have their data analyzed regardless of whether he/she completed the assigned study protocol and study visits
- At the 18-month study visit,* the number of participants with completed TQ forms by treatment group were as follows:
  - TRT group (n = 33/51)
  - Partial TRT group (n = 39/51)
  - Standard of Care group (n = 37/49)

* 6- and 12-month TQ completions were similar to those at 18 months

Change in TQ Scores from Baseline to 18 Months by Treatment Group for Intention to Treat Analysis

Treatment group	Change in TQ score	95% CI	P value
Standard of care	-16.5	-21.9 to -11.1	<0.0001
Partial TRT	-19.0	-24.0 to -13.9	<0.0001
TRT	-18.2	-23.5 to -12.9	<0.0001

Comparison of Overall Change in TQ Scores Across Treatment Groups for Intention to Treat Analysis*

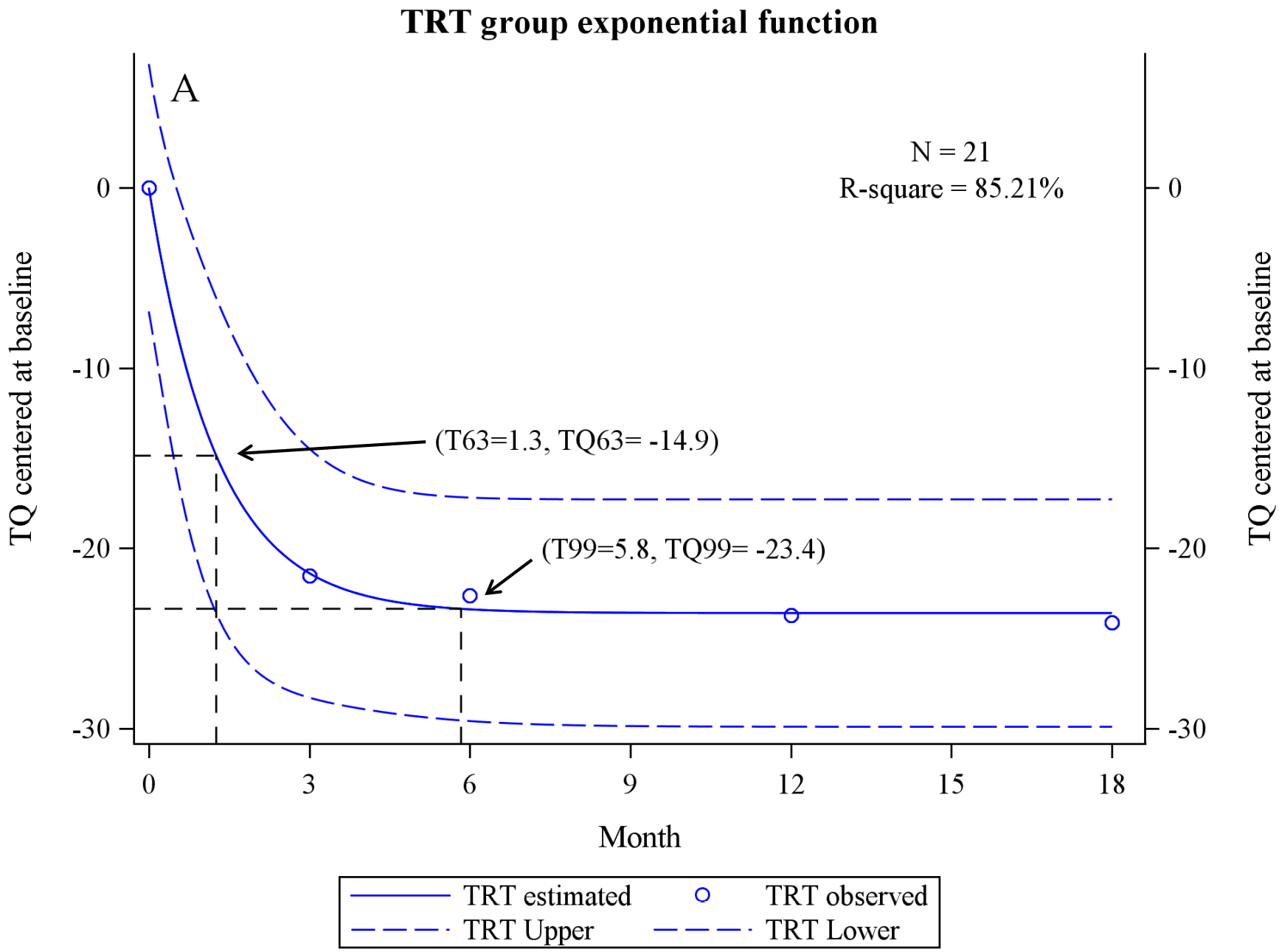
Standard of Care	Partial TRT	TRT
	Estimate (SE) (95% CI)	**Estimate (SE) (95% CI)**
reference	-3.72 (2.71) (-9.04 to 1.60)	-3.98 (2.66) (-9.20 to 1.23)

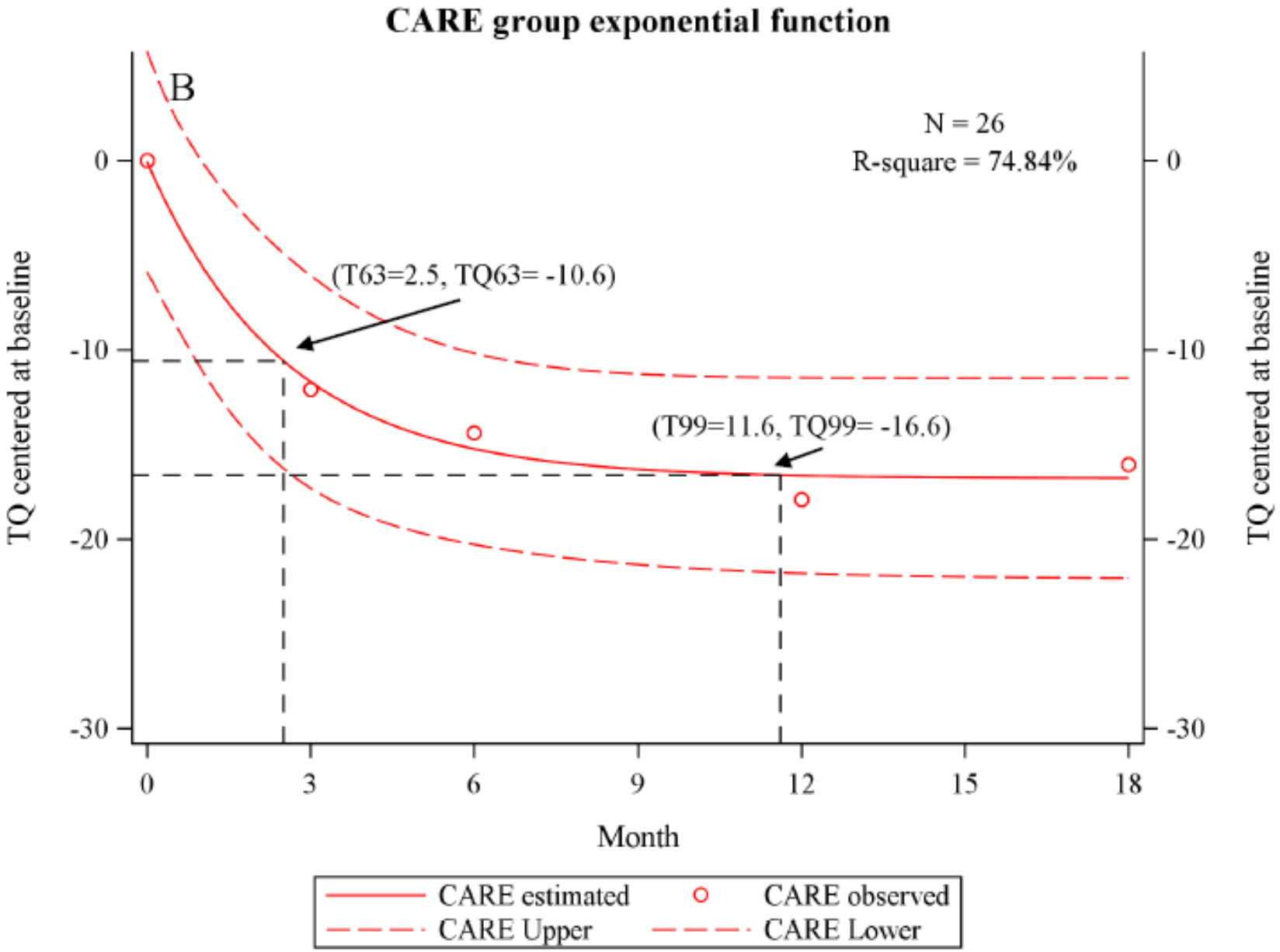
* Models were run using GEE, adjusted for age, baseline TQ as continuous variable, visit, clinical center and gender. Audiologist and type sound generator assigned not found to be significant predictors of change in TQ score.

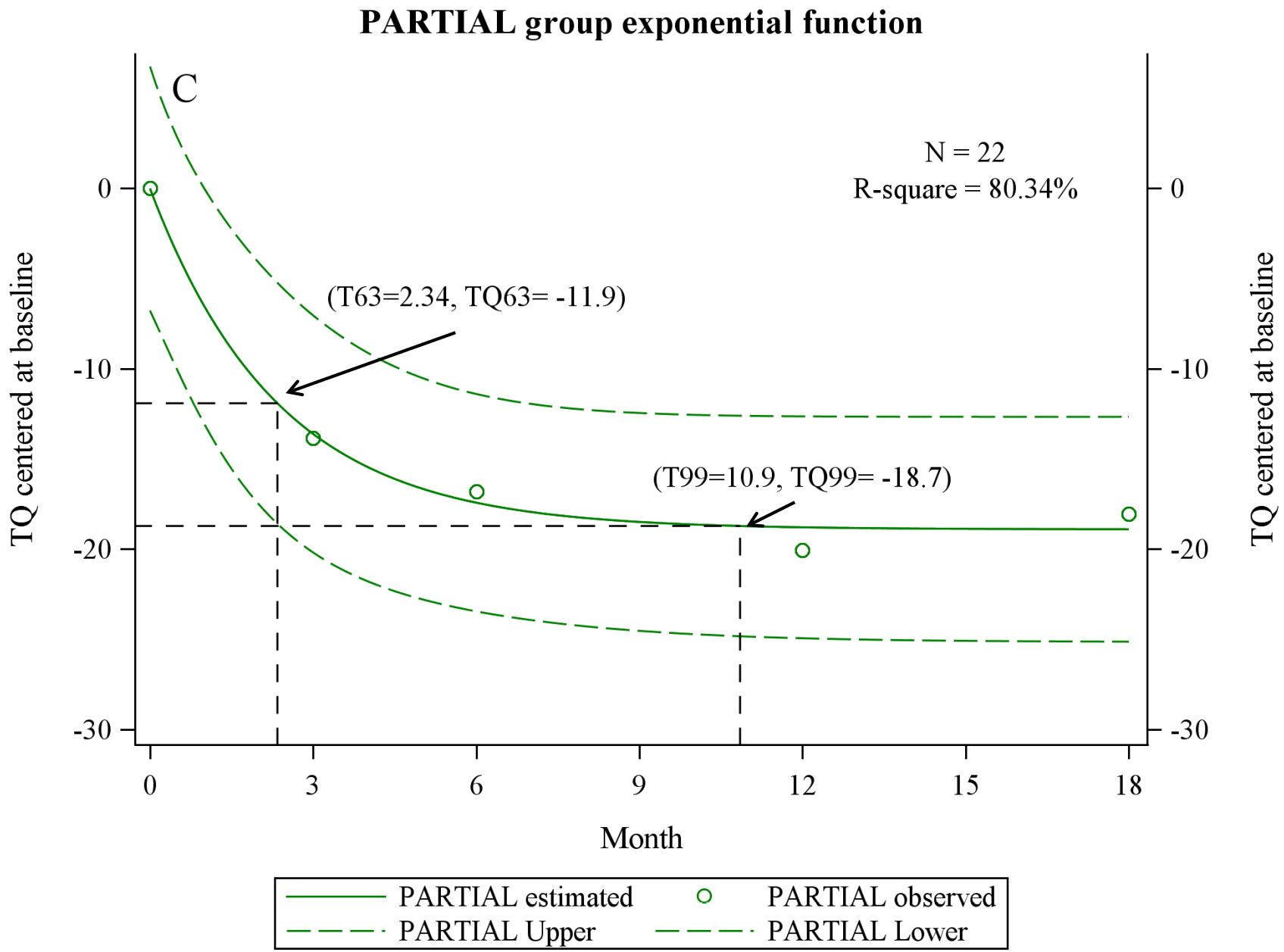
No statistical differences were found among the treatment groups.

Per Protocol Analysis

- Because of appreciable participant attrition and loss to follow up over the 18-month trial, we conducted a per protocol analysis, including comparison of exponential models of the Tx response dynamics for each group
- This analysis was based only on study data from participants who completed all study visits and for whom corresponding study data were available
- The number of participant TQ forms for those completing their assigned treatment by group was:
  - TRT group (n = 21)
  - Partial TRT group (n = 22)
  - Standard of Care group (n = 26)

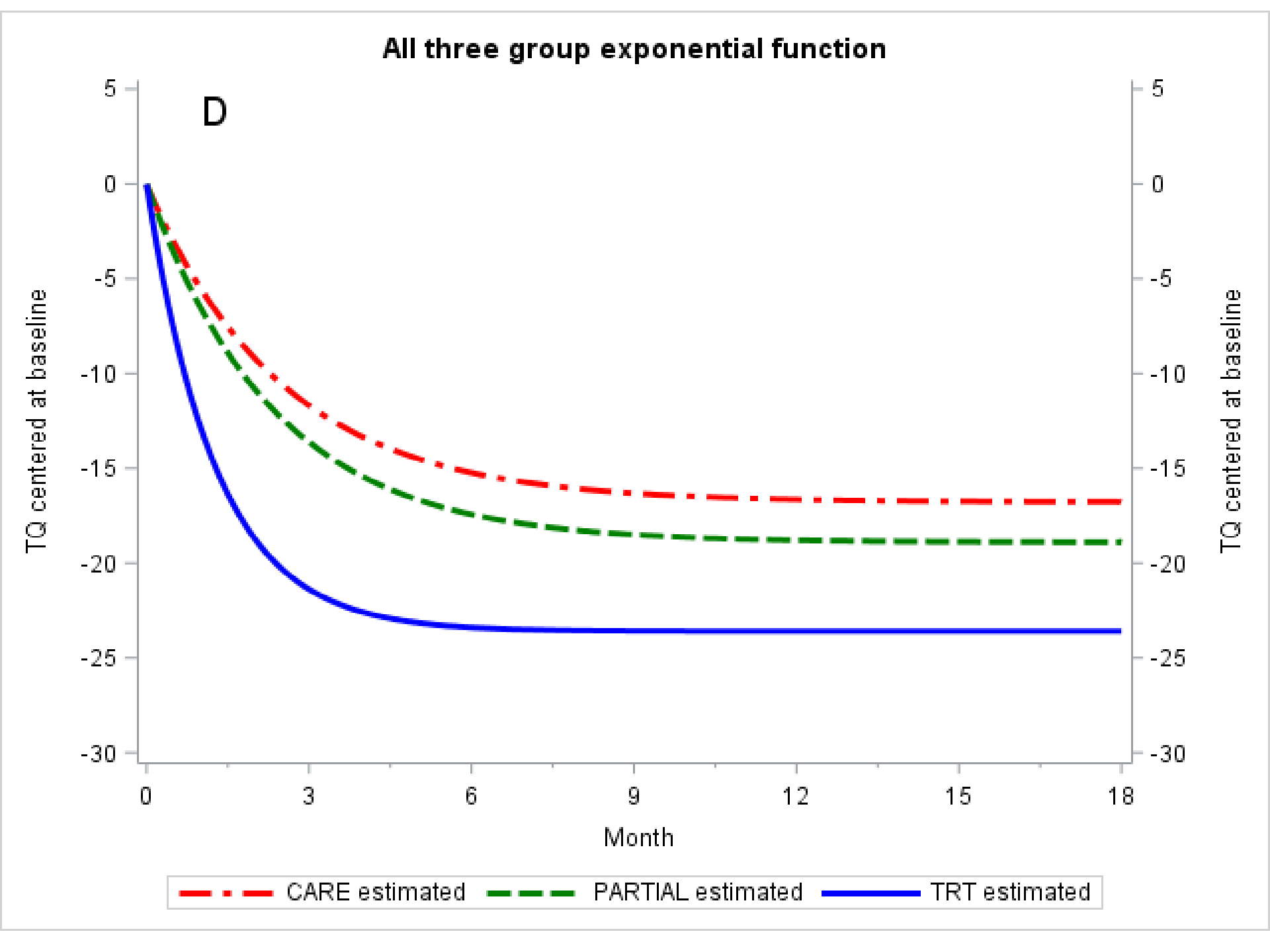

TRT group exponential function
A
N = 21
R-square = 85.21%
(T63=1.3, TQ63= -14.9)
(T99=5.8, TQ99= -23.4)
TQ centered at baseline
0
-10
-20
-30
0
3
6
9
12
15
18
Month
TRT estimated
TRT observed
TRT Upper
TRT Lower


CARE group exponential function
B
N = 26
R-square = 74.84%
(T63=2.5, TQ63= -10.6)
(T99=11.6, TQ99= -16.6)
TQ centered at baseline
0
-10
-20
-30
0
3
6
9
12
15
18
Month
CARE estimated
CARE observed
CARE Upper
CARE Lower


PARTIAL group exponential function
C
N = 22
R-square = 80.34%
(T63=2.34, TQ63= -11.9)
(T99=10.9, TQ99= -18.7)
TQ centered at baseline
0
-10
-20
-30
0
3
6
9
12
15
18
Month
PARTIAL estimated
PARTIAL observed
PARTIAL Upper
PARTIAL Lower

Time constants and corresponding TQ change values by treatment group estimated from the exponential models for the per protocol analysis

Treatment Group	n (# of participants)	T_{63} (months)	T_{99} (months)	TQ_{63} change	TQ_{99} change
TRT	21	1.30	5.80	-14.90	-23.40
Partial TRT	22	2.34	10.90	-11.90	-18.70
Standard of Care	26	2.50	11.60	-10.60	-16.60


All three group exponential function
D
5
0
-5
-10
-15
-20
-25
-30
TQ centered at baseline
0
3
6
9
12
15
18
Month
CARE estimated
PARTIAL estimated
TRT estimated

Statistical comparisons of differences in the exponential models between treatment groups for the per protocol analysis

Treatment Comparison	Numerator DF	Denominator DF	F Value	PR > F
TRT vs Standard of Care	3	46	3.52	**0.0223***
TRT vs Partial TRT	3	42	1.88	0.1474
Partial TRT vs Standard of Care	3	47	0.27	0.8496

*Statistically significant

TRTT Conclusions

- All three treatment groups – TRT, Partial TRT and Standard of Care – showed improvement as measured by a significant decrease in the TQ scores from baseline to 18 months
- There were no differences between treatment groups in the TQ results measured longitudinally for the intention to treat analysis, which included data for all enrollees
- The same patterns were verified across all measures of tinnitus distress:
  - Tinnitus Functional Index
  - Tinnitus Handicap Inventory
  - Visual analogue scale from the TRT Interview Form

TRTT Conclusions (continued)

- The per protocol analysis of TQ change scores (characterized by the exponential models) for participants completing all visits yielded a significantly greater decrease in TQ scores for TRT than for Standard of Care, with an asymptotic treatment result for TRT in about half the time of that for Standard of Care (i.e., T_{99} = 5.8 vs 11.6 months of treatment)

TRTT Conclusions (continued)

- The exponential models for the TQ change scores for TRT and Partial TRT were not significantly different, albeit the Partial TRT time constant for T_{99} was approximately twice that for TRT (T_{99} = 5.8 vs 10.9 months), suggesting the use of sound generators for ST expedited the habituation process for the TRT group

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