Variance in Measures of the Theta/Beta Ratio: Validating Target Ranges on an in-clinic Platform

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Abstract

Background: The Theta/Beta ratio (TBR) extracted from an EEG exam has been described as a novel source of information often seen to correlate with inattention. While this controversial metric has been leveraged for FDA clearance as an adjunct to ADHD diagnosis, and after 30 years of research, no clear agreement still exists regarding its utility. Published age-related trends are lacking or inconsistent while efficacy varies widely between studies. This may partly be due to the lack of standardized techniques where, for example, this measurement may be sensitive to device settings, filters, and differing definitions of the frequency bands. The goal of this study is to validate a standard technique that also incorporate other EEG protocols to extract TBR.

Objective 1: To compare different common methods for obtaining the TBR toward validating a standard.

Objective 2: To compare age-related eyes-open focused (and during an ERP) to eyes-closed resting values (and during P300) for the TBR.

Objective 3: To compare age-related changes of the TBR collected in-vivo with published trends toward validating a method for presenting age-stratified target ranges.

Objective 4: To investigate test-retest variation of the TBR for data collected in-clinic.

Participants: One thousand, nine hundred and twenty-eight subjects aged 13-90.

Methods: EEG with audio P300 was measured as part of a health screening exam for studies through Colorado University, Children's Hospital Colorado, Boone Heart Institute, WAVi Co., and various clinics alongside other clinical evaluations. Theta/Beta power ratios were extracted from these data.

Results: Different methods of extracting TBR produced different values but no difference was seen between EEG protocols. A standard method was evaluated that produced similar trends and values of previous age-matched studies and this was extended throughout the life span to create a validated standard. Finally, intra-person variation in TBR was sufficiently low to suggest TBR a stable trait adequate for longitudinal tracking.

Conclusion: When standard methods of extraction are used, TBR data collected in clinic compares to data collected in controlled research, where the data match age-related trends both in shape and value and test-retest variation. Further, we validate the use of extracting TBR during eyes-open Flanker and eyes-closed P300 ERP.

Keywords

Electroencephalogram (EEG), P300, Event Related Potential (ERP), Brainwave, Amplitude, Theta-Beta Ratio (TBR), Attention, ADHD, Cortical Arousal

Introduction

The theta/beta ratio at Cz (TBR) is an often-studied EEG parameter that compares slow to fast waves at the central midline of the cortex (Cz), with slow wave Theta activity generally around 4-8 Hz and the faster Beta activity around 13-21 Hz (the exact frequency ranges varies from study to study). The TBR has been described as a comparison of free-thinking versus focused states, with some studies hypothesizing it to represent an arousal mechanism while other hypothesize the ratio represents cognitive processing capacity.[1] The ratio has also been long studied as a trait that correlates with ADHD. While some studies show high sensitivities and specificities, high enough to warrant an FDA clearance as an adjunct to ADHD, other studies have failed to reproduce the result.[2][3][4][5][6] It is interesting to note that many of the studies that failed to reproduce positive findings also found different normal or control values for this ratio. In addition, the TBR drops drastically at the younger ages which may create a confusion as to weather a high recording at a younger age is really a condition or slow maturation.[7][8]

Even though the study of TBR in ADHD is the most noted, and controversial, other studies have suggested TBR as a useful marker of cognitive control over emotional information and anxiety–cognition interactions, among others.[9][10] These tests are generally performed in the eyes-open condition, but eyes-closed resting state measures are also performed. The latter may be confounded by extreme alpha power bleeding into the theta band on a minority of subjects who produce such alpha power in the eyes-closed condition.

The issues of diagnostic accuracy notwithstanding, TBR remains a fairly stable metric that can provide novel sources of information to compliment a clinical evaluation.[11][12] What is missing is an overall standard against which subjects can be measured on a large scale and against which different studies can be realistically compared. To that end, the first objective here is to investigate differences between various filter shapes and methods of calculating TBR in order to create a standard. The second objective is to compare eyes-closed versus eyes-open protocols. In particular, we want to validate a clinical method involving a low-cost system designed to maximize information and minimize testing times. This includes, therefore, concurrent testing of eyes-closed resting EEG protocols with eyes-closed EEG evoked response protocols and eyes-open focused EEG protocols with eyes-open EEG evoked response protocols.[13] The third objective

is to analyze data collected in clinic across the lifespan with this standard to create target ranges to be validated against select existing studies. The fourth objective is to understand the stability of the TBR by quantifying the test-retest intra-person variance in real-clinical settings.

Methods

Subjects

The subjects for this study were comprised of 1928 subjects from previous or ongoing studies and is not intended that they represent a normal control for a general population, rather it is intended to provide a target reference. One of the goals of this study is to compare in-vivo data with historical research to test the validity of large-scale screening. This study does have 3 control groups (13-16 years of age, 17-23, and 81-90) and these will anchor the resulting age-matched curves as discussed below. It may be the case that these controls perform differently from a found in a normal population, where 2 of these control groups were taken from elite club, High School, or NCAA athletic teams while those in the oldest age range were volunteers living independently, still interested in brain science, and still interested in their brain performance. Each group will be discussed individually, but because of the suspected other-than-normal performance, we will focus on age trends and refer to this reference group as a target reference, with end points as discussed, rather than a normal reference.

It is important to note that male/female differences may exist for the younger age groups but this is not the focus of this paper which is to compare trends to literature to establish a reference target.

All studies were approved by appropriate IRB's and written informed consent was obtained from the participants before study intake.

Ages 8-12

73 subjects aged 8-12 were taken from three previous studies: a study that followed athletes over the course of their sports seasons in Texas and Washington, control subjects measured as part a beta test to explore the outcome of an educational/wellbeing

intervention program in an economically-challenged school, [14] and wards accompanying WAVi study volunteers discussed below. Of these, 57 were accepted as per the artifacting criteria discussed below.

Ages 13-16

This control group comprises 94 subjects from a previous study following athletes aged 13-16 over the course of their sports seasons and at 4 different sites. These subjects are participants in youth soccer and youth basketball representing all players from single teams. To follow the objectives of this study (as well as the above-mentioned studies) which involves real clinical settings, our exclusion criteria are minimal. Therefore the only exclusions are players who had lower than 80% yield as per the artifacting criteria outlined above. [15] Of these subjects, 75 were deemed to have sufficient yield and 66 returned and completed a valid post-season second test which will be used to discuss test-retest variability.

Ages 17-23

This second control group is taken from a previous study that followed 364 athletes aged 17-23 over the course of up to 4 sports seasons and at 5 different sites. These subjects are participants in NCAA Div. 1 men's football (172 players, representing all players from a single team), woman's soccer (29 NCAA Div. 1, representing all players from a single team), men's high school football (142 players, representing all seniors from a single team), and semipro men's ice hockey (20 players, representing all players from a single team). [9]

In these previous studies, these subjects were controls against which pre-contact, post-concussion and return-to-play groups could be compared. To follow the objectives of this study (as well as the above-mentioned studies) which involves real clinical settings, and because the primary marker being studied is nonspecific, our exclusion criteria are minimal. The "control" group, therefore, is a reference group taken from all players participating on these teams and exclusions are limited to the players who fell asleep during the first-year test and passing the artifact criteria discussed below, leaving a total

of 313 players comprising the baseline reference group of Table I. Of these subjects, 70 returned injury free to completed a valid second test, which will be used to discuss test-retest variability.

Ages 24-30

138 assessment were included for individuals aged 24-30 who were measured in clinic at baseline, where some were to be tracked over the course of various interventions. Subjects include patients who visited the Boone Heart Institute Colorado for a combined preventative cardiology and EEG/ERP evaluation from June 2014 through June 2017. Only first-time patients receiving an initial evaluation were included in the sample, which was also used for a preventative cardiology study.[6] Because this is a target reference study, the exclusion criteria are minimal, the criteria being those who were taking beta-blockers or psychiatric medication and those who had lower than 80% yield on evoked responses due to artifact.

Also included were subjects from Natural Bio Health (NBH) Texas for a first-time preventative wellness exam, evaluated from 2017 through 2018; and a random sample of subjects measured for demonstration purposes at 5 medical conferences.

The remaining subjects were volunteers who were known to or associated with the study team and wanted to become pro-active in their brain health. In general these reference subjects were well educated and wanted to use WAVi to compare pre-intervention to post-interventions where interventions typically included some form of lifestyle change. To follow the objectives of this study, which involves real clinical settings our exclusion criteria are minimal and all volunteers in this age group were analyzed for the purposes of this study.

Ages 31-40

217 individuals aged 31-40 were tracked over the course of various interventions and the above-mentioned clinics, conferences, and volunteers.

Ages 41-50

325 individuals aged 31-40 were tracked over the course of various interventions and the above-mentioned clinics, conferences, and volunteers.

Ages 51-60

397 individuals aged 31-40 were tracked over the course of various interventions and the above-mentioned clinics, conferences, and volunteers.

Ages 61-70

249 individuals aged 31-40 were tracked over the course of various interventions and the above-mentioned clinics, conferences, and volunteers.

Ages 71-80

64 individuals aged 31-40 were tracked over the course of various interventions and the above-mentioned clinics, conferences, and volunteers.

Ages 81-90

Our third control group comprises 42 people taken as volunteers, discussed above. This group were living independently, had not been diagnosed with dementia, and were by definition a population who had experienced what could be called successful cognitive aging. They provide an end point against the 20-year old athletes for our target reference. Of these subjects, 26 were deemed to have sufficient yield to be included in the study.

Ages 24-85 Test-Retest Study Group

This group comprises 67 tests from 8 volunteers to study test-retest for various ERP and qEEG parameters during eyes-closed audio P300. This group is to be compared against the test-retest values extracted from the 13-16 and 17-23 age groups.

Ages 24-58 Default Network Study Group

This group comprises 134 total tests taken from 8 volunteer control subjects from the test-retest study above and from 22 subjects collected at a clinical site testing various

conditions such as mood, attention, and for baseline wellness. These tests are of the reliability of audio P300 protocol as a default network by comparing the qEEG metrics extracted during the standard eyes-closed qEEG protocol to those extracted during the eyes-closed audio P300 protocol, including the theta/beta ratio, left-right alpha asymmetry, and alpha mean frequency in both a control and a clinical setting. It is also a test of EEG during a Flanker task as an eyes-open focused protocol. [16] [17]

	Table I Profile of Assessments.	
Age (yrs)	***# Assessments included***	***Subject Profile***
8-12	57	Youth Sports and Educational studies: *initial assessment upon enrollment into study*.
13-16	75	Youth Sports study: *initial pre-contact assessment upon enrollment into study*.
17-23	313	High School and University Soccer, Hockey, and US Football study: i*nitial pre-contact assessment upon enrollment into study*.
24-30	138	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
31-40	217	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
41-50	325	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
51-60	397	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
61-70	249	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
71-80	64	Preventative Cardiology and Healthy Aging studies: i*nitial pre-intervention assessment upon enrollment into study*.
81-90	26	Healthy Aging study: *initial assessment upon enrollment into study*.
24-85	67 (test-retest)	Eyes-closed Resting and Audio P300 study: *67 test-retest assessments on 8 subjects testing audio P300 as an eyes-closed qEEG test.*

EEG acquisition and preprocessing

The WAVi Brain Assessment (WAVi Co., Boulder, CO USA) was used to record an electroencephalogram (EEG) at 250 Hz with the position of the electrodes following the International 10-20 system. Reference electrodes were clipped onto the earlobes.

EEG eyes-closed resting parameters were recorded on each patient during a 4-min audio P300 and, for some subjects, during a 4-min eyes-closed protocol. EEG eyes-open parameters were

recorded on each patient during a 4-min visual Flanker and, for some subjects, during a 4-min eyes-open focused protocol.

EEG extraction and analysis

The WAVi Brain assessment platform includes extracting qEEG from the eyes-closed and eyes-open EEG protocols using standard Fourier methods. All trials include automatic artifact rejection that exclude any errors from averaging, where noise from EEG data with higher than acceptable amplitudes and excessive band frequency activities in the standard EEG bands (Delta, Theta, Alpha, and Beta) were excluded on an individual channel basis. Files were also manually artifacted to confirm proper noise extraction. Only tests with greater ((than an 80% yield were included in these calculations what extra do we do for t/b?)) Eye blinks can have an effect on the result and so the WAVi platform has automatic blink suppression ((Joffe)) with warnings if the yield from suppression becomes too low in order to preserve the goal of minimizing testing times and maximizing information.

For the theta and beta bands, we use 4-7.5 Hz and 13-20.5 Hz respectively. The choice of frequency bands varies from study to study and this obviously impacts the calculation. Differing filters and methods of calculating the ratio can also have an impact on the value. These three issues may account for some of the differing between-study results, both in the reported values and in the diagnostic accuracy.

Methods for Calculating the Theta/Beta Ratio

The ratio can be calculated by a "sum of squares" method or a "square of the sums" method. While these different methods can have an effect on the result, the choice of method is seldom presented in literature. The first method, "sum of squares," involves computing total theta and beta power for each 3-second epic, then summing the powers before taking the ratio. This is the method used in the Lexicor Neurosearch software and other software that formed the basis for early studies of ADHD. ((Lubar and lexicor ref?)) The other method, presumably as common is the "square of sums" method and involves computing the theta/beta ratio at each epic and then taking the average.

Filter Choices

EEG extraction and/or analysis requires the use of filters which can either be in the hardware or software. While the filter selection in various TBR studies is seldom mentioned in the literature, it can affect the outcome and may also explain differing results. The WAVi platform uses software filters and here we explore 2 choices: a Finite Impulse Response filter (FIR) based on the Neurosearch software with enhanced beta to match its frequency response curve, and an Infinite Impulse Response filter (IIR).

Statistics

Comparisons were analyzed using unpaired two-tailed t-tests. We hypothesize that there should be a difference between TBR and various filters and blink suppression methods, and that eyes-open TBR should be different than eyes-closed TBR because of alpha contamination.

Results

Comparisons of Methods

Table II shows the difference in TBR calculations using the 2 different filters for 2 different age groups. Here there is a significant difference in TBR value, where the IIR filter method produces values approximately 20% higher.

Table III shows the difference between the "square of sums" versus "sum of square" methods and a sample patient. While the patient is not a representative sample, this table does show how the methods can produce differing results. It also shows how the "square of sums" method can be more sensitive to blinks, leading to false positives if care is not made to manage this artifact.

Table II Effects of two different EEG filters on the TBR calculation.

Age	*TBR(SD) IIR Filter*	*TBR((SD) FIR Filter*	*Difference Pvalue (CohenD)*
13-16yrs	2.6(1.1)	2.2(0.9)	0.016 (0.40)
17-23yrs	2.4(1.1)	1.9(0.9)	<0.001 (0.50)

Table III Differences between Square of Sums vs Sum of Squares methods for the TBR calculation on a sample patient. Note that the Square of Sums is more sensitive to eye blinks.

Protocol	*TBR (Square of Sums)*	*TBR (Sum of Squares)*
Eyes Closed (Blink Suppression)	1.7	1.3
Eyes Open	1.7	1.6

(Blink Suppression)		
Eyes Open (No Blink Suppression)	4.6	2.3

Comparison of Eyes Open vs Eyes Closed Protocols

Table IV Comparison of eyes open versus eyed closed TBR on a sample clinical data set comprising mood or ADHD evaluations (10-45 years).

Group	**N**	***TBR* Eyes Open (SD)**	***TBR* Eyes Closed (SD)**
All	26	2.9(1.9)	2.9(1.9)
Tested for ADHD	14	3.4(2.2)	3.4(2.5)
Unknown	12	2.3(1.3)	2.3(1.4)

In order to maximize information and minimize testing time, it's informative to know how TBR calculations vary between different eyes-open and eyes-closed protocols. Regarding eyes-closed resting versus eye-open focused, while we hypothesized that very high alpha producers would skew the ratio for eyes-closed patients, our clinical samples do not confirm this hypothesis. Table IV shows a sample clinical data set of 26 patients seeking mood or ADHD evaluations. There is no difference in TBR between eyes open versus closed, and no difference in the patients specifically seeking an evaluation for ADHD.

Regarding comparisons between eyes-open, P300, and during Flanker, we compared TBR extracted during a 4-min eyes-closed Audio P300 and those during a 4-min eyes-open Flanker task to those values extracted during standard eyes-open focused resting (Table V). To minimize subject bias, the same number of eyes-open and P300 tests and or Flanker were analyzed for each of the 30 subjects (22 subjects measured in clinic and 8 volunteer controls). From 116 matched tests, no difference was seen between the protocols. Because we assume no difference in between these protocols, and to be consistent with the goal of validating a platform that maximizes information and minimizes testing times, the age-related TBR trends of this study are extracted from this audio P300 protocol.

Table V Difference between TBR extracted during ERP protocols and standard eyes-open focused protocols.

TBR(SD) Eyes-Open	***n***	***TBR(SD) Flanker***	***n***	***Difference Pvalue (CohenD)***
2.2(1.3)	49	2.2(1.1)	49	0.79 (0.05)
TBR(SD) Eyes-Open	***n***	***TBR(SD) P300***	***n***	***Difference Pvalue (CohenD)***

2.0(1.1)	67	1.9(0.8)	67	0.34 (0.16)

Age-Stratified Targets

Table VI shows the TBR results for data collected from the eyes-closed audio P300 protocol of the WAVi platform for the age various groups, processed using IIR filtering and "sum of squares" methods. While we hypothesized that there would be a difference between blink suppression versus non, our eyes-closed clinical data do not confirm this hypothesis on a group basis. There was no significant difference between blink suppression versus no suppression for any age group (P>0.20), with the resulting data loss as shown. Because there may still be an affect on an individual basis, and because this particular WAVi platform is intended to maximize information and minimize testing times, good practice still warrants the use of blink suppression but it can safely be excluded in cases where the data loss is too great as long as the user is informed.

Fig 1 shows the complete TBR curve across the lifespan for this WAVi in clinic data analyzed with IRR filtering, "sum of squares," and blink suppression. The data can be best fit with a power curve as shown and agree with previous studies using similar analysis methods—studies that notably showed positive correlation with ADHD.

A final note regarding standard deviations. It cannot be assumed that between-person variance follows a Gaussian curve where 16% of the population is guaranteed to fall above one sigma (standard deviation). Here higher TBR may be a result of random physiology and genetics, which presumably follow more Gaussian distributions, *as well as* conditions affecting health which may not. It is important to know where a subject or patient falls relative to peers, however, so a useful method for presenting normal ranges here is to enforce standard deviations such that they highlight clinically useful information: ensuring the highest 16% of the population in TBR are outside the standard deviation used in the reference. To this end, a SD of +-40% captures a useful and actionable target range.

Table VI. Eyes-closed TBR values extracted during eyes-closed P300 across the age span, with and without blink suppression. The differences were not significant for any age (pval >0.2)

Age	*θ/β (SD) Blinks Included*	*θ/β (SD) Blinks Excluded*	*% Loss in Data (by excluding blinks)*
8-12yrs	3.8(1.8)	3.4(1.8)	23%
13-16yrs	2.2(0.9)	2.2(0.9)	6%
17-23yrs	1.9(0.9)	1.9(0.8)	2%

24-30yrs	1.8(0.9)	1.7(0.8)	5%
31-40yrs	1.6 (0.9)	1.5(0.9)	5%
41-50yrs	1.5(1.3)	1.4(1.0)	7%
51-60yrs	1.3(1.0)	1.2(0.8)	5%
61-70yrs	1.1(0.9)	1.1(0.9)	7%
71-80yrs	1.2(0.9)	1.1(0.8)	6%
81-90yrs	1.3(0.7)	1.2(0.8)	13%

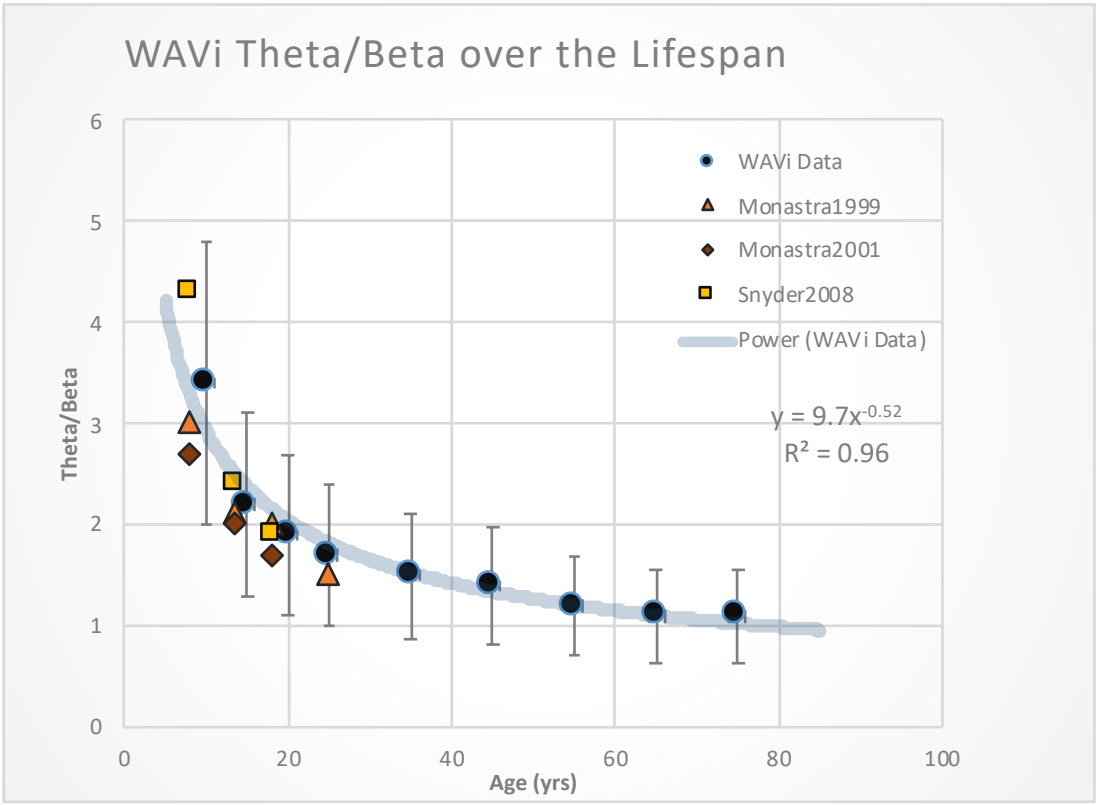

Figure 1. TBR, extracted from P300 protocols in routine clinical settings, across the lifespan.

Test-Retest Variance

For longitudinal tracking it's important to determine the within-person variance in routine clinical settings. As discussed above, while Gaussian distributions cannot be assumed for these variations, particularly with changing states, it is important to know the highest 16% to provide clinical context. This expected intrapersonal differences in TBR calculations from these data are shown in Table VII, where all ages above 13 years vary around the +-0.2 value, indicating a fairly stable trait as indicated in many previous studies. This study

did not include ages less than 13 for this test-retest study where it is presumed more variance due to maturation effects.

Also shown in Table VII are coefficients of variation (CV), calculated as 100*SD/Average for each person and then averaged over each group. This provides context to compare TBR to other methods of physiologic assay, say for example HDL (CV~24), cholesterol (CV~14), and tryglicerides (CV~42).[18] Table VII CV values are lower than many other clinical assays, suggesting clinical utility in tracking, noting that the younger ages have expectedly more variation. In this regard, we could consider TBR to be a combination of state and trait inasmuch as maturation can be considered state.

Table VII Expected longitudinal change of the eyes-closed TBR for a person, from the personal average, over a period of 2-6 months for 13-16 years and 1-2 years for those > 16 yrs.

Age	***TBR (SD)***	***Δ TBR***	***CV***
13-16yrs	2.2(0.9)	+-0.3	36.1
17-23yrs	1.9(0.9)	+-0.2	13.0
24-85yrs (test sample)	1.7(0.8)	+-0.2	16.7

Discussion

The choice of filters and the methods of calculating power can make a difference in the TBR results. If we create a standard, data collected in clinic can reproduce the same trends as research studies that helped first identify the ADHD correlates, both in value and as an age-matched curve. Furthermore, eyes-closed versus eyes-open protocols are surprisingly similar and within-person variance low.

If the TBR is to be considered a novel source of information to be added to a clinical examination, care must also be made as maturation effects can be mistaken for a high TBR trait (i.e. ADHD) for younger ages.

Conclusion

The Theta/Beta ratio has been studied for decades as a correlate of various conditions, including ADHD. Methods for obtaining this value, however, vary from study, where the frequency band selection is often differs and moreover the selection of filters and the method for calculating the

power (sum of squares versus square of sums) are seldom mentioned. This lack of standardization makes it difficult to reproduce results and obtain clinical utility. Other questions also remain regarding the protocol used (eyes-open versus eyes-closed), the TBR variance across the lifespan, the TBR test-retest stability within a person, and how well these results translate into real-life clinical settings.

Here, with data collected in clinic, we validate a method of extracting, calculating, and presenting the TBR where TBR extracted during eyes-closed and eyes-open ERP protocols agrees with other standard protocols which allows for concurrent measurements of both ERP and TBR to be obtained. When we match methods used by the original studies that found positive ADHD correlates as closely as possible, these in-vivo data match both the values and age-related shape of these studies. Finally, the within-person test-retest variance is low enough to be comparable to other methods of physical assay, meaning the TBR is a stable trait that can useful for longitudinal tracking.

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