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Martijn Arns^{1,2}, C. Keith Conners³, and Helena C. Kraemer^{4,5}

Abstract

Objective: Many EEG studies have reported that ADHD is characterized by elevated Theta/Beta ratio (TBR). In this study we conducted a meta-analysis on the TBR in ADHD. **Method:** TBR data during Eyes Open from location Cz were analyzed from children/adolescents 6-18 years of age with and without ADHD. **Results:** Nine studies were identified with a total of 1253 children/adolescents with and 517 without ADHD. The grand-mean effect size (ES) for the 6-13 year-olds was 0.75 and for the 6-18 year-olds was 0.62. However the test for heterogeneity remained significant; therefore these ESs are misleading and considered an overestimation. Post-hoc analysis found a decreasing difference in TBR across years, explained by an increasing TBR for the non-ADHD groups. **Conclusion:** Excessive TBR cannot be considered a reliable diagnostic measure of ADHD, however a substantial sub-group of ADHD patients do deviate on this measure and TBR has prognostic value in this sub-group, warranting its use as a prognostic measure rather than a diagnostic measure. (*J. of Att. Dis.* 2012; XX(X) 1-XX)

Keywords

ADHD, EEG, QEEG, theta, beta, Theta/Beta ratio, neurofeedback

Introduction

ADHD is one of the most common neurodevelopmental and psychiatric disorders of childhood with prevalence rates between 3% and 7% of school-age children (Cormier, 2008). In the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., *DSM-V*) field trial, ADHD was evaluated at two child clinic sites. The prevalence at those two sites were 68% and 58%, certainly among the highest prevalence among those coming into child psychiatric clinics. The reliabilities (kappa) were .707 and .455, which would be considered good (.455) to very good (.707). Currently, the disorder is primarily diagnosed by referring to the criteria of the *DSM-IV-TR* (4th ed., text. rev.; American Psychiatric Association [APA], 2000) or the International Statistical Classification of Mental Disorders (ICD-10). ADHD is not only the most common of the childhood psychiatric disorders but also the most researched disorder (Rowland, Lesesne, & Abramowitz, 2002). According to the *DSM-IV-TR* (*DSM-IV*; APA, 1994), the disorder presents itself in three primary subtypes: predominantly inattentive type (ADD), predominantly hyperactive-impulsive type, and the combined type (ADHD).

Many studies have investigated brain activity, especially using electro-encephalography (EEG), in children with ADHD compared with normal controls to shed more light on the underlying neurophysiology of ADHD and to

investigate subtypes of ADHD with differential responses to treatment. Ever since the first description of fronto-central slow EEG activity (“at frequencies of 5-6/sec”) in “behavioral problem children” in 1938 (Jasper, Solomon, & Bradley, 1938; p. 644), which in 1944 was termed *theta activity* (Walter & Dovey, 1944), the finding of increased absolute power in the theta EEG band in ADHD is the most consistently reported finding (Bresnahan, Anderson, & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001b; DeFrance, Smith, Schweitzer, Ginsberg, & Sands, 1996; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Lazzaro et al., 1999; Lazzaro et al., 1998; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Matsuura et al., 1993). Some studies have also reported decreased activity in the beta band (Callaway, Halliday, & Naylor, 1983; Mann et al., 1992; Matsuura et al.,

¹Research Institute Brainclinics, Nijmegen, Netherlands

²Utrecht University, Netherlands

³Duke University, Durham, NC, USA

⁴Stanford University, Palo Alto, CA, USA

⁵University of Pittsburgh, PA, USA

Corresponding Author:

Martijn Arns, Research Institute Brainclinics, 6524AD Nijmegen, Netherlands

Email: martijn@brainclinics.com

1993). However, this finding has not been replicated in other studies (Barry, Clarke, Johnstone, & Brown, 2009; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Lazzaro et al., 1999; Lazzaro et al., 1998) and was actually found to be increased in one study (Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996).

Based on the initial findings of increased theta and decreased beta, in 1991, Lubar suggested the Theta/Beta power ratio (TBR) as a measure for discriminating “normal” children from children with ADD, learning disorders, and ADHD (Lubar, 1991). Many studies have investigated this TBR measure further, with the clearest replication from Monastra and colleagues (1999). They reported in a multicenter study in 482 participants that using a single electrode location (Cz) and a 1.5 *SD* cut-off, a sensitivity of 86% and a specificity of 98% for classifying if someone would have ADHD or not, based on the TBR.

Note that most of these studies focused on the EEG as a diagnostic tool for ADHD. However, there is increasing interest in using the EEG for prognostic purposes to identify subgroups that respond to various treatments (as part of Personalized Medicine). These two uses obviously have conflicting implications, where the diagnostic use of EEG assumes homogeneity among patients with ADHD, whereas the prognostic approach assumes heterogeneity. For an overview of the prognostic value of EEG in predicting treatment outcome, see several other articles (Arns, 2011, 2012). This meta-analysis will focus on evaluating the proposed diagnostic value of EEG, more specifically the TBR for ADHD.

Two previous meta-analyses have investigated the diagnostic value of theta power and the TBR in ADHD compared with healthy controls. Boutros and colleagues (Boutros, Fraenkel, & Feingold, 2005) examined 1,109 patients with ADHD/ADD and 542 healthy controls, and concluded that increased theta power in ADHD is a sufficiently robust finding to warrant further development as a diagnostic test for ADHD, with data suggesting that relative theta power (theta power as a percentage of total power) is even a stronger predictor than absolute theta power. They reported a weighted mean effect size (ES; Hedges's *D*) for absolute theta power of 0.70 and for relative theta power of 1.07. In 2006, Snyder and Hall (2006) conducted a meta-analysis specifically investigating the TBR, theta, and beta, and concluded that an elevated TBR is “a commonly observed trait in ADHD relative to controls . . . By statistical extrapolation, the effect size of 3.08 predicts a sensitivity and specificity of 94%” (p. 453). However, there is a problem with this extrapolation from an ES to a sensitivity/specificity measure,¹ and hence these extrapolated values from Snyder and Hall (2006) should not be considered accurate.

Both meta-analyses were conducted around the same time. Therefore, it is surprising to note the reported differences in the ES for absolute theta (ES = 0.70) and relative theta (ES = 1.07) by Boutros et al. (2005) versus an ES of

1.31 (95% confidence interval [CI] = 1.14-1.48) from Snyder and Hall (2006), who combined relative and absolute theta. In line with this, the reported ES of 3.08 for the TBR (Snyder & Hall, 2006) seems rather high, knowing that the TBR in ADHD is on average about 5.5 implicating that the power of theta is 5.5 times larger than the power of beta. Note that the ES reported by Snyder and Hall is Glass's *D*, which is calculated using the *SD* of the control group only and does not use the pooled *SD* as is the case with Hedges's *D*, thereby perhaps explaining this difference. Furthermore, both meta-analyses calculated the ESs from *F* statistics and *p* values when no means and *SD*s were available, which is known to result in a less accurate ES. Neither study standardized for electrode location and recording condition (e.g., Eyes Open, Eyes Closed, Task, etc.), and many large-scale recent studies have also investigated this measure in ADHD with variable results.

Therefore, in this meta-analysis, we only included studies if the means and *SD*s could be obtained from electrode location Cz during Eyes Open condition. Furthermore, with this meta-analysis, we include more recent studies to ascertain how reliably different this TBR measure is between ADHD and appropriately chosen control groups.

Method

Study Selection

As two previous meta-analyses on this topic conducted a comprehensive literature search, in 2005 (Boutros et al., 2005) and 2006 (Snyder & Hall, 2006), we took references up to 2003 from these meta-analyses and included them if they met inclusion criteria. The literature was searched between 2003 and March 2012 using the query “EEG AND ADHD OR ADD” which yielded 486 hits (Scopus), and articles were then scanned for inclusion criteria.

Inclusion criteria were (a) diagnosis of ADHD or ADD according to the *DSM-IV* or *DSM-IV-TR*; (b) age range between 6 and 18 years; (c) availability of mean, *SD*, and sample size of the TBR at electrode site Cz during Eyes Open; (d) availability of a healthy control group; and (e) the study published in English.

In this study, we sought to standardize the TBR as much as possible and hence only incorporate the TBR recorded from Cz. All studies were checked for the recording condition, and only data for Eyes Open condition were included. If authors only reported on Eyes Closed condition or other locations, or if authors did not report means and *SD*s, authors were contacted to request the data specifically for Eyes Open condition and location Cz. By using this a priori definition and selection of EEG location and recording condition, we further attempted to reduce publication bias and Type I error. For example, some studies find a more significantly deviating TBR at Fz (Williams et al., 2010), whereas

Table 1. An Overview of All Included Studies in the Meta-Analysis

No	Study	Age range	TBR ADHD group				TBR control group			EEG details			
			<i>n</i>	<i>M</i>	<i>SD</i>	% ↑TBR	<i>n</i>	<i>M</i>	<i>SD</i>	Montage	Recording time	TBR frequency	Deartifacting
1	Monastra et al. (1999)	6-16	304	6.846	3.222	86%	64	2.565	0.794	LE	90 s	4-8/13-21	Manual
2	Monastra, Lubar, and Linden (2001)	6-16	79	5.877	2.415	90%	18	2.269	0.938	LE	90 s	4-8/13-21	Manual
3	Snyder et al. (2008)	6-18	97	6.300	3.300	87%	62	3.300	1.700	LE	10 min	4-7.5/13-20.5	Manual
4	González Castro et al. (2010)	6-12	164	0.472	0.117	NA	56	0.550	0.050	Earlobe	< 10 min	NA	Two channel (Cz and Fp1)
5	Sohn et al. (2010)	16-17	11	3.690	0.310	NA	12	3.480	0.380	LE	2 min	4-8/13-30	Manual
6	Williams et al. (2010)	6-18	169	6.539	4.028	38% ^a	167	5.704	2.717	LE	2 min	4-7.5/14.5-20	EOG: Gratton et al.
7	Nazari, Wallois, Aarabi, and Berquin (2011)	7-13	16	4.319	2.245	NA	16	3.624	1.373	R-Mastoid	3-4 min	4-8/12-24	Visual and computerized
8	Ogrim, Kropotov, and Hestad (2012)	7-16	61	6.136	3.490	26%	39	5.001	2.831	Common reference	NA	4-8/13-21	EOG: ICA
9	Loo et al. (2012)	6-18	352	9.761	5.850	NA	83	8.458	4.671	LE	5 min	4-8/13-21	Manual
Total			1,253				517						

Note: TBR = Theta/Beta ratio; EEG = electro-encephalography; LE = linked ears; EOG = electrooculography; ICA = independent component analysis. Note that González Castro et al. (2010) reported the Beta/Theta ratio instead of the Theta/Beta ratio.

^aExcess TBR percentage for the Williams et al. (2010) sample was obtained from Gordon (2012).

others have focused more on Cz (e.g., Monastra et al., 1999; Monastra, Lubar, & Linden, 2001). For studies reporting ADD versus ADHD separately, we recalculated the weighted mean and pooled *SD* to reflect the whole group to make data comparable (e.g., González Castro et al., 2010; Monastra et al., 2001; Monastra et al., 1999). Furthermore, data were collected separately for the age range 6 to 13 years and also for a broader range of 6 to 18 years.

Meta-Analysis Approach

In a meta-analysis, ESs (Cohen's *d* or standardized mean difference) are calculated based on the TBR from the ADHD group and control group means and *SD*s, and a 95% CI per study was calculated. This ES is a scale-free statistic, thus allowing comparison of scores from various studies. Based on multiple studies, a grand mean ES is calculated with a 95% CI, which provides the weighted ES for all studies, which can be considered the true ES for the whole population. ES for the different studies are plotted in a forest plot providing a graphical overview of all results. The ES is regarded as a measure of "clinical relevance" in that the higher an ES, the higher the clinical relevance of the measure.

ESs were calculated as Hedges's *D* using the pooled *SD* and the TBR difference using MetaWin 2.1. The grand mean ES, 95% CIs, *Qt* (heterogeneity of ESs), and fail-safe number (Rosenthal's method: $\alpha < .05$, and Orwin's method) were calculated using MetaWin Version 2.1. The fail-safe number is the number of studies, indicating how many unpublished null findings are needed to render an effect nonsignificant.

When the total heterogeneity of a sample (*Qt*) was significant—indicating that the variance among ESs is greater

than expected by sampling error—studies were omitted from the meta-analysis one by one, and the study contributing most to the significance of the *Qt* value was excluded from further analysis for that variable until the *Qt* value was no longer significant. This was done for a maximum of three iterations. If more than three studies needed to be excluded to obtain a nonsignificant *Qt* value, then other explanatory variables for the effects have to be assumed (Rosenberg, Adams, & Gurevitch, 2000) and were investigated in post hoc tests.

Results

A total of 32 relevant studies were identified between 1980 (release of *DSM-III*; APA, 1980) and 2003 (covered by Snyder & Hall, 2006, and Boutros et al., 2005) and an additional 38 relevant studies after 2003. Most studies were excluded due to the unavailability of Eyes Open data ($n = 17$), overlapping data sets ($n = 15$), or unavailability of midline sites, including Cz ($n = 8$). Nine studies met all inclusion criteria and were included in this meta-analysis; see Table 1 for an overview.

For most of the nine studies incorporated, the means and *SD*s could be separated into a younger group aged between 6 and 13 years (eight studies) and a group aged 6 to 18 years (six studies). These data will be reported and analyzed separately.

6 to 13 Years Group

For the 6 to 13 years group, there were eight studies that included participants in this age range, and there were a total of 835 ADHD children and 259 control children. A fixed-effects model meta-analysis yielded a significant

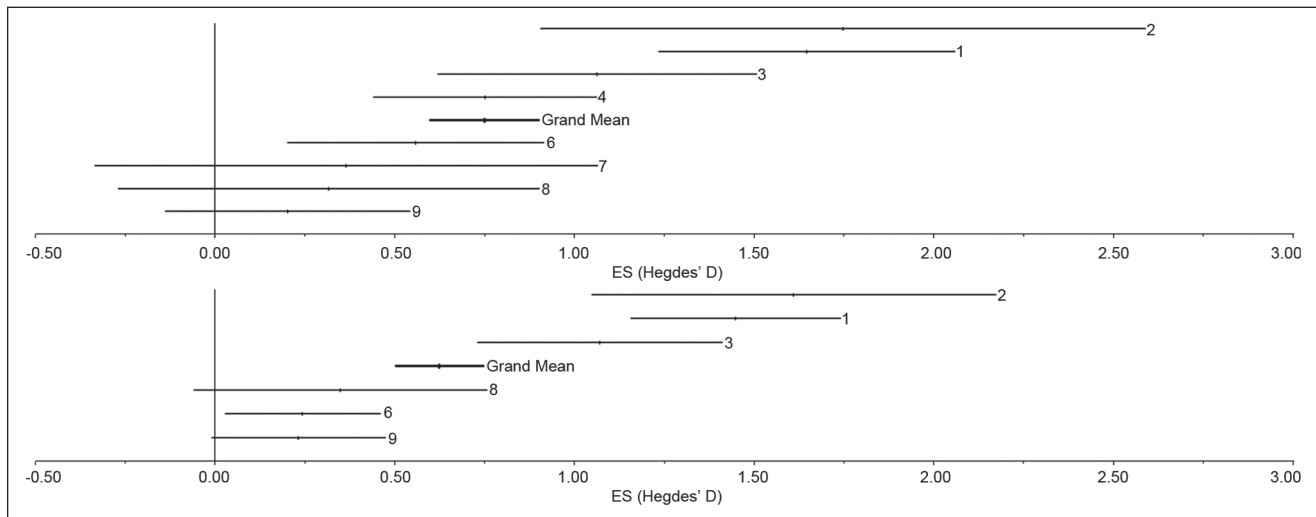


Figure 1. Forest plot of the ES and grand mean ES for the TBR for different studies

Note: ES = effect size; TBR = Theta/Beta ratio. Top forest plot is for the 6 to 13 years group, and the bottom forest plot is for the 6 to 18 years group. The lines represent the 95% confidence intervals. Note that numbers represent studies as per Table 1 and are also in chronological order.

heterogeneity test ($Q_t = 40.03, p < .00001$), a grand mean ES of 0.75 (CI = [0.568-0.930]), and a fail-safe number of 275 (Rosenthal's method) and 22 (Orwin's method). In subsequent post hoc analysis, we found the source of heterogeneity (outlined below); hence, this ES is considered the ES for the 6 to 13 years group.

Excluding different combinations of studies still resulted in a significant heterogeneity test. The most substantial improvement in Q_t was obtained after excluding Monastra et al. (1999; $Q_t = 18.93, p = .00428$). After excluding this study, the most substantial further improvement was obtained by excluding Monastra et al. (2001), $Q_t = 11.65, p = .0399$. Finally, when excluding Loo et al. (2012), heterogeneity was no longer significant ($Q_t = 5.80, p = .21468$). In this analysis, the ES was 0.68 (CI = [0.414-0.946]) with a fail-safe number of 74 (Rosenthal's method) and 12 (Orwin's method). The exclusion order above further supports the time effect described below, as first the two oldest studies (Monastra et al., 1999; Monastra et al., 2001) and then the most recent study (Loo et al., 2012) had to be excluded to obtain a nonsignificant heterogeneity test.

6 to 18 Years Group

For the 6 to 18 years group, there were six studies that included participants in this age range, and there were a total of 1,062 ADHD children and 433 control children. A fixed-effects model meta-analysis yielded a significant heterogeneity test ($Q_t = 73.57, p < .00001$), ES of 0.62 (CI = [0.465-0.782]), and a fail-safe number of 270 (Rosenthal's method) and 13 (Orwin's method). In subsequent post hoc

analysis, we found the source of heterogeneity (outlined below); hence, this ES is considered the ES for the 6 to 18 years group.

Excluding different combinations of studies still resulted in a significant heterogeneity test. The most substantial improvement in Q_t was obtained after excluding Monastra et al. (1999; $Q_t = 36.24, p < .00001$). After excluding this study, the most substantial further improvement was obtained by excluding Monastra et al. (2001; $Q_t = 18.96, p = .00028$). Finally, when excluding Snyder et al. (2008), a nonsignificant heterogeneity was obtained ($Q_t = 0.25, p = .8836$). Exclusion of these three studies resulted in a nonsignificant grand mean ES of 0.25 (CI = [-0.08-0.58]) and a fail-safe number of 9 (Rosenthal's method) and 0.8 (Orwin's method).

In addition, see the forest plot in Figure 1.

Post Hoc Tests

As different studies use slightly different frequency ranges for theta and beta (e.g., beta 13-21 Hz; Monastra et al., 1999; Monastra et al., 2001; or beta 12-24 Hz; Nazari, Wallois, Aarabi, & Berquin, 2011), we performed a post hoc test where the relationship between the ES and the width of the theta and beta band in hertz (in the above example, 8 Hz for Monastra et al., 1999, 2001, or 12 Hz for Nazari et al., 2011) was investigated, as well as the duration of the EEG recording and year of publication.

For the 6 to 13 years of age group, there was no significant correlation between the ES and the width of the theta ($r = .034, p = .942, df = 7$) and beta ($r = -.175, p = .708, df$

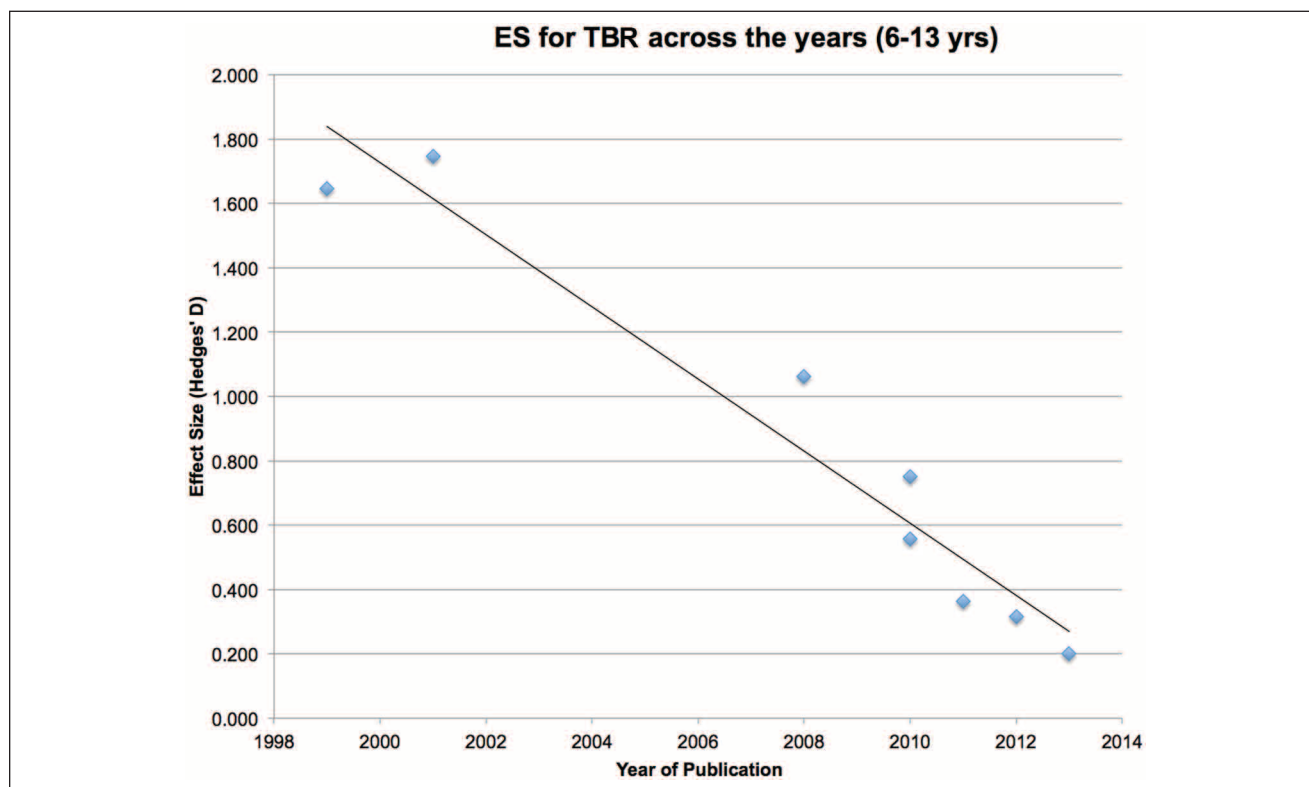


Figure 2. The ES for the TBR across years of publication and the linear trend for a decreased TBR across years
 Note: ES = effect size; TBR = Theta/Beta ratio.

= 7) frequency band or duration of the EEG recording ($r = -.267, p = .562, df = 7$), but a significant correlation for year of publication ($r = -.968, p < .001, df = 8$). This is seen in Figure 2. Even after excluding Monastra et al. (1999) and Monastra et al. (2001; the studies on the far left), this effect remained significant ($r = -.960, p = .002, df = 6$). Similar results were found for the 6 to 18 years group ($r = -.931, p = .007, df = 6$), which was no longer significant when excluding Monastra et al. (1999) and Monastra et al. (2001; $r = -.813, p = .187, df = 4$), which is most likely due to the low sample size of four studies.

Given the interesting finding of the relationship between year of publication and the ES of the TBR, we also plotted and calculated the TBR for ADHD and control groups across studies (in chronological order) for both groups, as can be seen in Figure 3. From this figure, it appears (especially for the 6 to 18 years group, which in general includes the larger sample sizes) that the decrease in TBR difference across years is not driven by a decrease in TBR for the ADHD group but by an increase in TBR for the control groups over time. For the 6 to 13 years group, there were no significant correlations between year of publication and TBR for the control and ADHD groups (all $p > .125, r_{\text{control}} = .589$, and $r_{\text{ADHD}} = .046$). However, for the 6 to 18 years

group, there was a significant correlation between year of publication and TBR for controls ($p = .037, r = .838, df = 6$) but not for the ADHD group ($p = .390, r = .434, df = 6$), further substantiating that the TBR for ADHD children did not change across time, but the TBR for the control groups has increased across the years. Although the 6- to 13-year-olds showed a tendency in the same direction, it was not significant: all $p > .125, r_{\text{control}} = .589$, and $r_{\text{ADHD}} = .046$. No consistent differences in inclusion and exclusion criteria between studies could be found that could explain these effects.

Discussion

This meta-analysis investigated the difference in TBR between patients with ADHD and a healthy control group without ADHD. The ESs obtained were 0.75 for the 6- to 13-year-olds and 0.62 for the 6- to 18-year-olds. However, both meta-analyses demonstrated a significant heterogeneity test suggesting that other explanatory variables for the effects have to be assumed (Rosenberg et al., 2000). Post hoc tests revealed a strong relationship to year of publication, visualized in Figures 2 and 3 providing one explanation for this heterogeneity in obtained ES. Therefore, the

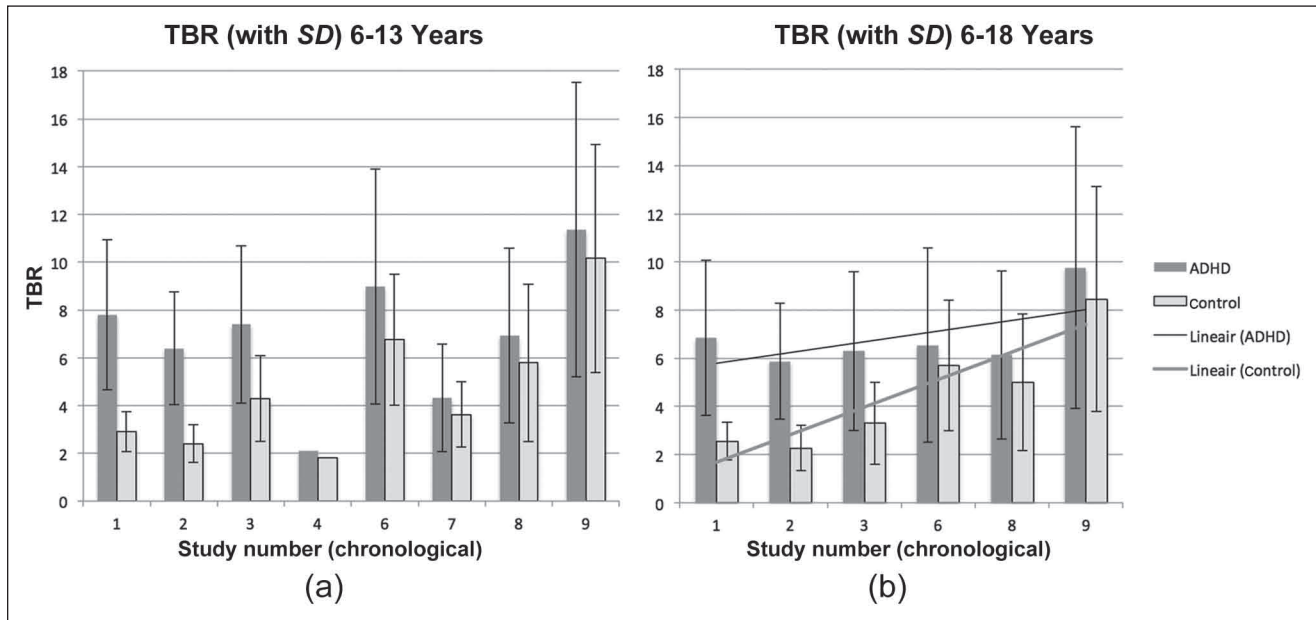


Figure 3. The change in TBR across studies (in chronological order) for ADHD and control groups for (a) the 6 to 13 years group and (b) the 6 to 18 years group with *SD* error bars

Note: TBR = Theta/Beta ratio. This figure shows the TBR effects across time are more related to an increase in TBR across years for the control groups and not a decrease across years for the ADHD groups. The trend lines in the left graph represent linear trends for both group means, and a significant correlation was found between the TBR for controls (6-18 years) and year of publication but not for ADHD. Note that the *SDs* for González Castro et al. (2010) are not available, as these were only available for the Beta/Theta ratio and not the Theta/Beta ratio.

above grand mean ES for the TBR may be misleading and considered an overestimation of the TBR.

How can we understand and explain this finding of a strong decline in ES for the TBR across years? This effect was mainly related to an *increase* in TBR for control groups and not related to a *decrease* in TBR for ADHD groups—as visualized in Figure 3. If anything, a small, but nonsignificant increase in TBR for ADHD was observed. Therefore, this finding is not likely to be explained by differences in ADHD symptom severity or differences in inclusion criteria for ADHD patients used in different studies. For example, the Monastra et al. (1999, 2001) studies used more stringent inclusion criteria, requiring an ADHD diagnosis based on *DSM-IV* criteria as well as a confirmation from performance on a continuous performance test (CPT). Further post hoc inspection of inclusion and exclusion criteria for the control groups did not provide a likely explanation to explain this. For example, the Monastra et al.'s (1999, 2001) studies also used a rigorous control for screening their control group. Not only was their control group required to be free of any other *DSM-IV* diagnosis but also free of any medical condition known to affect attention such as, for example, Vitamin D deficiency, anemia, skipped breakfast, or not enough sleep in the night prior to testing (Monastra, V. J., personal communication). This might explain that these studies contributed most to the

heterogeneity of ES as reported in the results and might partly explain the time effect. However, the time effect was still significant even after excluding the Monastra studies. However, the study by Snyder et al. (2008), which had the third highest ES, included participants all suspect of ADHD and subdivided that group into ADHD and non-ADHD. Hence, this non-ADHD control group was likely more heterogeneous than the control groups from Monastra, albeit the TBR from the non-ADHD group in this study was among the lowest. Future studies should further investigate and replicate the effects of factors such as Vitamin D deficiency, anemia, and skipped breakfast, among others, on TBR. Furthermore, other studies not included in this meta-analysis (due to for example missing *SD* or missing control group) tend to further support the above time effect. For example, the study by Bresnahan et al. from 1999 reported a TBR of 2.4 for controls and 3.7 for ADHD (6-11 years), and normative data from the Skil database yielded a TBR of 2.74 (6-11 years, $n = 30$) and were recorded in 2002 (Kaiser, personal communication), thereby providing further support for a TBR of non-ADHD populations of $TBR < 3.3$ pre-2008 (Bresnahan et al., 1999; Monastra et al., 1999; Monastra et al., 2001; Snyder et al., 2008; Kaiser, D. A., et al., personal communication). Further replication is also found in the studies by Clarke and colleagues (Clarke et al., 2011; Clarke et al., 2001b), who only investigated Eyes

Closed EEG and hence was not included in this meta-analysis. In 2011, they conducted a cluster analysis on EEG data from 155 patients with ADHD and 109 controls (Clarke et al., 2011), thereby replicating their study on 184 patients with ADHD and 40 controls from 2001 (Clarke et al., 2001b). In their 2001 study, they found two clusters with an increased TBR representing 80% of the population, whereas in their 2011 replication, the clusters with excess TBR only constituted 35%. Although the Clarke et al. studies did not report TBR from the control groups, at least their data confirm the decreased prevalence of excess TBR in ADHD from a single research group using identical methodology. Several possible explanations for this unexpected finding will be discussed below.

One potential explanation could be the difference in EEG equipment and EEG analysis software, and methods used, for example, the use of a DC amplifier versus an AC amplifier, use of a single-channel device versus the use of multichannel EEG equipment, use of filtering techniques, EEG windowing, filter details, EEG deartifacting method, and so on. Such a finding could potentially explain the increase of TBR for the normative controls but would not explain the decrease in ES between groups (as the same equipment and analysis was used in all studies for ADHD and non-ADHD groups). However, this seems an unlikely explanation given the linear decrease for TBR in non-ADHD groups across time and sufficient detail of these parameters was not provided in most articles. Further research could investigate this by reanalyzing the TBR from a single sample using various methods and EEG amplifiers.

Another conceivable explanation could be related to the observed trend that sleep duration of children across time is decreasing. A recent meta-analysis incorporating data from 35,936 healthy children reported that sleep duration is clearly positively associated with school performance and executive function, and negatively associated with internalizing and externalizing behavior problems (Astill, Van der Heijden, Van Ijzendoorn, & Van Someren, 2012). A well-known EEG signature for fatigue or drowsiness is increased theta (Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003; Tanaka, Hayashi, & Hori, 1996; Tanaka, Hayashi & Hori, 1997) suggesting this would result in increased TBR. For example, Iglowstein, Jenni, Molinari, and Largo (2003) investigated sleep duration in three large cohorts of healthy children in a longitudinal design. The cohorts started in 1974, 1979, and 1986, and they found a dependence of total sleep duration on "birth year," where sleep duration diminished with age across cohorts. This effect was caused by increasingly delayed evening bedtime in younger children across cohorts; for example, the bedtime for 3-year-olds was 19.08 hr (1974), 19.53 hr (1979), and 20.07 hr (1986) suggesting a trend that children are going to bed later. This was also confirmed by Dollman, Ridley, Olds, and Lowe

(2007) who found that 10- to 15-year-old children in a cohort from 2005 compared with a cohort from 1985 slept 30 min less with later bed times. The strongest evidence for this notion stems from a recent systematic review, which also performed a trend analysis in 690,747 children and found support for a clear trend of a decline in sleep duration across the last 100 years (Matricciani, Olds, & Petkov, 2012). It would be interesting to investigate whether there is an association between this finding and the increased TBR in non-ADHD control groups, and whether this might explain the increased prevalence of ADHD over the last decade as well as the increased incidence of obesity in ADHD (which is also consistently reported to be related to shorter sleep duration in children; for systematic review, also see Magee & Hale, 2012). For further reviews discussing the role of sleep in the etiology of ADHD, also see Miano, Parisi, and Villa, 2012 and Arns and Kenemans (Under Review). A final explanation could be what has been termed a *winner's curse*, with large ES found in a few early studies and increasingly smaller ES in later studies, which was also recently reported for the relationship between the brain-derived neurotrophic factor val66met allele and hippocampal volume (Molendijk et al., 2012).

The ES reported above are similar to what Boutros et al. (2005) reported for theta and relative theta power but much lower than the ES reported by Snyder and Hall (2006) of 3.08. Snyder and Hall used the Glass's *D* to calculate their ES and hence only relied on the *SD* from the control group (rather than a pooled *SD*). As those *SD*s were much smaller (see Table 1), such large ESs were obtained, explaining the discrepancy between their study and the current study. Earlier studies reported that using the TBR as a diagnostic measure using 1.5 *SD* as a cut-off resulted in a sensitivity and a specificity, respectively, of 86% and 98% (Monastra et al., 1999), 90% and 94% (Monastra et al., 2001), 95% and 100% (Quintana, Snyder, Purnell, Aponte, & Sita, 2007), and 87% and 94% (Snyder et al., 2008). However, more recent studies have only found that 38% (Williams et al., 2010, from Gordon, 2012) and 26% (Ogrim, Kropotov, & Hestad, 2012) of patients with ADHD significantly deviated from the control group based on the TBR, also in agreement with the 38% found by Arns and colleagues (Arns, Drinkenburg, & Kenemans, 2012) and the reduction found by Clarke et al., (2001b) from 80% (2001) to 35% (2011). Note that for the sensitivity and specificity values above, Monastra et al. (2001) used their normative data from their 1999 study, and Snyder et al. (2008) as well as Quintana et al. (2007) used a commercially available EEG database (Neuroguide, children normative data were collected between 1979 and 1987; Thatcher, personal communication). Given the clear time effect on the TBR of normative groups might hence explain the relative overestimation from Monastra et al. (2001), Snyder et al. (2008), and Quintana et al. (2007) studies by relying on norm data recorded years earlier, and not based on the control groups collected at the same time as ADHD groups.

Excess theta and elevated TBR have been found favorable predictors for treatment outcome to stimulant medication (Arns, Gunkelman, Breteler, & Spronk, 2008; Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002; Suffin & Emory, 1995) and neurofeedback (Arns et al., 2012; Monastra, Monastra, & George, 2002), thereby demonstrating the prognostic value of this measure (assuming a slow alpha peak frequency is ruled out; also see Arns et al., 2008; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011).

Concluding the grand mean ES obtained in this meta-analysis is rather misleading and is considered an overestimation. Thus, an increased TBR cannot be considered a reliable measure used for the diagnosis of ADHD at this time. However, based on recent studies, this excess theta and TBR is found in a substantial subgroup of patients with ADHD (25%-40%) and has been demonstrated to be of prognostic value in predicting treatment outcome to stimulant medication and neurofeedback, warranting its use as a prognostic measure rather than a diagnostic measure. Future research should further investigate how the elevated TBR for non-ADHD groups is explained and whether that is indeed explained by the reported decreased sleep duration, methodological factors, or other factors such as inclusion and exclusion criteria.

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Note

1. Under the assumptions underlying Cohen's d (two normal distributions with equal variances), one can always convert Cohen's d to area under the receiver operating curve (ROC), $AUROC = \Phi(d/\sqrt{2})$, where $\Phi()$ is the standard cumulative

normal distribution function. The ROC is a graph of the locus of all sensitivity versus 1-specificity pairs corresponding to all possible cut-points on the measure underlying Cohen's d . The range of sensitivities or specificities always ranges from 1.0 at an extreme cut point in one direction to 0 at the other. It is true that if it is stipulated that sensitivity and specificity are equal, that sensitivity/specificity must equal $\Phi(d/2)$, but the sensitivity and specificity are not usually equal. Moreover, if the two distributions are normal but with unequal variances, or one or the other distribution is nonnormal, even the above relationships do not necessarily hold even approximately. In short, there is no direct conversion from Cohen's d to sensitivity/specificity.

References

- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Arns, M. (2011). *Personalized medicine in ADHD and depression: A quest for EEG treatment predictors* (Unpublished doctoral dissertation). Utrecht University, Netherlands.
- Arns, M. (2012). EEG-based personalized medicine in ADHD: Individual alpha peak frequency as an endophenotype associated with nonresponse. *Journal of Neurotherapy*, *16*, 123-141.
- Arns, M., Drinkenburg, W. H. I. M., & Kenemans, J. L. (2012). The effects of QEEG-informed neurofeedback in ADHD: An open label pilot study. *Applied Psychophysiology and Biofeedback*, *37*, 171-180. doi:10.1007/s10484-012-9191-4
- Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, *7*, 421-438.
- Arns, M., & Kenemans, J. L. (Under Review). Neurofeedback in ADHD and insomnia: Vigilance stabilization through sleep spindles and circadian networks. *Neuroscience & Biobehavioral Reviews*.
- Astill, R. G., Van der Heijden, K. B., Van Ijzendoorn, M. H., & Van Someren, E. J. (2012). Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed. *Psychological Bulletin*. doi:10.1037/a0028204
- Barry, R. J., Clarke, A. R., Johnstone, S. J., & Brown, C. R. (2009). EEG differences in children between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, *120*, 1806-1811.
- Boutros, N., Fraenkel, L., & Feingold, A. (2005). A four-step approach for developing diagnostic tests in psychiatry: EEG in ADHD as a test case. *Journal of Neuropsychiatry and Clinical Neurosciences*, *17*, 455-464.

- Bresnahan, S. M., Anderson, J. W., & Barry, R. J. (1999). Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *46*, 1690-1697.
- Callaway, E., Halliday, R., & Naylor, H. (1983). Hyperactive children's event-related potentials fail to support underarousal and maturational-lag theories. *Archives of General Psychiatry*, *40*, 1243-1248.
- Chabot, R. J., & Serfontein, G. (1996). Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biological Psychiatry*, *40*, 951-963.
- Clarke, A. R., Barry, R. J., Dupuy, F. E., Heckel, L. D., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2011). Behavioural differences between EEG-defined subgroups of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *122*, 1333-1341.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention-deficit/hyperactivity disorder: A comparative study of two subtypes. *Psychiatry Research*, *81*, 19-29.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001a). Age and sex effects in the EEG: Differences in two subtypes of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *112*, 815-826.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001b). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *112*, 2098-2105.
- Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Croft, R. J. (2002). EEG differences between good and poor responders to methylphenidate in boys with the inattentive type of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *113*, 1191-1198.
- Cormier, E. (2008). Attention deficit/hyperactivity disorder: A review and update. *Journal of Pediatric Nursing*, *23*, 345-357.
- DeFrance, J. F., Smith, S., Schweitzer, F. C., Ginsberg, L., & Sands, S. (1996). Topographical analyses of attention disorders of childhood. *International Journal of Neuroscience*, *87*, 41-61.
- Dollman, J., Ridley, K., Olds, T., & Lowe, E. (2007). Trends in the duration of school-day sleep among 10- to 15-year-old South Australians between 1985 and 2004. *Acta Paediatrica*, *96*, 1011-1014.
- González Castro, P., Alvarez Pérez, L., Núñez Pérez, J. C., González-Pianda García, J. A., Alvarez García, D., & Muñiz Fernández, J. (2010). Cortical activation and attentional control in ADAH subtypes. *International Journal of Clinical and Health Psychology*, *10*, 23-39.
- Gordon, E. (2012). *Application of HRV & Resonant Frequency Biofeedback to Brain-Body Health*. Presentation at the AAPB conference March 10th, 2012, Baltimore.
- Iglowstein, I., Jenni, G., Molinari, L., & Largo, H. (2003). Sleep duration from infancy to adolescence: Reference values and generational trends. *Pediatrics*, *111*, 302-307.
- Janzen, T., Graap, K., Stephanson, S., Marshall, W., & Fitzsimmons, G. (1995). Differences in baseline EEG measures for ADD and normally achieving preadolescent males. *Biofeedback and Self-regulation*, *20*, 65-82.
- Jasper, H. H., Solomon, P., & Bradley, C. (1938). Electroencephalographic analyses of behavior problem children. *American Journal of Psychiatry*, *95*, 641.
- Kuperman, S., Johnson, B., Arndt, S., Lindgren, S., & Wolraich, M. (1996). Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *35*, 1009-1017.
- Lansbergen, M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*, 47-52.
- Lazzaro, I., Gordon, E., Li, W., Lim, C. L., Plahn, M., Whitmont, S., & Meares, R. (1999). Simultaneous EEG and EDA measures in adolescent attention deficit hyperactivity disorder. *International Journal of Psychophysiology*, *34*, 123-134.
- Lazzaro, I., Gordon, E., Whitmont, S., Plahn, M., Li, W., Clarke, S., & Meares, R. (1998). Quantified EEG activity in adolescent attention deficit hyperactivity disorder. *Clinical EEG*, *29*, 37-42.
- Loo, S. K., Cho, A., Sigi Hale, T., McGough, J. J., McCracken, J.T., & Smalley, S. L. (2012). Characterization of the theta to beta ratio in ADHD: Identifying potential sources of heterogeneity. *Journal of Attention Disorders*.
- Lubar, J. F. (1991). Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Applied Psychophysiology and Biofeedback*, *16*, 201-225.
- Magee, L., & Hale, L. (2012). Longitudinal associations between sleep duration and subsequent weight gain: A systematic review. *Sleep Medicine Reviews*, *16*, 231-241.
- Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R. A. (1992). Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: Controlled study with clinical implications. *Pediatric Neurology*, *8*, 30-36.
- Matricciani, L., Olds, T., & Petkov, J. (2012). In search of lost sleep: Secular trends in the sleep time of school-aged children and adolescents. *Sleep Medicine Reviews*, *16*, 203-211.
- Matsuura, M., Okubo, Y., Toru, M., Kojima, T., He, Y., Hou, Y., & Lee, C. K. (1993). A cross-national EEG study of children with emotional and behavioral problems: A WHO collaborative study in the western pacific region. *Biological Psychiatry*, *34*, 59-65.
- Miano, S., Parisi, P., & Villa, M. P. (2012). The sleep phenotypes of attention deficit hyperactivity disorder: The role of arousal during sleep and implications for treatment. *Medical Hypotheses*, *79*, 147-153. doi:10.1016/j.mehy.2012.04.020
- Molendijk, M. L., Bus, B. A., Spinhoven, P., Kaimatzoglou, A., Voshaar, R. C., Penninx, B. W., & Elzinga, B. M. (2012). A systematic review and meta-analysis on the association between BDNF val(66) met and hippocampal volume-a

- genuine effect or a winners curse? *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 159B, 731-740. doi:10.1002/ajmg.b.32078
- Monastra, V. J., Lubar, J. F., & Linden, M. (2001). The development of a quantitative electroencephalographic scanning process for attention deficit-hyperactivity disorder: Reliability and validity studies. *Neuropsychology*, 15, 136-144.
- Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., & Fenger, T. N. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology*, 13, 424-433.
- Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback*, 27, 231-249.
- Nazari, M. A., Wallois, F., Aarabi, A., & Berquin, P. (2011). Dynamic changes in quantitative electroencephalogram during continuous performance test in children with attention-deficit/hyperactivity disorder. *International Journal of Psychophysiology*, 81, 230-236.
- Ogrim, G., Kropotov, J., & Hestad, K. (2012). The QEEG theta/beta ratio in ADHD and normal controls: Sensitivity, specificity, and behavioral correlates. *Psychiatry Research*. doi:10.1016/j.psychres.2011.12.041
- Quintana, H., Snyder, S. M., Purnell, W., Aponte, C., & Sita, J. (2007). Comparison of a standard psychiatric evaluation to rating scales and EEG in the differential diagnosis of attention-deficit/hyperactivity disorder. *Psychiatry Research*, 152, 211-222.
- Rosenberg, M. S., Adams, D. C., & Gurevitch, J. (2000). *MetaWin: Statistical software for meta-analysis, version 2.1*. Sunderland, MA: Sinauer.
- Rowland, A. S., Lesesne, C. A., & Abramowitz, A. J. (2002). The epidemiology of attention-deficit/hyperactivity disorder (ADHD): A public health view. *Mental Retardation and Developmental Disabilities Research Reviews*, 8, 162-170.
- Snyder, S. M., & Hall, J. R. (2006). A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology*, 23, 440-455.
- Snyder, S. M., Quintana, H., Sexson, S. B., Knott, P., Haque, A. F., & Reynolds, D. A. (2008). Blinded, multi-center validation of EEG and rating scales in identifying ADHD within a clinical sample. *Psychiatry Research*, 159, 346-358.
- Sohn, H., Kim, I., Lee, W., Peterson, B. S., Hong, H., Chae, J. H., . . . Jeong, J. (2010). Linear and non-linear EEG analysis of adolescents with attention-deficit/hyperactivity disorder during a cognitive task. *Clinical Neurophysiology*, 121(11), 1863-1870. doi:10.1016/j.clinph.2010.04.007
- Strijkstra, A. M., Beersma, D. G., Drayer, B., Halbesma, N., & Daan, S. (2003). Subjective sleepiness correlates negatively with global alpha (8-12 Hz) and positively with central frontal theta (4-8 Hz) frequencies in the human resting awake electroencephalogram. *Neuroscience Letters*, 340, 17-20.
- Suffin, S. C., & Emory, W. H. (1995). Neurometric subgroups in attentional and affective disorders and their association with pharmacotherapeutic outcome. *Clinical EEG*, 26, 76-83.
- Tanaka, H., Hayashi, M., & Hori, T. (1996). Statistical features of hypnagogic EEG measured by a new scoring system. *Sleep*, 19, 731-738.
- Tanaka, H., Hayashi, M., & Hori, T. (1997). Topographical characteristics and principal component structure of the hypnagogic EEG. *Sleep*, 20, 523-534.
- Walter, W., & Dovey, V. J. (1944). Electro-encephalography in cases of sub-cortical tumour. *Journal of Neurology, Neurosurgery & Psychiatry*, 7, 57.
- Williams, L. M., Hermens, D. F., Thein, T., Clark, C. R., Cooper, N. J., Clarke, S. D., & Kohn, M. R. (2010). Using brain-based cognitive measures to support clinical decisions in ADHD. *Pediatric Neurology*, 42, 118-126.

Bios

Martijn Arns is director at Research Institute Brainclinics and researcher at Utrecht University. He is specialized in research focused on Personalized Medicine in ADHD and Depression and Neuromodulation techniques such as Neurofeedback and rTMS.

C. Keith Conners is Professor Emeritus at Duke University, Department of Psychiatry and Behavioral Sciences.

Helena C. Kraemer is Professor of Biostatistics in Psychiatry, Stanford University (Emerita) and Professor, Department of Psychiatry, University of Pittsburgh. Her focus is on biostatistical approaches in the behavioral areas of medicine, particularly in Psychiatry.