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Click-evoked auditory brainstem responses & autism spectrum disorder: A meta-analytic investigation of disorder specificity

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Abstract

Background—Click-evoked auditory brainstem response (ABR) alterations are associated with autism spectrum disorder (ASD), but the specificity of these findings to the disorder are unclear. We therefore performed a meta-analysis on ABRs and attention deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder that shares some etiologic and symptom overlap with ASD.

Method—Seven papers compared ABR latency components (I, III, V, I–III, III–V, I–V) between participants with and without ADHD. We used random-effects regression to generate component-specific estimates (Hedges' *g*) that adjusted for study sample sizes and the number of studies contributing to each estimate. We compared these estimates to our recently published meta-analysis of ABRs and ASD.

Results—All ADHD studies employed cross-sectional designs. ADHD was associated with longer latencies for Waves III and V (*g*=0.6, 95%CI 0.3,1.0 and *g*=0.6, 95%CI 0.2,0.9) and Waves I–III and I–V (*g*=0.7, 95%CI 0.2, 1.3 and *g*=0.6, 95%CI 0.3, 1.0). Effect sizes from the ASD and ADHD meta-analyses did not differ from each other.

Conclusion—Similar patterns of ABR alterations are observed in ADHD and ASD. However, studies rarely screen for middle ear dysfunction or hearing loss and rely upon cross-sectional designs. Addressing these issues will inform the viability of ABRs as a prognostic and/or etiologic biomarker for these disorders.

Introduction

Biomarkers garner considerable interest in the study of autism spectrum disorder (ASD) due to their potential to inform etiology as well as diagnostic risk prediction.[1,2] To this

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end, researchers have made much progress in documenting the range of biological processes implicated in the disorder. These include epigenetic mechanisms as well as alterations to immune and metabolic functioning.[2–4] Despite the diversity of biological processes implicated in ASD, final common pathways involve disruptions in neuronal proliferation, migration, and connectivity in prenatal and/or early postnatal brain development.[3,5,6] As a result, brain-based biomarkers, particularly those that can be assessed during early infancy, hold unique promise in advancing our understanding of the disorder.[4,7,8]

For this reason, auditory brainstem responses (ABRs) have received renewed interest in the ASD literature. ABRs are electrophysiologic potentials that are most commonly assessed in response to broadband acoustic stimulation (e.g., clicks). The most well-characterized ABR components are waves I, III, and V, which are generated by the auditory nerve, cochlear nucleus, and lateral lemniscus, respectively.[9] Component-specific latency and amplitude measures, in turn, reflect conduction time as well as the synchronization of neuronal firing within the auditory pathway.[10] Relevant to ASD, ABR indices differ by sex, are sensitive to perinatal health risks, and are correlated within families.[11–16]

Links between ABRs and ASD have been investigated for more than 30 years, and two recent meta-analyses summarizing this literature concluded that ABR wave latencies are longer among ASD compared to typically developing (TD) participants.[7,17] These effects were medium to large in size, with stronger associations observed among children compared to adults. A noted limitation of this literature is its reliance on cross-sectional data.[18,19] It is also unclear whether ABR findings linked to ASD generalize to other neurodevelopmental disorders, particularly those with which it shares some etiologic, endophenotypic, and/or symptom overlap, such as attention deficit hyperactivity disorder (ADHD).[20–24]

Like the ASD literature, studies investigating links between ABRs and ADHD rely almost exclusively upon cross-sectional designs, small samples, and assessments of wave latencies as opposed to amplitudes. Study findings are also mixed, with some reporting null associations and others reporting slower and even faster ABR latencies with ADHD.[25–28] A thorough and quantitatively-based summary is needed to bring clarity to this literature. In addition, no study to date has directly compared ABR findings among TD, ADHD, and ASD groups. Addressing these research gaps can inform whether ABRs hold potential as a transdiagnostic biomarker or are linked to processes and/or symptoms that are disorder-specific.

The overarching goal of this study is to evaluate the specificity of ABR alterations to ASD. To do this, we performed a meta-analytic review of ABRs and ADHD. Important parts of this effort included: 1) generating effect size estimates that are specific to different elements of the ABR waveform, and 2) comparing these estimates to those generated by our recent meta-analysis on ABRs and ASD (using identical data abstraction, aggregation, and analytic techniques) to evaluate the specificity of any findings observed.

Methods

Data Sources & Search Strategy

We identified candidate papers by searching PubMed, PsycInfo, PsycArticles, & Google Scholar using the following strategy: ((“auditory brain stem” or “auditory brainstem” or “audit$”)) AND (“ADHD” or “attention deficit hyperactivity disorder” or “attention deficit disorder” or “attention problems”) in June 2020. These searches returned 135 results, which were reviewed independently by two abstractors for inclusion into the meta-analysis. We began by removing duplicates (n=35), reviews/commentaries (n=6), and animal studies (n=2). We also excluded papers that did not include ADHD or click-evoked ABR data (n=68) or a typically developing (TD) comparison group (n=3). To remain sensitive to changes in ADHD terminology across time, we considered any of the following as indicative of the disorder: ADHD, ADHD-Combined type (ADHD-C), ADHD-Predominantly Inattentive type (ADHD-PI), ADHD-Hyperactive Impulsive type (ADHD-HI), and attention deficit disorder (ADD. We then reviewed the references cited within these remaining 21 papers and identified an additional 10 papers to consider for inclusion. Next, we examined the full-text of these 31 papers to determine whether standardized mean differences between ADHD and TD participants could be calculated for at least one ABR latency component. Seven papers met this criterion and were included in the meta-analysis (Figure 1).[25–31] Because our analyses used published, aggregate-level data, our study is considered exempt by the Michigan State University Institutional Review Board. This meta-analysis was not pre-registered.

ABR components and effect size scoring

Well-characterized ABR components include waves I, III, and V, which can be reliably generated and measured across the lifespan.[11,32] Waves can be assessed using latencies and amplitudes, but this meta-analysis focuses exclusively on latencies because only one study presented information on amplitudes.[28] To this end, we abstracted two sets of latency information from individual studies for analysis: absolute (I, III, V) and inter-peak (I–III, III–V, I–V) latencies. Absolute latencies are calculated as the time from stimulus (click in all cases) to a specified wave peak and reflect the conduction of sound through the middle ear in addition to central nervous system processing within the auditory nerve and brainstem. In contrast, inter-peak latencies are calculated as the time from peak-to-peak and can be delayed uniformly in the presence of a middle ear condition, such as effusion.

We estimated effect sizes using Hedges’s *g*, a standardized mean difference score corrected for studies with small sample sizes. Hedges’s *g* is interpreted similarly to Cohen’s *d*, with estimates of 0.2, 0.5, and 0.8 corresponding to small, medium, and large effects, respectively. We calculated study- and component-specific estimates of Hedges’s *g* to reflect latency differences between ADHD and TD participants ($g>0$: ADHD latency>TD latency; $g<0$: ADHD latency<TD latency). We then weighted and averaged across all variable conditions (e.g., ear of stimulation) and subsets of participants to generate one estimate per component per study.[33] Disaggregated effect sizes by study and component are summarized in eTable 1 and were independently verified by two abstractors. ABR assessment in all studies were obtained using diagnostic-level equipment.

Effect Heterogeneity

We used the Q statistic to evaluate the likelihood of effect heterogeneity across studies (heterogeneity: $p<0.05$), and the I^2 Index to assess the magnitude of the heterogeneity observed (small: 25%, medium: 50%, large: 75%) for each ABR component.[33,34] Due to the small number of studies in this meta-analysis, we did not perform moderator analyses to formally interrogate systematic sources of heterogeneity when present. However, we evaluated each of the seven studies to describe the study populations and ABR data acquisition parameters that may affect the interpretation of any findings observed. To do this, we used the coding scheme employed in our recently published meta-analysis on ABRs and ASD to facilitate comparisons across these literatures.[7] In brief, we scored studies according to the following factors: participant age group (< 8 years; ≥ 8 years), sex matching across the ADHD and TD groups (yes, no, unspecified), click presentation rate (< 27.5 clicks/sec; ≥ 27.5 clicks/sec), exclusion of participants born preterm (included, excluded, not reported), and exclusion of participants with intellectual disabilities (included, excluded, not reported), middle ear abnormalities (included, excluded, not reported), or elevated auditory thresholds (included, excluded, not reported). We also scored ADHD subtype (ADHD-C, ADHD-PI, ADHD-HI, unspecified). These coding decisions were verified by two independent abstractors and are summarized in Table 1.

Publication Bias

We evaluated publication bias using Kendall's tau and Eggert's intercept, and interpreted significant findings on either test as indicative of bias ($p<0.05$, two-tailed). Because these tests may be underpowered,[33] we also calculated the fail-safe N to estimate the minimum number of studies with an effect size of 0 needed to attenuate findings to non-significance.

Analytic Plan

We began by describing the studies contributing to this meta-analysis. We then used random-effects regression (one per component) to evaluate whether latency differences between ADHD and TD participants differed from zero. Random effects variance was based upon method of moments estimation. To adjust for multiple comparisons and reduce the probability of Type I error, we used a false discovery rate of 5% to identify significant findings (corrected $p=0.016$, two-tailed). We assessed heterogeneity in effects for each component using the Q statistic and I^2 Index and evaluated publication bias for effects that exceeded significance thresholds. As a preliminary examination of whether ABR findings reported here generalize to other neurodevelopmental disorders, we compared the effect sizes from this paper to those generated in our meta-analysis on ABRs and ASD using random effects regression (one per component).[7] This meta-analysis used identical methods for data abstraction, aggregation, and analysis, is based upon diagnostic-level ABR assessments, and published effect sizes for all components under investigation here.

Results

All seven studies included in the meta-analysis employed cross-sectional designs. The total number of participants per study ranged from 30 to 155, and ages ranged between 5 and 13 years (see eTable 1). Although ADHD subtype information was not reported for one study,

participants with ADHD in the remaining six studies met criteria for ADHD-C (n=3 studies) or individual subtypes (n=3 studies). Most participants with ADHD were male, ranging from 67% to 100% across individual studies; two of these studies matched a corresponding proportion of males in the TD group. Most studies (71%) excluded participants with intellectual disability. Middle ear and hearing loss assessments were not reported in three studies, but children with abnormal findings in either domain were excluded from the remaining four.

The number of studies contributing to each wave-specific effect size ranged from 5 to 7, representing data from 315 to 433 participants (Table 2). ADHD was not associated with absolute Wave I or III–V interpeak latencies. However, ADHD was associated with longer absolute ABR latencies for Waves III (g=0.6, 95%CI 0.3, 1.0), V (g=0.6, 95%CI 0.2, 0.9) and interpeak latencies I–III (g=0.7, 95%CI 0.2, 1.3), and I–V (g=0.6, 95%CI 0.3, 1.0), all p<0.016. The Q statistic suggested that these effects lacked heterogeneity (Table 2; eFigure 1), and the I^2 Indices for these components were correspondingly small in magnitude, with the exception of Wave I (45%). We did not observe evidence of publication bias across two measures assessing this effect (Kendall's tau and Eggert's test, all p>0.09, eTable 2). Approximately 39 (IPL I–V) to 59 (Wave III) studies with an effect size of 0 would be needed to attenuate findings to non-significance.

Figure 2 compares the effect sizes from this meta-analysis to those obtained from our recent meta-analysis on ABRs and ASD that was based upon 15 studies. We observed no differences for any absolute or inter-peak latency measure, all p>0.46. Because the ASD effect sizes were based upon studies with a larger age range than those contributing to the current analysis, we repeated our comparisons after excluding ASD studies with participants older than 13 years.[35–39] Results were unchanged (all p>0.41).

Discussion

Click-evoked ABRs exhibit cross-sectional associations with ASD that are medium-to-large in size, but the specificity of these findings to the disorder are unclear. To address this issue, we performed a meta-analysis of the association between ABRs and ADHD, a neurodevelopmental disorder that shares some etiologic and symptom overlap with ASD. We observed that the latencies for several ABR components were significantly longer among ADHD compared to TD participants (III, V, I–III, I–V). These are the same latency components implicated in our ABR and ASD meta-analysis that employed identical data abstraction, aggregation, and analytic methods. Effects were comparable in size between these two papers.

Our meta-analysis of the ABR and ADHD literature points to longer latencies for some components (III, V, I–III, I–V), but not others (I, III–V). This configuration of findings may be driven by alterations in neural and synaptic conduction between the auditory nerve and the cochlear nucleus, the only segment of the central auditory pathway that is shared among the latencies that differ between ADHD and TD participants. Larger axons, hypomyelination, lower levels of synaptic efficacy, and increased inhibitory inputs can independently or in combination contribute to decreases in action potential velocity.[40,41]

However, to date, ADHD studies have not localized such findings to the auditory brainstem or any specific segment of this pathway. A small, but growing neuroimaging literature points to brainstem involvement in ADHD,[42–44] but the brain regions most associated with the disorder include the prefrontal cortex and basal ganglia.[45,46] Importantly, corticofugal projections provide descending anatomical and functional connections between the prefrontal cortex and the auditory brainstem, including the cochlear nucleus.[47] Thus, the ABR findings described here may not only reflect functioning within the brainstem itself, but also more distal brain regions, including those implicated in ADHD. Thus, the contribution of brainstem-mediated processes to the etiology of ADHD is decidedly uncertain. Future studies that employ multimodal brain-based assessments will be helpful in addressing this issue.

ADHD is characterized by considerable variability in symptoms, most notably reflected in the primarily inattentive (PI), hyperactive-impulsive (HI), and combined diagnostic subtypes. These subtypes, in turn, may be driven by alterations in specific cognitive processes and the neural substrates upon which they are based.[45,48] We therefore examined whether studies defined their samples according to symptom presentation to gain additional insights into the ABR findings, particularly given the corticofugal connections referenced above. In general, the strongest effect sizes were based on samples limited to the combined subtype and the weakest based upon samples that included all three. The significance of these findings is unclear given the small number of studies upon which they are based, but they point to a pressing need to characterize ADHD symptom dimensions when elucidating links between the disorder and ABR findings.

The cognitive and neural processes thought to underlie inter-individual variability in ADHD symptoms may also contribute to co-occurring conditions, including learning disabilities, oppositional defiant disorder, and most germane to this paper, ASD.[43,48–50] However, these comorbid diagnoses were not considered in the studies of ABRs and ADHD, and as a result, the extent to which they account for any of the observed findings is unclear. One exception includes intellectual disability (ID), which served as an exclusion criterion for five of the seven ADHD papers. Thus, the longer ABR latencies observed among ADHD participants are not likely driven by this issue, particularly given that the one study including children with ID reported shorter ABR latencies relative to TD participants across all components.[26] However, the lack of information regarding co-occurring ASD generates significant interpretational challenges given the increasing recognition that ADHD and ASD may exhibit some etiologic and phenotypic overlap. Indeed, approximately 17–20% of children with ADHD have comorbid diagnoses of ASD,[51–53] a phenomenon that is more common in males and may be driven by genetic influences.[54] In addition, ASD is associated with longer ABR latencies in the same components implicated here,[7] and those studies have likewise not characterized co-occurring ADHD, which is estimated to affect 20–48% of children with ASD.[20,51–53] Disentangling the impacts of comorbidity represent a critical next step to elucidating whether ABRs yield etiologic and prognostic value as a specific- or trans-diagnostic marker of neurodevelopmental risk.

We also found that ADHD and ASD are associated with a similar pattern of ABR latency findings, even after standardizing for age at ABR assessment. However, the literatures

upon which these analyses are based differ in other important ways. For example, ABRs were assessed almost exclusively in response to slower click rates in the ADHD literature; however, in the ASD literature, some studies used slower click rates (< 27.5/sec) and others used faster click rates (≥ 27.5/sec).[7,55] Because faster click rates increase processing demands on the auditory nerve and may reveal findings not otherwise present,[55,56] it is possible that the ADHD effect sizes and any differences with ASD effect sizes are underestimated. Alternatively, the ASD effect sizes may be inflated due to the presence of fast click rate studies and contribute to the apparent similarity in findings across the literatures. Thus, we repeated our analyses following the exclusion of ASD studies that used fast click rates, but our findings differed by ≤ 0.1 across all components. In addition, no studies to date have directly compared ABRs between ASD and ADHD participants or against the same group of TD participants. Thus, the findings presented here must be interpreted as preliminary and inform development of subsequent studies that directly address the specificity of associations between ABR findings and neurodevelopmental disorders. Our study provides an up-to-date, comprehensive basis from which to launch those efforts.

Nonetheless, there are some caveats to consider when interpreting our findings, some of which apply to the analysis at hand and others that pertain to the ABR and neurodevelopmental disorder literature more broadly. First, our meta-analysis of ABRs and ADHD was based upon a small number of studies (n=7), and as a result, our analyses may be underpowered. This might be reflected in an imprecise estimation of effect size heterogeneity and the apparent comparability of findings with those from our ASD meta-analysis. In addition, several studies had a greater proportion of males in the ADHD group compared to the TD group. Because males also produce longer ABR latencies for all components across the lifespan,[11,12] sex differences may confound the findings presented here. We therefore reexamined our findings after limiting analyses to the two studies that matched on sex.[28,31] Our findings were unchanged, but this must be replicated in subsequent work. The ADHD literature also rarely described medication history or exposure prior to ABR assessment. This is a significant omission, given the demonstrated impacts of ADHD medication on the functioning of widescale brain networks.[57,58] One study required a 24 -hour “washout” prior to participation and reported significantly longer latencies for only Wave V and I–V (Hedges’s g=0.7 and 0.8, respectively).[28] Although this suggests that medication exposure cannot fully account for the findings reported here, careful attention to the issue in future work is sorely needed.

Thinking about the ABR and neurodevelopmental disorders more generally, perinatal risk factors such as preterm birth are not often considered despite the fact such factors are linked to longer ABR latencies as well as neurodevelopmental risk.[59–63] As a result, it is unclear whether perinatal risk confounds or modifies the associations in the ADHD or ASD literature, information that will be key to understanding the significance and scope of the associations reported here. Participants are also not routinely examined for hearing loss or middle ear pathology. If such findings are present, longer ABR latencies are expected, and in the case of hearing loss, conductive problems may be misinterpreted as disturbances in sensorineural processing. In addition, studies to date are based almost entirely upon cross-sectional data. It is therefore uncertain whether ABR findings precede diagnosis,

though some recent papers in the ASD literature suggest this is a possibility.[17,19] Addressing this issue will be critical to determining whether ABRs hold promise as an etiologic or prognostic biomarker for neurodevelopmental disorder risk. Studies linking ABRs to neurodevelopmental disorders also rely upon latency as opposed to amplitude assessments. Given that these parameters may reflect different neural processes,[10] a more comprehensive evaluation of the ABR waveform in future work may yield insights that have yet to be appreciated. Finally, as mentioned previously, participants with ADHD or ASD were not compared against each other in the context of the same study or against the same group of TD participants. Thus, although our findings suggest that longer ABR latencies are not specific to ADHD or ASD, these results point to the need for more rigorous evaluation in future work.

In sum, our meta-analysis suggests that ABR findings that are linked to ADHD may not be specific to the disorder. However, given the limitations described above, it will be important to compare ASD, ADHD, and TD participants within the same study to directly address this issue. Although the utility of ABRs for neurodevelopmental disorder etiology and prediction remains unclear, the associations that we and others report justify further investigation into the plausibility of these applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPACT:

- Click-evoked auditory brainstem response (ABR) alterations are associated with ASD, but the specificity of these findings to the disorder are unclear. We therefore performed a meta-analysis of the association between ABRs and ADHD, a disorder that shares etiologic and symptom overlap with ASD.
- ADHD was associated with longer ABR latencies for several components. These components are identical to those implicated in ASD. Effect sizes were similar in magnitude across disorders.
- The viability of ABRs as prognostic and/or etiologic biomarkers for neurodevelopmental risk requires addressing limitations in the literature (e.g., cross-sectional data, non-standardized ABR protocols, minimal characterization of symptom heterogeneity)

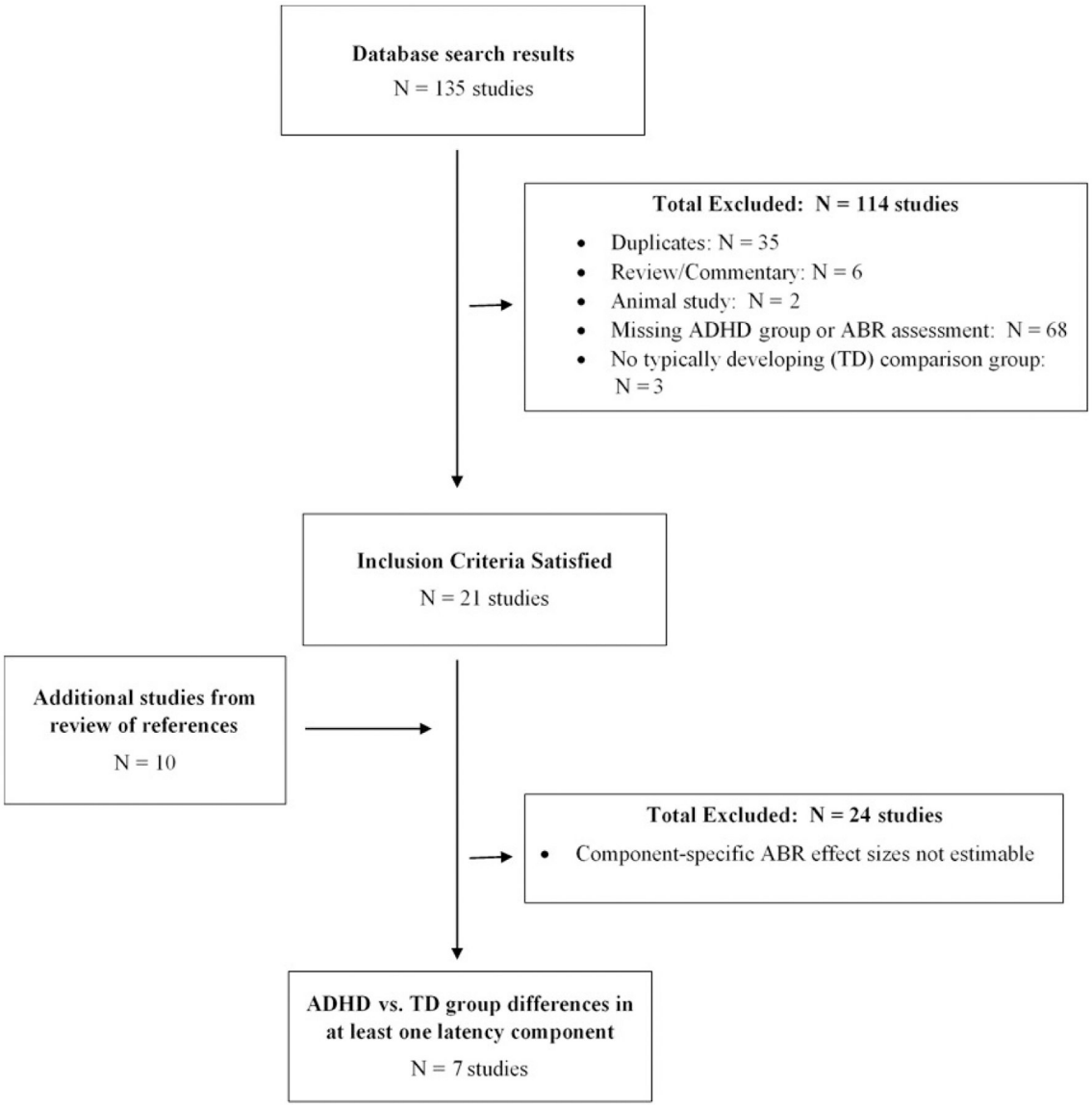

Figure 1.
Study identification and selection process

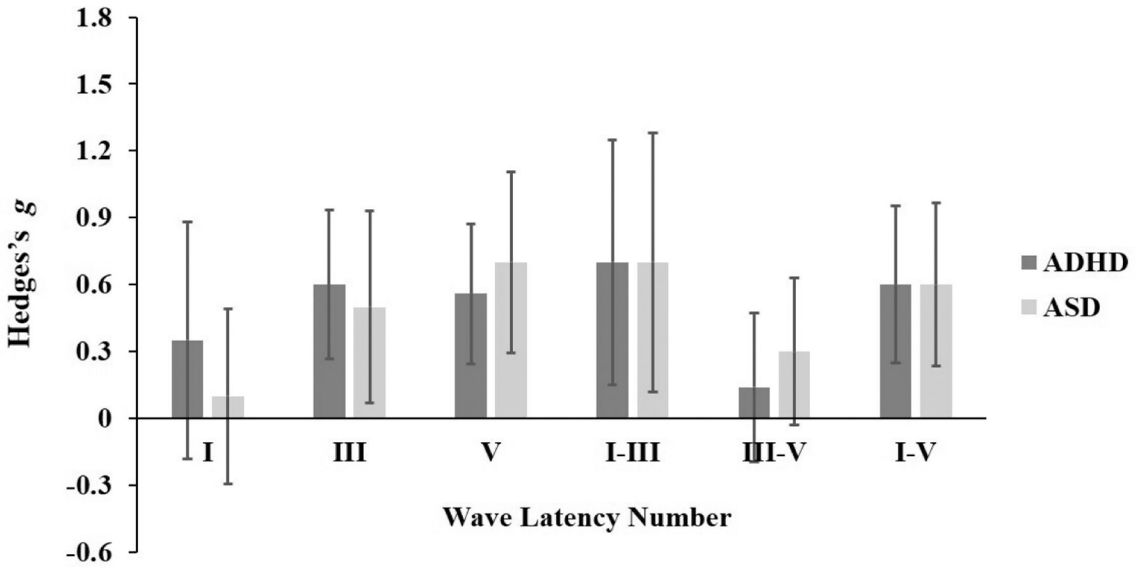

Figure 2.

Comparison of ABR latency effect size estimates (Hedges's *g*, 95%CI) between participants with ADHD (current meta-analysis) and participants with ASD (Talge, Tudor, Kileny, 2018).

Table 1.

Coding decisions for study characteristics

	Age Group	Sex Matching	ADHD subtype	ID	Middle Ear Abnormality	Elevated Auditory Threshold	Click Rate	Preterm birth	Waves Available
Lahat et al. (1995)	> 8 years	No	ADHD-PI; ADHD-HI	Excluded	Excluded	Not reported	< 27.5/s	Excluded[1]	I, III, V, I–III, III–V, I–V
Ismail et al. (1999)	< 8 years	No	ADHD-C; ADHD-PI; ADHD-HI	Included	Excluded	Excluded	< 27.5/s	Not reported	I, III, V, I–III, III–V, I–V
Puente et al. (2002)	> 8 years	Yes	unspecified	Not reported	Not reported	Excluded	≥ 27.5/s	Not reported	I, III, V, I–III, I–V
Azzam et al (2010)	> 8 years	Not reported	ADHD-C	Excluded[2]	Excluded	Excluded	< 27.5/s	Not reported	I, III, V, I–III, III–V, I–V
Vaney et al. (2011)	> 8 years	Yes	ADHD-C	Excluded	Not reported	Not reported	< 27.5/s	Excluded	I, III, V, I–III, III–V, I–V
Ahmed et al. (2014)	> 8 years	No	ADHD-C; ADHD-PI; ADHD-HI	Excluded	Not reported	Not reported	< 27.5/s	Not reported	I, III, V, I–III, III–V, I–V
Jafari et al. (2015)	> 8 years	No	ADHD-C	Excluded	Excluded	Excluded	< 27.5/s	Not reported	I, III, V

Note. **ADHD**: Attention Deficit/Hyperactivity Disorder; **ADHD-C**: attention deficit/hyperactivity disorder – combined type; **ADHD-HI**: ADHD-Hyperactive Impulsive; **ADHD-PI:** ADHD-Primarily Inattentive; **ID**: intellectual disability; **s:** second

[1] preterm delivery defined as < 36 weeks

[2] ADHD group: all have normal Wechsler Intelligence Scale for Children scores; typically developing group: "no history suggestive of behavioural, attention problems, medical, hearing or neurological disorders"

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Table 2.

Attention deficit/hyperactivity disorder and its association with wave specific click-evoked auditory brainstem responses

			Random Effects					
Wave Latency	**No. of Studies**	**Sample Size**	***g***	**95%CI**	***p***	***Q***	***p***	I^2
I	7	433	0.4	(−0.2, 0.9)	0.18	11.0	0.09	45.4
III	7	433	0.6	(0.3, 1.0)	< 0.001	7.2	0.30	17.0
V	7	433	0.6	(0.3, 0.9)	< 0.001	6.1	0.41	2.3
I–III	6	351	0.7	(0.2, 1.3)	0.011	8.0	0.16	37.4
III–V	5	315	0.1	(−0.2, 0.5)	0.39	4.1	0.39	3.7
I–V	6	351	0.6	(0.3, 1.0)	0.001	4.9	0.43	0.00

Note. **CI:** confidence interval; ***g*** (Hedges's g), I^2 (percent variance due to heterogeneity); ***p*** (p value); **Q** (Q statistic for heterogeneity)