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# Brain Connectivity Reflected in EEG Coherence in Individuals with Autism: A Meta-Analysis

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**Abstract**

**Introduction**: Many theories about the etiology of autism have been proposed. One is related to brain connectivity in individuals with autism. Several studies have reported brain connectivity changes in autism disease. This study was performed on EEG studies that evaluated patients with autism using functional brain connectivity and compared them with typically developing individuals.

**Methods:** Three scientific databases were systematically searched through their online search engines, ScienceDirect, Medline (PubMed) and BioMed Central. Comprehensive Meta-Analysis software was used to analyze the data.

**Results:** The systematic search led to 10 papers in which EEG coherence was used to obtain brain connectivity of people with autism. To determine the effect size, the Cohen's d parameter was utilized. In the first meta-analysis, the study of the maximum effect size has been considered and all significant effect sizes evaluation has been done in the second meta-analysis. Evaluating the effect size was done using a random-effects model in both meta-analysis. The results of the first meta-analysis indicated that heterogeneity is not present among the studies ($Q = 13.345$, $p > 0.1$). Evaluation of all effect sizes in the second meta-analysis showed a significant lack of homogeneity among the studies ($Q = 56.984$, $p = 0.0001$).

**Conclusion:** As a total result, autism was found to be related to neural connectivity, and the present research showed the difference in the EEG coherence of people with autism and healthy people. These conclusions require further studies involving larger data, considering different brain regions, and novel analysis techniques for calculating brain connectivity.

**Key Words:** Autism spectrum disorder, Electroencephalography, Coherence, Meta-analysis.

**Highlights**

Autism Spectrum Disorders change functional brain connectivity.

EEG coherence in people with autism and healthy people are different.

Connectivity can be an appropriate biological marker for early diagnosis of autism

**Plain Language Summary**

Autism Spectrum disorders are neurodevelopmental disorders affect the normal functioning of the brain and unfortunately, the cause of them is still unknown. Various factors have been reported as a cause of autism. According to some research, it may be related to brain aberrant connectivity. Articles that studied brain connectivity in autistic individuals have reported a variety of results about connections between different brain regions, which are sometimes contradictory. These contradictory results lead to ambiguity in the interpretation of how the brain connectivity change in autism. Our goal in this study is to compare the results of all these papers with the aim of concluding their outputs to determine whether brain connections are different in autistic and normal individuals. As a total result, autism was found to be related to neural connectivity, and the present research showed the difference in the coherence (a simple connectivity measure) of people with autism and healthy ones. According to this result, we can say that connectivity can be an appropriate biological marker for early diagnosis of autism. The golden age for identifying and treating autism is a short period between two and five years old. If the training and treatment interventions are not carried out within this short period, then the next steps will not yield much. Therefore, the prevention and early detection of this disorder will be of great importance.

ning title: EEG Coherence in Autism: A Meta-Analysis

## Introduction

Autism Spectrum Disorder (ASD) is a neurobehavioral condition that changes the normal brain function. It is characterized by impairments in social interaction, speech and non-verbal communication, eye contact, repetitive behaviors, group activities, and imagination (Kanner, 1943; Landa, 2008). The prevalence rate of autism in USA has raised from 1 in 150 children in 2006 to 1 in 68 in 2014 and according to the newest report of Center for Disease Control and Prevention (CDC), remained unchanged until 2016 (Port et al., 2016). The rates of autism were accounted to be less than 3 per 10000 individual in the 1970s and rose to more than 30 per 10000 in the 1990s. This is a 10 times increase during 20 years, and it imposes a heavy cost on society. So assessment of autistic individuals is an important issue (Blaxill, 2004).

After the introduction of autism, many studies have been done to assess brain functions in individuals with autism. The main research areas are the genetic of autism, brain networks involved in the incidence of this disorder, looking for the appropriate biological markers to early diagnosis and also measuring brain connectivity. Researches showed that individuals with autism have different brain connectivity patterns compared with typically developing groups. A leading theory of autism spectrum disorders suggests that autism may be due to aberrant neural connectivity patterns (Cantor, Thatcher, Hrybyk, & Kaye, 1986; Mak-Fan et al., 2013; Minshew & Williams, 2007). Evidence in support of this theory was based on PET, MRI and EEG studies' investigations and also microscopic researches after death (Coben & Myers, 2008). Abnormal neural connectivity results in different levels of processing in brain networks and therefore deficits in the neural and cognitive integration of information (Hernandez, Rudie, Green, Bookheimer, & Dapretto, 2015). Autism has a strong genetic basis and has a highly heritable nature, so changes in functional and structural connectivity are possible phenotypes for this disease and may be an important aspect of the ASD profile (Moseley et al., 2015).

Connectivity is classified in two major categories: structural and functional. Structural connectivity is defined as physical connections and usually assessed by fiber tractography. Functional connectivity refers to the statistical dependencies between neurophysiological events which are spatially independent. Different tools can be utilized to measure the brain connectivity. Diffusion Tensor Imaging (DTI) and Magnetic Resonance Imaging (MRI) are common methods for measuring structural connectivity that represent fibers within brain networks. Functional connectivity can be achieved by utilizing imaging techniques such as functional MRI (fMRI) or other measures of brain activity such as EEG and MEG. Investigation of brain connectivity using EEG has advantages such as significantly lower cost than other devices, availability and high precision time measurements, so EEG is a suitable tool for describing dynamic activation and deactivation of functional networks and their connectivity. This review will focus on researches that measure the connectivity using EEG signals in patients with ASD and typically developing individuals.

A simple measure of connectivity, linear coherence, has been evaluated in most EEG studies. It was first utilized for representing connectivity impairments of autism in the 1980s (Cantor et al., 1986). Coherence measure is a function of frequency and explains synchronization between two EEG signals of the same frequency. A large number of papers in the field of autism focus on connectivity issue and report a variety of results. Many reasons justify this differences in findings including theoretical models, the measurement procedure and participant characteristics. In the following, the studies used coherence and obtained heterogeneous results are referred. Connectivity between two hemispheres during visual task were assessed in (Isler, Martien, Grieve, Stark, & Herbert, 2010) for autistic participants. In this study, coherence measures within occipital region and between hemispheres were examined, the results indicated that the EEG coherence between two hemispheres in individuals with autism were low. In

another research (Catarino et al., 2013), inter-hemispheric coherence was evaluated utilizing wavelet coherence in which children with ASD represented reduced inter-hemispheric coherence.

Reduced connectivity between long-range distances have appeared also in task free studies (Barttfeld, Wicker, Cukier, Navarta, & Lew, 2011; Cantor et al., 1986; Coben & Myers, 2008; Duffy & Als, 2012; Lazarev, Pontes, Mitrofanov, & C, 2010; Murias, Webb, Greenson, & Dawson, 2007). In low frequency bands (delta and theta), weaker coherence between frontal and occipital brain regions has been reported (Barttfeld et al., 2011; Lazarev et al., 2010). In contrast, increased coherence in theta band and reduced coherence in alpha band have obtained between the frontal and the temporal, parietal, and occipital regions (Murias et al., 2007). In another study decreased connectivity in the beta band has been reported between frontal and temporal regions (Duffy & Als, 2012). Researches on short-range connections in resting state EEG studies are less consistent. Intra-hemispheric and inter-hemispheric connections in all brain regions have claimed to be decreased in delta and theta bands (Lazarev et al., 2010). Coherence over frontal region has been reduced in delta and alpha bands (Barttfeld et al., 2011; Murias et al., 2007). However, increased coherence has been shown within the frontal region in the delta band (Barttfeld et al., 2011), and within frontal and temporal regions in the theta band (Murias et al., 2007).

A systematic review of EEG and MEG studies have demonstrated reduced long-range connectivity in individuals with ASD compared to controls (O'Reilly, Lewis, & Elsabbagh, 2017). In this paper, due to different modalities and connectivity metrics, quantitative analysis was not done.

There are differences in brain connectivity evaluation results across studies. The age of patients participated in the study, the brain regions considered, and the frequency bands in which connectivity was analyzed, resulted in different outcomes. So, studies show different brain connectivity patterns in autistic and typically developing individuals. There are many important factors that can influence the results of coherence analyses such as sample characteristics, EEG reference, frequency band, task/

resting state, brain regions, etc. and also it has some pitfalls (e.g., particular susceptibility to volume conduction; the choice of reference, of electrode montage, and of coherence estimator) that is beyond the scope of this paper. Regardless of all of these in this meta-analysis, papers that have utilized EEG to study the effects of autism on functional brain connectivity reflected in coherence are outlined. A meta-analysis is an analysis technique in the statistical field that considers the results of multiple scientific studies so the accumulation of data resulting in a better statistical power and more robust point estimate in comparison to using individual papers to extract the measures.

The remaining part of the paper is organized as follows. In the "Methods," the methods of searching and selecting the papers are introduced. The third section of the paper shows the results of meta-analysis, and finally, the discussion are provided in the last section.

## 1. Methods

### 1.1. Search strategy

Relevant papers through a five steps procedure of search and inclusion/exclusion criteria were selected for current meta-analysis. Steps are listed in Table 1. Based on the aim of this paper, a literature search was done on Sciencedirect, PubMed and BioMed Central for papers evaluating EEG coherence associated with autism. Studies published after April 2016 were not included. The following search terms were used in this search: [Autism Spectrum Disorder or ASD or Autism] and [EEG or electroencephalogram] and [Brain connectivity or Connectivity] and [Functional or Coherence]. At "Literature Search" step, 140 English papers found.

### 1.2. Study selection

Titles and abstracts were reviewed to determine whether the studies included autism, EEG, and connectivity. Studies that did not involve EEG and coherence, were excluded. Of the 140 papers, 32 remained. Then full papers were reviewed for the reporting of the results of coherence estimation and the analysis of data in terms of autism versus typically developing groups. Studies were excluded if did not have controls or compared with those of subjects with other disorders, not Autism and also did not have sufficient information about the output. Review articles were discarded too. After applying all these criteria, 12 papers remained.

The last step of the inclusion/ exclusion criteria is verifying quality of data and eligibility of study. Only those studies reported the source of subjects and utilized standard autism diagnostic protocol were included. Studies did not involve at least one between-groups statistical comparisons were excluded. If the data sets overlapped among some studies, the research which contain the most complete set was included and the others were excluded. After this step, 10 papers remained for current meta-analysis. The selection flow chart is pictured in Figure 1.

### 1.3.Statistical analysis

In the meta-analysis of these studies, standardized difference in mean was computed as effect sizes for coherence of autism versus controls. Effect sizes were calculated based on either study's sample size (N), sample mean, and sample's standard deviation (SD), or statistical data such as t-value and F-value. Since variety of conditions such as different frequency bands, brain regions, and hemispheres have been considered in the studies, the effect sizes for all of them were taken into account in this research. Effect sizes were reported for studies using weights assigned to them. Confidence interval (CI) of 95% were calculated using standard approaches. Analysis of heterogeneity were applied using the Q-statistic to inspect the differences among the studies.

The comprehensive meta-analysis software (CMA) was used to perform a random effects meta-analysis. Cohen's *d* and its related variance were computed for the outcome of each study.

## 2. Results

10 studies met the full inclusion criteria and were included in the meta-analysis. Information of these studies were summarized in Table 2.

A total of 26 effect sizes were computed for all conditions considered in studies. The effect size results (Cohen's *d*) ranged from 0.001 to 2.701 and the average was 0.722 (SD: ± 0.12). Difference of coherence measure in left hemisphere in Beta frequency band had the largest effect size ($d$ = 2.701) (Lazarev et al., 2010). The smallest effect size was related to difference of coherence measure in left prefrontal region and eyes-open condition (Mathewson et al., 2012).

The largest effect sizes in each study were considered in the first meta-analysis ($Q$ = 13.345, $p$ = 0.148) (Figure 22, Table 3). This analysis indicated no significant difference between effect sizes in the studies. Second analysis examined all of the effect sizes reported in each study. A significant difference between effect sizes in studies was revealed ($Q$ = 56.984, p = 0.0001) (Figure 33, Table 3).

## 3. Discussion

The hypothesis of the current meta-analysis is considering studies that investigate ASD-related changes in connectivity. Coherence as a linear measure of connectivity that is based on similarity of activations in different regions, was accounted. The purpose of the current study was to probe the effect of autism spectrum disorders on functional connectivity reflected in EEG coherence.

Comparing the connectivity in patients with autism and typically developing controls showed that altered neural connectivity is associated with autism. Two steps meta-analysis of Cohen's d data showed

that when the largest effect size of each study was considered, estimated heterogeneity and I-squared statistics showed that the null hypothesis in favor of the alternative, was not rejected (i.e. the heterogeneity of studies). So the result of ($Q$ = 13.345, $p$ = 0.148) indicates that heterogeneity is not present among the included studies (Table 3). It would not lead to a conclusive homogeneity, due to the small number of studies.

It can be interpreted from the obtained results that the included articles are suitable for the estimation of a single underlying effect size and the low variance between studies is fully described by within study variances. However, when all effects were taken into consideration, estimated heterogeneity and I-squared statistics showed that the null hypothesis in favor of the alternative, was rejected ($Q$ = 56.984, p= 0.0001), demonstrating that heterogeneity is present among the included studies (Table 3) and so further exploring the studies for potential sources of heterogeneity such as heterogeneous in autism spectrum, age patterns and the brain regions considered may be helpful. Altogether heterogeneity analysis shows that the studies, despite the prominent differences among them, are compatible for meta-analysis.

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**Conflict of Interest**

The authors declared no conflict of interest in this study.

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Table 1: Five- step inclusion criteria for the researches reviewed in the Meta-analysis

| Steps | Inclusion Criteria |
|---|---|
| **Literature Search** | SciencedDirect, PubMed, BioMed Central, (1980 to 2016).<br>Search terminology: "Autism Spectrum Disorder" OR "ASD" OR "Autism" AND<br>"brain connectivity" OR "functional connectivity" OR "coherence" AND<br>"EEG" and any other derivatives of these words. |
| **Language** | English |
| **Review of Titles and Abstracts** | EEG, Autism (any version) and connectivity or coherence.<br>No reviews.<br>No studies of medication effects.<br>No neurofeedback.<br>No infants.<br>No single case studies. |
| **Review of Full Papers** | Coherence (any version) variables.<br>Analysis of data in terms of Autism vs. controls (must have controls for relative comparison, grouped by Autism vs. controls) |

| | |
|---|---|
| | Studies with other disorders not Autism, were exclude. |
| **Quality of Data** | Eligibility of study. Describes the source of subjects.<br>RCT (Randomized Clinical Trials) studies.<br>The results of between group statistical comparisons are reported for at least one outcome. |

Table 2: Details of the studies included in this meta-analysis.

| First author and date | Brain region (frequency band) | Coherence | Participants ASD/TD | Cohen's *d* (max) |
|---|---|---|---|---|
| **Chan et al. (2011)** | Short and long range fronto-posterior (Theta) | Enhanced | 21/21 | 1.239 |
| **Mathewson et al. (2012)** | Short intrahemispheric, posterior (Alpha) | Reduced | 15/16 | 1.412 |
| | long range intrahemispheric, fronto-central (Alpha) | Reduced | | |
| **Lazar et al. (2010)** | Intrahemispheric, fronto-central (entire frequency range) | Reduced | 18/14 | 0754 |
| **Lzarev et al. (2010)** | Short and long range (Delta & Theta) | Reduced | 6/8 | 2.701 |
| | Frontal-temporal (Delta) | Enhanced | | |
| | Frontal-temporal (Theta) | Enhanced | | |
| **Le ´veille et al. (2010)** | Short and long range intrahemispheric, Occipital (entire frequency range) | Enhanced | 9/13 | 0.923 |

| | | | | |
|---|---|---|---|---|
| | Short and long range intrahemispheric, Frontal (entire frequency range) | Reduced | | |
| **Duffy et al. (2012)** | Short and long range intrahemispheric (Theta) | Reduced | 447/ 99 | 0.842 |
| | Short and long range intrahemispheric (Alpha) | Reduced | | |
| | Frontal-temporal (Beta) | Reduced | | |
| | Short and long range intrahemispheric (Beta) | Reduced | | |
| **Coben et al. (2008)** | Short and long range intrahemispheric (Delta & Theta) | Reduced | 20/20 | 0.949 |
| | Interhemispheric<br>Frontal (Delta & Theta)<br>Temporal (Delta & Theta)<br>Central/parietal/occipital (Delta & Theta) | Reduced | | |

| | | | | |
|---|---|---|---|---|
| | Interhemispheric Temporal (Alpha ) | Reduced | | |
| | Interhemispheric Central/parietal/occipital (Beta) | Reduced | | |
| **Yeung et al. (2014)** | Short and long range , fronto- posterior, frontal (Theta) | Reduced | 18/18 | 0.727 |
| **Sheikhani et al. (2012)** | Short and long range intrahemispheric, Frontal-temporal, Frontal- Central | Reduced | 17/11 | 1.793 |
| | Temporal (Gamma) | Enhanced | | |
| **Barttfeld et al. (2011)** | Lateral-frontal intrahemispheric (Delta) | Enhanced | 10/10 | 1.910 |
| | Middle frontal (Delta) | Reduced | | |
| | Occipital (Delta) | Reduced | | |

Table 3 : Results of random-effects meta-analysis comparing the relative difference in the impact of variants on functional connectivity.

| | **Effect size and 95% CI** | | | **Heterogeneity** | | | **Tau squared** | |
|---|---|---|---|---|---|---|---|---|
| | Number of studies | Point estimate | Variance | Q-value | P-value | I-squared | Tau squared | Variance |
| **Maximum estimate** | 10 | 1.159 | 0.023 | 13.345 | 0.148 | 32.56 | 0.071 | 0.011 |
| **All estimates** | 26 | 0.807 | 0.010 | 56.984 | 0.000 | 56.128 | 0.119 | 0.005 |

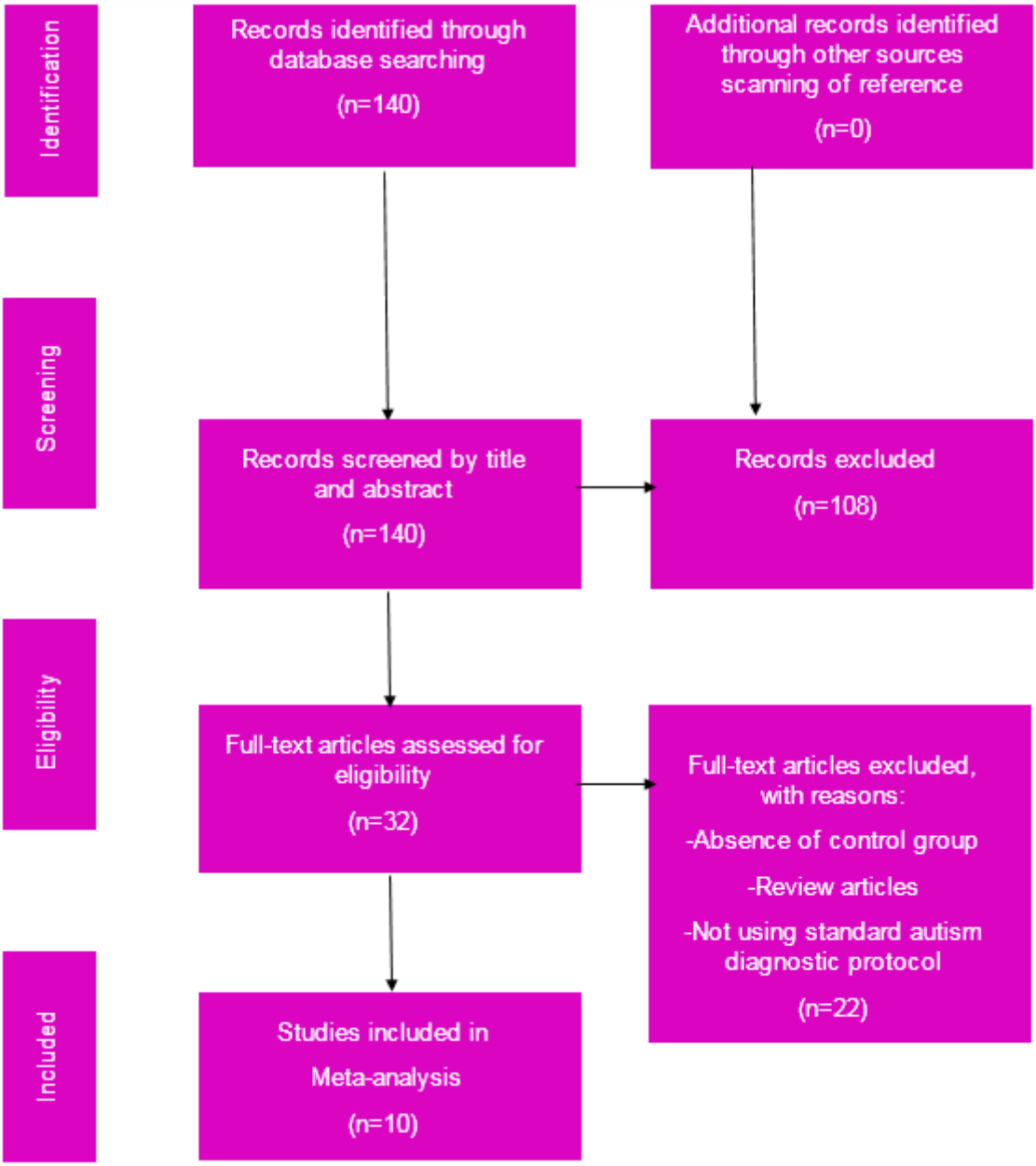


Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flowchart for selection procedure of articles.

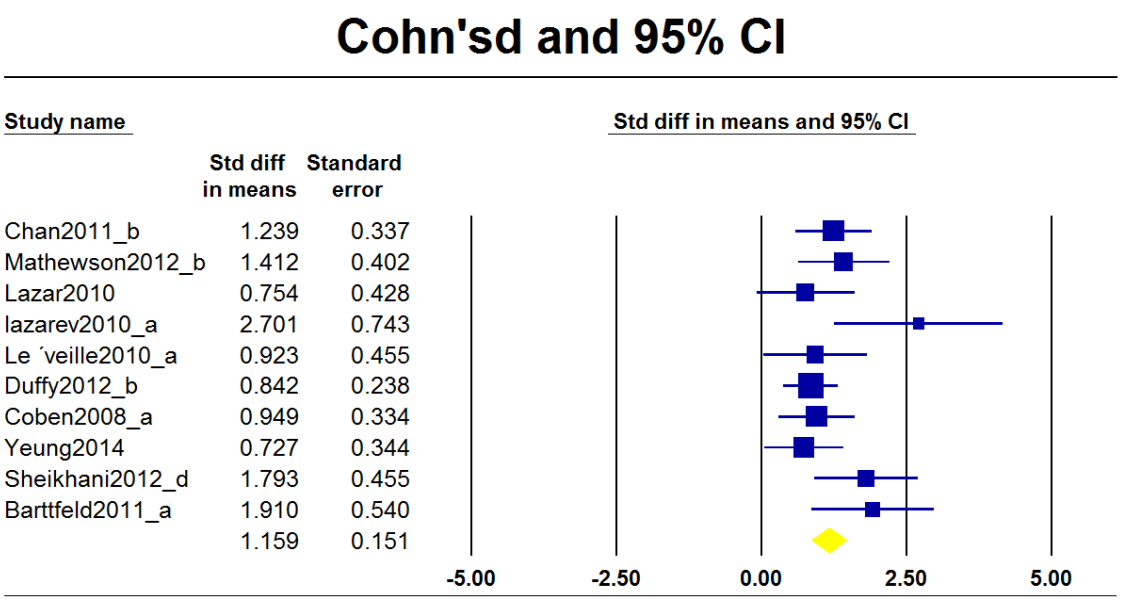


Figure 2: Forest plot considering the largest effect size for each study.

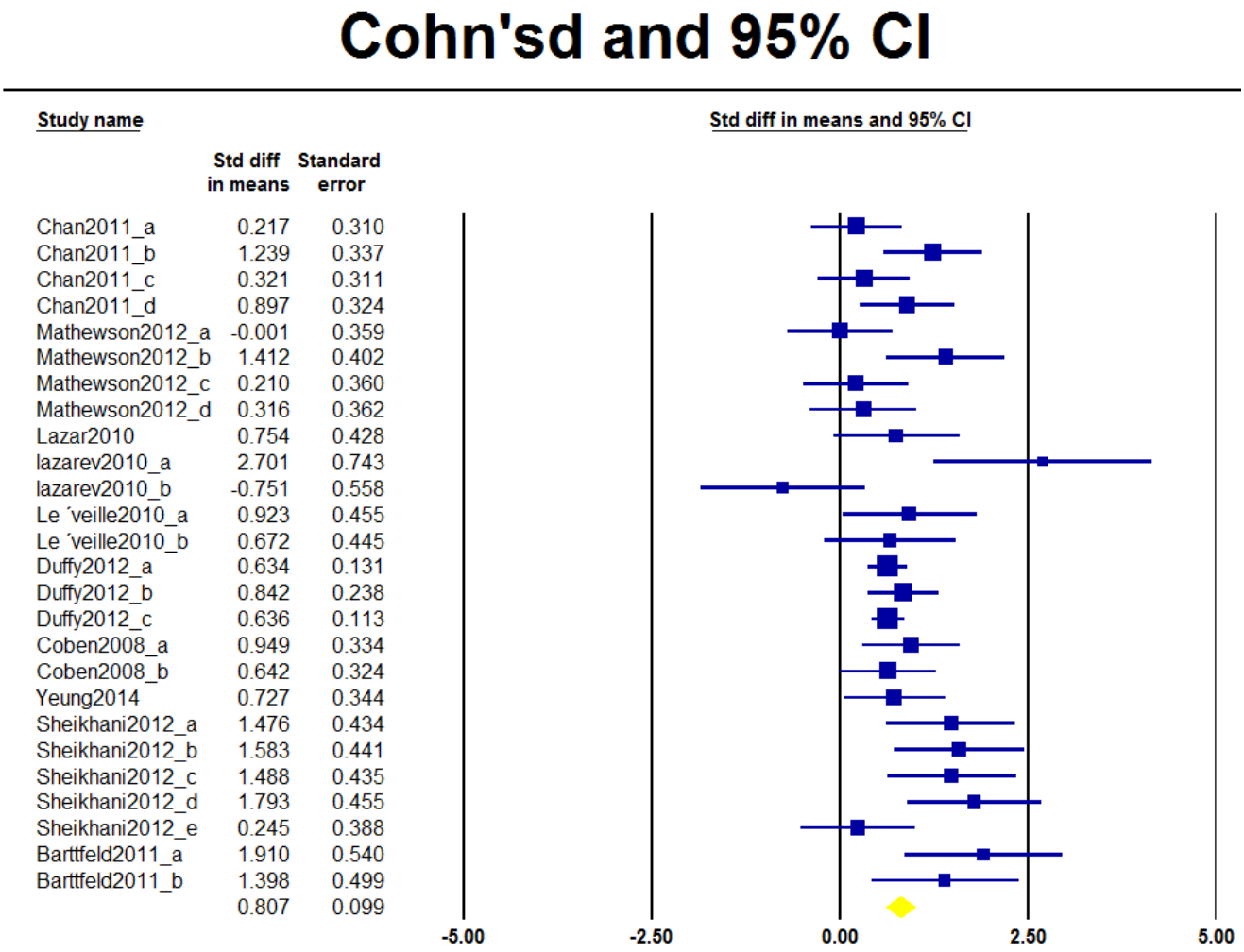


Figure 3: Forest plot considering the all effect sizes of studies.