

## Supplementary Material

**Article Title:** Role of Transcranial Direct Stimulation in the Management of Autism Spectrum Disorder in Children and Adolescents: A Systematic Review and Meta-Analysis

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## Supplementary Table 1. GRADE Pro Assessment of Evidence Certainty

### Summary of findings:

#### TDCS compared to Control in Autism core symptoms post intervention (tDCS vs Control)

**Patient or population:** Autism core symptoms post intervention (tDCS vs Control)

**Setting:** Hospital, Child Development Clinics or Rehabilitation centres

**Intervention:** tDCS

**Comparison:** Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with tDCS				
Autism Treatment Evaluation Checklist (ATEC) scores	The mean autism Treatment Evaluation Checklist (ATEC) scores were <b>75.26</b>	MD <b>8.03 lower</b> (17.51 lower to 1.44 higher)	-	196 (6 RCTs) <sup>a</sup>	⊕○○○ Very low <sup>b,c,d,e</sup>	The evidence is very uncertain about the effect of tDCS on ATEC scores. Sensitivity analysis, excluding one study with possible outcome misinterpretation (Nazari et al., 2023), showed a statistically significant benefit and reduced heterogeneity, suggesting the pooled estimate may be sensitive to this source of bias.
Autism Behavioral Checklist (ABC) scores	The mean autism Behavioral Checklist (ABC) scores were <b>65.37</b>	MD <b>7.53 lower</b> (15.97 lower to 0.91 higher)	-	93 (3 RCTs) <sup>a</sup>	⊕⊕○○ Low <sup>a,b</sup>	The evidence suggests that there is little to no statistically significant difference between the control and the intervention. This could be due to small sample size. Given the wide confidence interval and low certainty of evidence, no definitive conclusions can be drawn.
Childhood Autism Rating Scale (CARS) scores	The mean childhood Autism Rating Scale (CARS) scores were <b>36.27</b>	MD <b>3 lower</b> (7.26 lower to 1.26 higher)	-	116 (3 RCTs)	⊕⊕○○ Low <sup>c,f</sup>	The evidence suggests that there is no statistically significant difference between the control and the intervention. This could be due to high heterogeneity (I <sup>2</sup> = 86%) and small sample size.
Emotional Recognition Task (ERT) scores	-	SMD <b>0.36 higher</b> (1.03 lower to 1.76 higher)	-	67 (3 RCTs)	⊕⊕○○ Low <sup>c,f</sup>	The evidence suggests that tDCS results in little to no difference in emotional Recognition Task (ERT) scores. The SMD was 0.36 higher (95% CI: -1.03 to 1.76), indicating considerable uncertainty about the direction and magnitude of the effect. Given the wide confidence interval and low certainty of evidence, no definitive conclusions can be drawn.”

Summary of findings:

**TDCS compared to Control in Autism core symptoms post intervention (tDCS vs Control)**

**Patient or population:** Autism core symptoms post intervention (tDCS vs Control)

**Setting:** Hospital, Child Development Clinics or Rehabilitation centres

**Intervention:** tDCS

**Comparison:** Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with tDCS				
Social Responsiveness Scale (SRS) scores	The mean social Responsiveness Scale (SRS) scores were <b>141.04</b>	<b>MD 14.95 lower</b> (26.07 lower to 3.96 lower)	-	139 (3 RCTs)	⊕⊕⊕⊕ High	TDCS results in a reduction in social Responsiveness Scale (SRS) scores. The mean SRS score was 14.95 points lower in the tDCS group compared to the control (95% CI: -26.07 to -3.96), indicating a statistically significant and potentially clinically meaningful improvement in social responsiveness, with lower scores reflecting reduced social impairment.
Theory of Mind (ToM)	-	<b>SMD 0.38 higher</b> (0.03 lower to 0.8 higher)	-	98 (3 RCTs)	⊕⊕⊕○ Moderate <sup>c</sup>	tDCS may result in a small improvement in Theory of Mind, although the confidence interval includes the possibility of no effect. This variability may be influenced by the stimulation target, as subgroup analyses indicated greater improvements when the ventromedial prefrontal cortex (vmPFC) was used as the stimulation site.
Inhibitory control	-	<b>SMD 0.28 higher</b> (0.32 lower to 0.87 higher)	-	44 (2 RCTs)	⊕⊕⊕○ Moderate <sup>c</sup>	tDCS may lead to a small improvement in inhibitory control, but the evidence is uncertain and includes the possibility of no effect. The limited sample size and wide confidence intervals across studies contribute to imprecision.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; SMD: standardised mean difference

## Summary of findings:

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### TDCS compared to Control in Autism core symptoms post intervention (tDCS vs Control)

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**Patient or population:** Autism core symptoms post intervention (tDCS vs Control)

**Setting:** Hospital, Child Development Clinics or Rehabilitation centres

**Intervention:** tDCS

**Comparison:** Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with tDCS				

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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## Explanations

<sup>a</sup>1 Non-RCT (Robinson-Agramonte et al. 2021) included in the analysis.

<sup>b</sup>Some concerns regarding allocation concealment and lack of randomization in the non-randomized trial included in the analysis (Robinson-Agramonte et al., 2021). Nazari (2023) had a high risk of bias due to outcome reporting bias or interpretation error.

<sup>c</sup>Sensitivity to outcome misreporting: Nazari et al. (2023) appeared to misinterpret ATEC score changes, which influenced the pooled estimate. Exclusion of this study yielded a lower heterogeneity and more consistent effect.

<sup>d</sup>Statistical analyses indicate heterogeneity ( $I^2 = 87\%$ ); results for the ATEC outcome from Nazari et al. (2023) are attributed to this high heterogeneity.

<sup>e</sup>Downgraded one level for imprecision as the confidence interval includes both meaningful improvement and no effect.

<sup>f</sup>Downgraded one level due to high heterogeneity ( $I^2 = 86\%$ ).

## **Supplementary Material Table 2. Analyses**

### **Analysis group 1: Change in autism core symptoms post intervention (tDCS vs Control)**

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
<u>1.1 Autism Behavioral Checklist (ABC) scores</u>	3	93	Mean Difference (IV, Random, 95% CI)	-7.53 [-15.97, 0.91]
<u>1.2 Autism Treatment Evaluation Checklist (ATEC) scores</u>	6	196	Mean Difference (IV, Random, 95% CI)	-8.03 [-17.51, 1.44]
<u>1.3 Childhood Autism Rating Scale (CARS) scores</u>	3	116	Mean Difference (IV, Random, 95% CI)	-3.00 [-7.26, 1.26]
<u>1.4 Social Responsiveness Scale (SRS) scores</u>	3	139	Mean Difference (IV, Random, 95% CI)	-14.95 [-26.07 to -3.83]
<u>1.5 Emotional Recognition Task (ERT) scores</u>	3	67	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-1.03, 1.76]
<u>1.6 Theory of Mind (ToM)</u>	3	98	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.03, 0.80]
<u>1.7 Inhibitory control</u>	2	44	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.32, 0.87]

### **Analysis group 2: ATEC subscales**

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
<u>2.1 ATEC_Health</u>	4	159	Mean Difference (IV, Random, 95% CI)	-5.30 [-7.58, -3.01]
<u>2.2 ATEC_Social</u>	4	159	Mean Difference (IV, Random, 95% CI)	-3.33 [-4.77, -1.89]

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
<a href="#">2.3 ATEC_Sensory</a>	4	159	Mean Difference (IV, Random, 95% CI)	-2.62 [-4.84, -0.40]
<a href="#">2.4 ATEC_Language</a>	4	159	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.62, 0.82]

### **Analysis group 3: SRS subscales**

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
<a href="#">3.1 SRS_Social communication</a>	3	139	Mean Difference (IV, Random, 95% CI)	-4.48 [-10.10, 1.13]
<a href="#">3.2 SRS_Social Cognition</a>	2	117	Mean Difference (IV, Random, 95% CI)	-0.01 [-6.27, 6.24]
<a href="#">3.3 SRS_Autism Mannerism</a>	2	117	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-3.32, 1.99]
<a href="#">3.4 SRS_Motivation</a>	2	117	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-2.67, 1.08]
<a href="#">3.5 SRS_Social Awareness</a>	2	117	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-2.77, -0.78]

### **Analysis group 4: Subgroup analyses**

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
<a href="#">4.1 ATEC_Total subgrouped by age</a>	6	196	Mean Difference (IV, Random, 95% CI)	-8.03 [-17.51, 1.44]

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
4.1.1 ≤12 years	5	153	Mean Difference (IV, Random, 95% CI)	-7.49 [-18.85, 3.88]
4.1.2 >12-18 years	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.1.3 All ages included upto 18 years	1	43	Mean Difference (IV, Random, 95% CI)	-10.53 [-24.66, 3.60]
<a href="#"><u>4.2 ATEC Total subgrouped by tDCS target</u></a>	6	196	Mean Difference (IV, Fixed, 95% CI)	-9.86 [-12.81, -6.91]
4.2.1 Anodal Left DLPFC	4	137	Mean Difference (IV, Fixed, 95% CI)	-9.95 [-13.00, -6.89]
4.2.2 Anodal Right TPJ	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2.3 Anodal vmPFC	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2.4 Bifrontal DLPFC stimulation	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2.5 Bilateral Anodal stimulation	1	43	Mean Difference (IV, Fixed, 95% CI)	-10.53 [-24.66, 3.60]
4.2.6 Cathodal Left DLPFC	1	16	Mean Difference (IV, Fixed, 95% CI)	-5.30 [-24.36, 13.76]
4.2.7 Cathodal right cerebellar lobe	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2.8 Cz Anodal stimulation	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
<a href="#"><u>4.3 ATEC subgrouped by number of tDCS sessions</u></a>	6	196	Mean Difference (IV, Random, 95% CI)	-8.03 [-17.51, 1.44]

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
4.3.1 >10-20	2	52	Mean Difference (IV, Random, 95% CI)	-16.05 [-32.34, 0.23]
4.3.2 >5-10	2	64	Mean Difference (IV, Random, 95% CI)	1.77 [-21.63, 25.18]
4.3.3 ≤5	2	80	Mean Difference (IV, Random, 95% CI)	-10.09 [-13.48, -6.69]
<a href="#">4.4 Emotional Recognition Task subgrouped by cognitive training</a>	3	67	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-1.03, 1.76]
4.4.1 Simultaneous Cognitive therapy not used	1	21	Std. Mean Difference (IV, Random, 95% CI)	1.85 [0.79, 2.90]
4.4.2 Simultaneous Cognitive Therapy used	2	46	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.90, 0.26]
<a href="#">4.5 TOM subgrouped by tDCS target</a>	3	98	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.03, 0.80]
4.5.1 Anodal Left DLPFC	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.75, 0.85]
4.5.2 Anodal Right TPJ	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.5.3 Anodal vmPFC	1	42	Std. Mean Difference (IV, Random, 95% CI)	0.70 [0.04, 1.36]
4.5.4 Bifrontal DLPFC stimulation	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.5.5 Bilateral Anodal stimulation	1	32	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.41, 0.99]
4.5.6 Cathodal Left DLPFC	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
4.5.7 Cathodal right cerebellar lobe	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.5.8 Cz Anodal stimulation	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
<a href="#">4.6 ABC subgrouped by tDCS target</a>	3	93	Mean Difference (IV, Random, 95% CI)	-7.53 [-15.97, 0.91]
4.6.1 Anodal Left DLPFC	2	77	Mean Difference (IV, Random, 95% CI)	-7.47 [-18.96, 4.02]
4.6.2 Anodal Right TPJ	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.6.3 Anodal vmPFC	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.6.4 Bifrontal DLPFC stimulation	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.6.5 Bilateral Anodal stimulation	1	43	Mean Difference (IV, Random, 95% CI)	-10.50 [-24.63, 3.63]
4.6.6 Cathodal Left DLPFC	1	16	Mean Difference (IV, Random, 95% CI)	-4.90 [-25.05, 15.25]
4.6.7 Cathodal right cerebellar lobe	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.6.8 Cz Anodal stimulation	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
<a href="#">4.7 SRS Total Subgrouped by tDCS target</a>	3	139	Mean Difference (IV, Random, 95% CI)	-14.91 [-25.68, -4.15]
4.7.1 Anodal Left DLPFC	1	22	Mean Difference (IV, Random, 95% CI)	0.99 [-20.66, 22.64]

<b>Analysis or subgroup title</b>	<b>No. of studies</b>	<b>No. of participants</b>	<b>Statistical method</b>	<b>Effect size</b>
4.7.2 Anodal Right TPJ	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.3 Anodal vmPFC	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.4 Bifrontal DLPFC stimulation	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.5 Bilateral Anodal stimulation	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.6 Cathodal Left DLPFC	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.7 Cathodal right cerebellar lobe	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.7.8 Cz Anodal stimulation	2	117	Mean Difference (IV, Random, 95% CI)	-18.29 [-27.33, -9.24]