

Using non-invasive transcranial stimulation to improve motor and cognitive function in Parkinson's disease: a systematic review and meta-analysis

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Supplementary Table 1. Study characteristics of included studies for both rTMS and TES

	Reference	N (% male)	Age (mean yrs)	Disease duration (mean yrs)	H&Y stage	Medication during intervention	Outcome measure (Motor/Cognitive)
rTMS							
	Siebner et al. (2000)	12 (33)	58	6.3	1-2.5	Off	Motor: Finger ballistic aiming task
	Boylan et al. (2001)	10 (60)	63.5	6.6	2.0-3.0	Off	Motor: UPDRS III, Hand RT and MT, TUG, timed HPS
	Shimamoto et al. (2001)	18	65	7	1.5-4.0	On & Off	Motor: H&Y scale, England ADL scale, UPDRS III
	Okabe et al. (2002)	85 (60)	67	8.5	2.0-3.0	On	Motor: Total and UPDRS III
	Ikeguchi et al. (2003)	12 (25)	69	7.8	1.0-4.0	On	Motor: ADL, UPDRS III
	Khedr et al. (2003)	36 (69)	57.7	3.26	2.0-3.0	Off	Motor: UPDRS III, Walking speed
	Lefaucheur et al. (2004)	12 (58)	64	11	2.5-4.0	On & Off	Motor: UPDRS III, Ballistic finger task, PPT
	Koch et al. (2005)	8 (50)	60.8	16.5	-	On	Motor: AIMS, UPDRS
	Khedr et al. (2006)						
	Group 1	10	53.5	1.45	1.0-2.5	Off	Motor: UPDRS III, WT, FTT, motor self-assessment scale
	Group 2	25	62.5	5.8	3.0-5.0	Off	Motor: UPDRS III, WT, FTT, motor self-assessment scale

Group 3	10	60.2	4.6	3.0-5.0	Off	Motor: UPDRS III, WT, FTT, motor self-assessment scale
Group 4	10	60.6	4.6	3.0-5.0	Off	Motor: UPDRS III, WT, FTT, motor self-assessment scale
Lomarev et al. (2006)	18 (83)	64.5	12.3	2.0-4.0	On	Motor: 10m WT, complex movement test
del Olmo et al. (2007)	13 (46)	61.7	3.8	1.0-3.0	On	Motor: UPDRS III, FTT, reaching and grip movement, gait speed
Hamada et al. (2008)	98 (55)	66.4	8	2.0-4.0	On	Motor: Total and UPDRS III
Filipovic et al. (2009)	10 (50)	64.5	15.6	-	On	Motor: UPDRS III, GCRS
Hamada et al. (2009)	98 (55)	66.4	8	2.0-4.0	On	Motor: UPDRS III
Sedlackova et al. (2009)	10 (90)	63.7	7.8	-	On	Motor: UPDRS III; Cognition: CRT, VFT, WM, TMT A&B, F/BDS
Filipovic et al. (2010)	10 (50)	64.5	15.6	2.0-4.0	On	Motor: UPDRS III
Pal et al. (2010)	22 (50)	68.5	-	2.0-3.0	On	Motor: UPDRS III, H&Y scale; Cognitive: TMT A&B, Stroop test
Benninger et al. (2011)	26 (69)	63.9	8.7	2.0-4.0	On	Motor: 10m WT, hands opening/closing and elbow flexion, UPDRS III; Cognitive: SRTT

Gonzalez-Garcia et al. (2011)	17 (65)	64.4	-	2.0-3.0	On	Motor: UPDRS III, FTT; Cognitive: Random finger sequence test
Benninger et al. (2012)	26 (77)	64.1	9	2.0-4.0	On	Motor: 10m WT, hands opening/closing and elbow flexion, UPDRS III, FOG-Q; Cognitive: SRTT
Maruo et al. (2013)	21 (47)	63	12	2.0-4.0	On	UPDRS III/10m WT/finger tapping test/self-assessment motor score/VAS of motor symptoms
Shirota et al. (2013)						
Group 1- 1Hz TMS	34 (41)	68.8	8.5	2.0-4.0	On	Motor: UPDRS III
Group 2- 10Hz TMS	34 (35)	67.9	7.8	2.0-4.0	On	Motor: UPDRS III
Group 3- Sham	34 (56)	65.7	7.6	2.0-4.0	On	Motor: UPDRS III
Randhawa et al. (2013)	10 (90)	70.5	5.1	1-1.5	On	Motor: Handwriting kinematics
Lee et al. (2014)	20 (70)	71.6	4.7	3.0-4.0	On	Motor: UPDRS III, turning steps and time, TUG, FOG-Q
TES						
Boggio et al. (2006)						
Exp 1- 1mA	18 (67)	59.2 ±9.9	13.7	2.3 ± 0.9	Off	n-back task
Exp 2- 2mA		61.0 ± 21.1	12.7	2.4 ± 0.7	Off	n-back task
Fregni et al. (2006)						
Exp 1- Anodal tDCS	9 (56)	59.2 ± 3.3	13.7	2.4 ± 0.4	Off	Motor: UPDRS III/SRT/PPT

Exp 2- Cathodal tDCS	8 (88)	65.9 ± 4.6	10.7	2.3 ± 0.3	Off	Motor: UPDRS III/SRT/PPT
Benninger et al. (2010)	25 (64)	63.9 ± 8.7	9.9	2.0-4.0	On	Motor: 10m WT, hands opening/closing and elbow flexion, UPDRS III; Cognitive: SRTT
Krause et al. (2013)	10 (50)	49.4 ± 3.1	1.9	1.0-2.0	On	Motor: Fast FFT, diadochokinesia test, isometric power test
Doruk et al. (2014)	18 (33)	61.0 ± 8.0	-	1.3 ± 1.1	On	Motor: UPDRS III, SRT, FT, PPT, buttoning up, HPS, 4-CRT; Cognitive: TMT A&B, WCST, PCL, F/BDS, Stroop test, HPVOT, CPM
Manenti et al. (2014)	10 (60)	67.1 ± 7.2	8.1	2.0-4.0	On	Motor: TUG
Valentino et al. (2014)	10 (50)	72.3 ± 3.6	11	2.0-3.0	On	Motor: UPDRS III, SWST, FOG-Q
Ferrucci et al. (2015)	9 (56)	74.3 ± 7.5	10.8	1.0-2.5	On	Motor: UPDRS III and IV; Cognitive: VAT, SRTT
Salimpour et al. (2015)						
Exp 1	15 (60)	60 ± 7.4	8	1.0-2.5	On	Motor: UPDRS III
Exp 2	10 (60)	60 ± 6.9	7	1.0-2.5	On	Motor: UPDRS III
Exp 3	10 (90)	62 ± 10.8	9	1.0-2.5	On	Motor: UPDRS III
Exp 4	10 (60)	61 ± 9.2	8	1.0-2.5	On	Motor: UPDRS III

ADL- Activity of daily living; AIMS- Abnormal Involuntary Movement Scale; CDRS- Clinical Dyskinesia Rating Scale; CPM- Coloured progressive Matrices; CRT- Choice reaction time; F/BDS- Forwards/backwards digit span; FOG-Q- Freezing of gait questionnaire; FTT- Finger tapping task; GCRS- Graded Clinical Rating Scale; H&Y- Hoehn & Yahr; HPS- Hand pronation-supination; HPVOT- Hooper visual organisation test; MT- Movement time; PPT- Purdue pegboard test; RT- Reaction time; SRT- Simple reaction time; SRTT- Serial reaction time test; SWST- Stand walk sit test; TMT- Trail-making test; TUG- Timed up and go; VAS- Visual analogue scale; VAT- Visual attention task; VFT- Verbal fluency task; WCST- Wisconsin card sorting test; WM- Working memory; WT- Walking test.

Supplementary Table 2. Stimulation parameters used for rTMS and TES studies

	Reference	Site/coil	Freq.	Intensity	No. pulses	No. sessions
rTMS						
	Siebner et al. (2000)	M1/Figure-8	5 Hz	90% rMT	2250	Single
	Boylan et al. (2001)	SMA/Figure-8	10 Hz	110% rMT	2000	Single
	Shimamoto et al. (2001)	Frontal (F3)/circular	0.2 Hz	700 V	30 each hemisphere	1 session/ week x 8 weeks
	Okabe et al. (2002)	1. M1 2. Occipital (inion) /circular	0.2 Hz	110% aMT	100	1 session/ week x 8 weeks
	Ikeguchi et al. (2003)	1. PFC and OCC /circular	0.2 Hz	70% max SO	30 each hemisphere	6 sessions /week x 2 weeks
	Khedr et al. (2003)	M1/Figure-8	5 Hz	120% rMT	100 each hemisphere	10 consecutive days
	Lafaucheur et al. (2004)					
	Intervention 1 (L-dopa)	M1/Figure-8	NA	NA	NA	Single session
	Intervention 2	M1/Figure-8	5 Hz	80% rMT	600	Single session
	Intervention 3	M1/Figure-8	10 Hz	80% rMT	2000	Single session

Koch et al. (2005)	Intervention 1	SMA/Figure-8	1 Hz	90% aMT	900	Single session
	Intervention 2	SMA /Figure-8	5 Hz	110% aMT	900	
Khedr et al. (2006)	Group 1	M1	25 Hz	100% rMT	1000 each hemisphere	Single session
	Group 2	M1	25 Hz	100% rMT		
	Group 3	M1	10 Hz	100% rMT		
	Group 4	OCC/Figure-8	25 Hz	100% rMT		
Lomarev et al. (2006)	M1 & DLPFC/solid core		25 Hz	100% rMT	300 per site and side	2 sessions/week x 4 weeks
del Olmo et al. (2007)	DLPFC/Figure-8		10 Hz	90% rMT	450 (3 x 150-pulse trains)	10 consecutive days
Hamada et al. (2008)	SMA/Figure-8		5 Hz	110% aMT	1000 (20 x 50-pulse trains)	Single session
Sedlackova et al. (2009)	PMd, DLPC & OCC /Figure-8		10 Hz	100% rMT	1350 (15 x 30-pulse trains)	Single session

Filipovic et al. (2009)	M1/figure-8	1 Hz	90 rMT	1800 (3 x 600-pulse trains)	4 consecutive days/week x 2 weeks
Filipovic et al. (2010)	M1/Figure-8	1 Hz	90% aMT	1800 (3 x 600-pulse trains)	Single session
Hamanda et al. (2009)	SMA/Figure-8	5 Hz	110% aMT	1000 (20 x 50-pulse trains)	1 session/week x 8 weeks
Pal et al. (2010)	DLPC/Figure-8	5 Hz	90% rMT	600 (12 x 10-second trains)	10 consecutive days
Benninger et al. (2011)	M1 & DLPC	50 Hz	80% aMT	NA	4 consecutive days/week x 2 weeks
Gonzalez-Garcia et al. (2011)	M1/Figure-8	25 Hz	80% rMT	1000 (10 x 100-pulse trains)	5 consecutive days/month x 3 months
Benninger et al. (2012)	M1/Figure-8	50 Hz	80% aMT	Both hemispheres	4 consecutive days/week x 2 weeks
Maruo et al. (2013)	M1/Figure-8	10 Hz	100% rMT	1000	3 consecutive days

Shirota et al. (2013)	Exp 1.	SMA/Figure-8	1 Hz	110% aMT	1000 (20 x 50-pulse trains)	Single session
	Exp 2.	SMA/Figure-8	10 Hz		1000 (20 x 50-pulse trains)	
Randhawa et al. (2013)		SMA/Figure-8	5 Hz	110% of rMT	1200	Single session
Lee et al. (2014)		M1 & SMA/Double cone DLPFC/Figure-8	10 Hz	90% rMT	1000 (20 x 50-pulse trains)	Single session

Reference	Site	Electrode montage	Intensity/electrode surface/ current density	Duration	No sessions
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TES

Boggio et al. (2006)

Exp 1	Left DLPC and M1	Anodal	1mA/35cm ² /0.029mA.cm ²	20 mins	Single session
Exp 2	Left DLPC and M1		2mA/35cm ² /0.057mA.cm ²		

Fregni et al. (2006)

Exp A	M1	Anodal	1mA/35cm ² /0.029mA.cm ²	10 mins	Single session
Exp B	M1	Cathodal	1mA/35cm ² /0.029mA.cm ²		

Exp C	DLPFC	Anodal	1mA/35cm ² /0.029mA.cm ²		
Beninger et al. (2010)	M1 and PFC	Anodal	2mA/97.5cm ² /0.021mA.cm ²	20 mins	3/week x 2.5 weeks (8 total)
Krause et al. (2013)	M1	Anodal (tACS)	1mA/35cm ² /0.029mA.cm ²	15 mins	Single session
Doruk et al. (2014)					
Group 1.	Left DLPFC	Anodal	2mA/35cm ² /0.057mA.cm ²	20 mins	5 consecutive/week x 2 weeks
Group 2.	Right DLPFC				
Manenti et al. (2014)	Left or right DLPFC	Anodal	2mA/35cm ² /0.057mA.cm ²	7 mins	Single session
Valentino et al. (2014)	M1	Anodal	2 mA	20 mins	1/day x 5 consecutive days
Ferrucci et al. (2015)	M1	Bilateral	2mA/35cm ² /0.057mA.cm ²	20 mins	1/day x 5 consecutive days
Salimpour et al. (2015)					

Exp 1.	M1	Bilateral	1mA/25cm ² /0.04mA. cm ²		Single session
Exp 2.	M1	Bilateral	2mA/25 cm ² /0.08mA.cm ²	25 mins	Single session
Exp 3. Double blinded tDCS	M1	Anodal or cathodal	2mA/25 cm ² /0.08mA.cm ²		3 consecutive days
Exp 4. Long term tDCS	M1	Bilateral	2mA/25cm ² /0.08mA. cm ²		5 consecutive days

aMT- Active motor threshold; DLPFC- Dorsolateral prefrontal cortex; M1- Primary motor cortex; PMd- Dorsal premotor cortex; SMA- Supplementary motor area; OCC- Occipital cortex; rMT- Resting motor threshold; tACS- Transcranial alternating current stimulation.

Supplementary Table 3. Quality of study design as measured by the PEDro scale.

CRITERIA	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>	<u>(/10)</u>
<u>rTMS studies</u>											
Siebner et al. (2000)	Y	NA	Y	Y	N	N	Y	Y	Y	Y	7
Boylan et al. (2001)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Shimamoto et al. (2001)	N	N	Y	Y	N	N	Y	Y	N	Y	5
Okabe et al. (2002)	Y	N	Y	Y	N	Y	N	Y	Y	Y	7
Ikeguchi et al. (2003)	N	N	Y	N	N	N	Y	Y	Y	Y	6
Khedr et al. (2003)	Y	Y	Y	Y	N	Y	Y	Y	N	Y	8
Lafaucheur et al. (2004)	Y	NA	Y	Y	N	Y	Y	Y	Y	Y	8
Koch et al. (2005)	N	NA	Y	Y	N	Y	Y	Y	Y	Y	7
Khedr et al. (2006)	N	N	N	Y	N	N	Y	Y	Y	Y	5
Lomarev et al. (2006)	Y	Y	N	Y	N	Y	Y	Y	Y	Y	8
del Olmo et al. (2007)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Hamada et al. (2008)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Sedlackova et al. (2009)	Y	NA	Y	Y	N	N	Y	Y	Y	Y	7
Filipovic et al. (2009)	Y	NA	Y	Y	N	N	Y	Y	Y	Y	7
Hamada et al. (2009)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Filipovic et al. (2010)	Y	NA	Y	Y	N	N	Y	Y	Y	Y	7
Pal et al. (2010)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Benninger et al. (2011)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Gonzalez-Garcia et al. (2011)	N	N	Y	N	N	N	Y	Y	Y	Y	5
Benninger et al. (2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Maruo et al. (2013)	Y	NA	Y	Y	N	Y	Y	Y	Y	Y	9
Shirota et al. (2013)	Y	NA	Y	Y	N	Y	Y	Y	Y	Y	8
Randhawa et al. (2013)	Y	NA	Y	Y	Y	N	Y	Y	Y	Y	8
Lee et al. (2014)	Y	NA	Y	Y	N	Y	Y	Y	Y	Y	8
<u>TES studies</u>											
Boggio et al. (2006)	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Fregni et al. (2006)	N	N	Y	Y	N	Y	Y	y	y	y	7
Benninger et al. (2010)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Krause et al. (2013)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Doruk et al. (2014)	Y	N	Y	Y	N	Y	N	Y	Y	Y	7
Manenti et al. (2014)	N	N	Y	Y	N	Y	Y	Y	Y	Y	7
Valentino et al. (2014)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Ferrucci et al. (2015)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Salimpour et al. (2015)	N	N	N	Y	N	N	N	Y	Y	Y	4

Mean = 7.5

Supplementary Table 4. Assessment of bias using the Cochrane risk of bias assessment scale.

	<u>Sequence generation</u>	<u>Allocation concealment</u>	<u>Blinding of participants, personnel and outcomes</u>	<u>Incomplete outcome data</u>	<u>Selective outcome reporting</u>	<u>Other source of bias</u>
<u>rTMS studies</u>						
Siebnner et al. (2000)	L	U	L	L	U	U
Boylan et al. (2001)	L	U	L	L	L	U
Shimamoto et al. (2001)	U	U	U	L	L	L
Okabe et al. (2002)	L	U	L	L	L	L
Ikeguchi et al. (2003)	U	U	U	L	L	U
Khedr et al. (2003)	L	L	L	L	L	L
Lafaucheur et al. (2004)	U	U	L	L	L	L
Koch et al. (2005)	U	U	U	L	L	L
Khedr et al. (2006)	U	U	U	L	L	L
Lomarev et al. (2006)	U	U	U	L	L	L
del Olmo et al. (2007)	L	U	U	L	L	L
Hamada et al. (2008)	L	U	L	L	L	L
Filipovic et al. (2009)	L	U	L	U	U	L
Hamada et al. (2009)	L	L	L	L	L	L
Sedlackova et al. (2009)	U	U	U	L	L	L
Filipovic et al. (2010)	L	U	L	U	U	L
Pal et al. (2010)	L	L	L	L	L	L
Benninger et al. (2011)	L	L	U	L	L	L
Gonzalez-Garcia et al. (2011)	U	U	L	L	L	L
Benninger et al. (2012)	L	L	L	L	L	L
Maruo et al. (2013)	L	L	L	L	L	L
Shirota et al. (2013)	L	L	L	L	L	L
Randhawa et al. (2013)	U	L	L	L	L	U
Lee et al. (2014)	L	U	U	L	L	L
<u>TES studies</u>						
Boggio et al. (2006)	U	U	U	L	L	L
Fregni et al. (2006)	U	U	L	L	L	U
Benninger et al. (2010)	L	L	L	L	L	L
Krause et al. (2013)	U	U	L	L	U	L
Doruk et al. (2014)	L	L	L	L	L	L
Manenti et al. (2014)	U	U	U	L	L	L
Valentino et al. (2014)	L	U	L	L	L	L
Ferrucci et al. (2015)	L	U	L	L	L	L
Salimpour et al. (2015)	U	U	U	L	L	L
Low risk	19	10	21	31	29	28
High risk	0	0	0	0	0	0
Unclear	14	21	12	2	3	3