QUESTION

Should active neuromodulation (tDCS, TMS) vs. sham neuromodulation be used for all individuals with Friedreich ataxia?	
POPULATION:	all individuals with Friedreich ataxia
INTERVENTION:	active neuromodulation (tDCS, TMS)
COMPARISON:	sham neuromodulation
MAIN OUTCOMES:	Cognitive function;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 1/7 indicated disturbance of cognitive function was probably not serious, 3/7 indicated probably serious, 3/7 indicated serious. 4/7 indicated disturbance of cognitive function was probably not urgent, 3/7 indicated urgent. 2/7 indicated disturbance of cognitive function was probably not a priority, 2/7 indicated probably a priority, 2/7 indicated priority, 1/7 indicated varies/sometimes a priority. (Aug 2020).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		Needs to be tested in individuals with FRDA Need to understand neurophysiological effects of NIBS to establish treatment effects in the future.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with sham neuromodulation	Risk difference with active neuromodulation (tDCS, TMS)

Cognitive function assessed with: Frontal Assessment Battery	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c]	-	24 patients with spinocerebellar ataxia type 3, multiple systems atrophy cerebellar type, or post-lesion ataxia were randomised to five sessions each of sham and active cerebellar deep repetitive transcranial magnetic stimulation in randomised order. There were no significant differences in the FAB after active or sham rTMS. (Franca et al 2020).

1. Franca C., de Andrade D.C.,Silva V. et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. Parkinsonism & Related Disorders; 2020.

a. Participants has diagnoses of spinocerebellar ataxia and multiple system atrophy (not FRDA).
b. Only one published study with small sample size (n=4).
c. Confidence intervals not reported.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with sham neuromodulation	Risk difference with active neuromodulation (tDCS, TMS)
Cognitive function assessed with: Frontal Assessment Battery	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c]	-	24 patients with spinocerebellar ataxia type 3, multiple systems atrophy cerebellar type, or post-lesion ataxia were randomised to five sessions each of sham and active cerebellar deep repetitive transcranial magnetic stimulation in randomised order. There were no significant differences in the FAB after active or sham rTMS. (Franca et al 2020).	

	1. Franca C., de Andrade D.C.,Silva V. et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. Parkinsonism & Related Disorders; 2020. a. Participants has diagnoses of spinocerebellar ataxia and multiple system atrophy (not FRDA). b. Only one published study with small sample size (n=4). c. Confidence intervals not reported.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low certainty of evidence as per the evidence profile table.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Cognitive function assessed with: Frontal Assessment Battery</td><td>IMPORTANT[a]</td><td>⨁◯◯◯ VERY LOW[b,c,d]</td></tr></table> a. Identified as critical (1/6), important (3/6), low importance (2/6) by people with FA and important by expert authors on the topic. b. Participants has diagnoses of spinocerebellar ataxia and multiple system	Individuals with FRDA still unaware of cognitive impairment.

	atrophy (not FRDA). c. Only one published study with small sample size (n=4). d. Confidence intervals not reported.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		No evidence of benefit in FRDA. Trial needed – safe and interesting.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if the intervention was acceptable (weighing up the balance between benefits, harms and costs). 1/5 indicated neuromodulation to assist with thinking for all people with FA was not reasonable, 1/5 indicated probably reasonable, 1/5 indicated more informatoin on benefits and potential harms required, 2/5 indicated didn't know if reasonable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

We recommend that clinicians should not use active neuromodulation (tDCS, TMS) as part of clinical practice to improve cognitive function in individuals with Friedreich ataxia.

Justification

There are no data available to support positive effects of active neuromodulation to improve cognitive function in individuals with Friedreich ataxia.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with concerns about cognitive function.

Research priorities

Key research priorities in this area include identifying and evaluating the most appropriate method of active neuromodulation (including mode of intervention, montage, dosage, etc) to improve cognitive function in individuals with Friedreich ataxia. This should be evaluated by a RCT comprising active and sham neuromodulation. In addition, neurophysiological studies are required to delineate the neural mechanisms underlying potential efficacy of neuromodulation in enhancing cognitive function in Friedreich ataxia.