PAS-induced recovery of intracortical inhibition in patients with ALS

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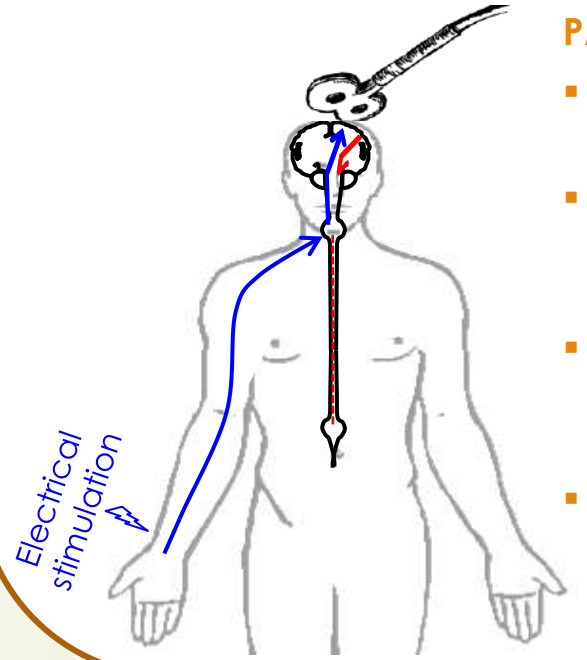
Introduction

- Evidence from transcranial magnetic stimulation (TMS) studies indicate that cortical hyperexcitability is an early mechanism involved in selective motor neuron death [1].
- In this view, electrophysiogical methods that are able to modulate the cortical excitability may help to improve the balance between excitation and inhibition in the motor cortex in attempt to slow down the disease progression.
- Paired associative stimulation (PAS) combines TMS applied over the motor cortex and electrical stimulation of peripheral nerve afferents. This method induces changes in synaptic transmission in cortical and spinal neuron networks that outlast the period of application [2].
- To date, only one study has revealed modification in motor evoked potentials (MEPs) after PAS in ALS [3].
- This study aims to explore the effects of PAS on intracortical inhibition (ICI) which is impaired in sporadic and familial ALS [1].

Method

- Fourteen newly-diagnosed ALS patients were included (54-77 years, 65.9 ± 2.2 yrs , 3 females).
- Short and long ICI were explored using electromyogram recordings and paired-pulse TMS methods [4].
- TMS was assisted by navigated brain device to ensure that cortical stimulating conditions were constant throughout the experiment.
- Both inhibitions were estimated in wrist muscles before and 60 minutes after one session of PAS [2,5]



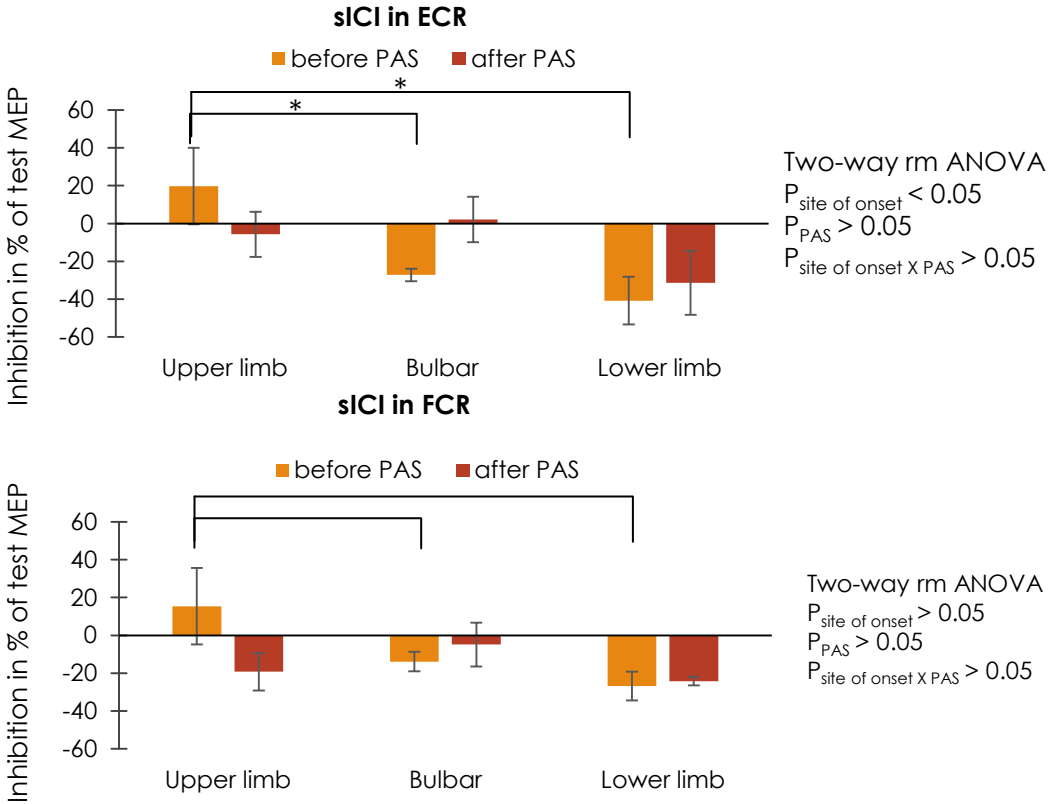
PAS Paradigm

- Repeated stimulation (N=200)
- Focal TMS was applied over the arm motor area
- TMS was combined with electrical stimulation of radial nerve afferents.
- Interstimulus interval was set at 25 ms

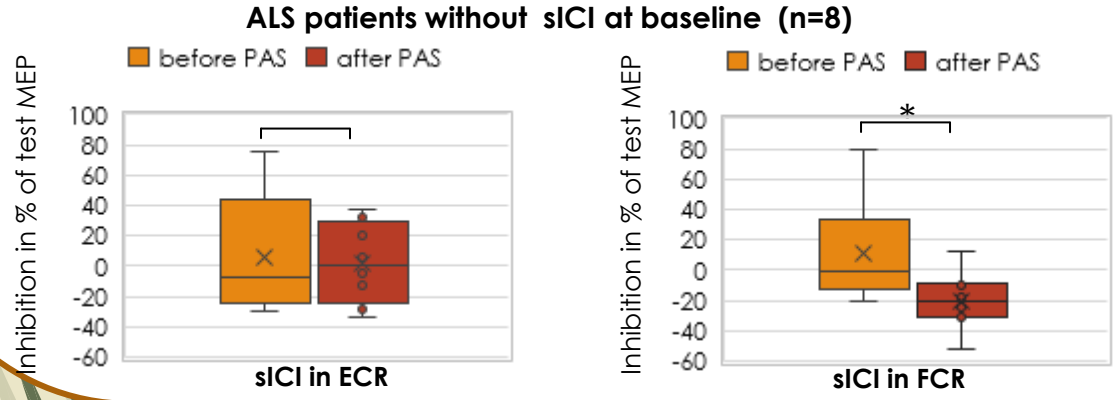
Results

Patients	sICI before PAS in ECR	sICI after PAS in ECR	sICI before PAS in FCR	sICI after PAS in FCR
P1	-57.85***	-41.52***	-40.51***	-22.33***
P2	74.95	-28.87	0.02	-24.30
P3	-16.68	36.71*	-20.10	-8.15
P4	-5.18	-4.18	-30.46***	8.28
P5	-3.22	-33.75**	43.15	-17.99*
P6	-29.46	20.40	-28.05*	16.65
P7	-27.93	6.40	-15.18	-52.56
P8	60.45	31.77	79.48	-9.80
P9	-32.73***	-17.50	-2.88	-31.31**
P10	-9.96	-13.11	-5.08	-28.64
P11	-64.72***	-74.11***	-28.22**	-18.73***
P12	-23.08**	0.43	-1.11	-28.03
P13	-34.17*	-29.41	-17.29*	26.46
P14	-30.63***	2.99	-33.50	-27.11**
Mean	**-14.30 ± 11.1**	**-10.27 ± 7.4**	**-7.12 ± 8.7**	**-15.54 * ± 5.6**

Individual values of sICI were estimated in extensor carpis radialis (ECR) and in flexor carpis radialis (FCR). Inhibitions were expressed in % of test MEP. Significance was calculated using one-sample signed ranked test. Values with an asterisk indicate a significant P-value. Significance was set at $P < 0.05$ (* P<0.05; ** P<0.01; *** P<0.001). Mean values are shown ± SEM



Histograms show the means level of sICI expressed in % of test MEP estimated in ECR and in FCR. ALS patients were stratified in three subgroups to evaluate the influence of the site of onset, location of the first symptoms on level of sICI. Significance was calculated using two way repeated measures ANOVA. Values with an asterisk indicate a significant P-value. Significance was set at $P < 0.05$. Mean values are shown ± SEM



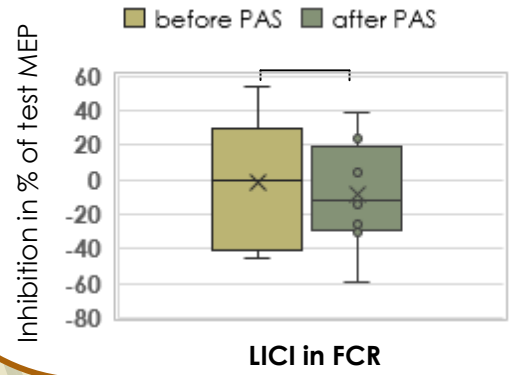
Box plot chart illustrating the distribution of the level of SICI expressed in % mean test MEP in a subgroup of ALS patient without sICI in ECR and FCR at baseline . Wilcoxon signed-rank test were used to compare the level of SICI estimated before and after PAS. Values with an asterisk indicate a significant P-value. Significance was set at $P < 0.05$

Results

Patients	LICI before PAS in ECR	LICI after PAS in ECR	LICI before PAS in FCR	LICI after PAS in FCR
P1	-19.35	-25.04	-38.54***	-18.44*
P2	-32.17	12.00	-52.00***	0.70
P3	-24.04	-9.01	60.10***	-12.23
P4	6.97	5.44	-21.42***	-63.70***
P5	-11.51	-7.45	-1.77	-25.43
P6	-14.48***	18.77	24.16	3.54
P7	-8.16	-25.02	-45.75	-59.85***
P8	-14.21	41.33***	-28.51	24.23
P9	-16.10	8.01	-44.68	-9.83
P10	-85.28***	-79.91***	-87.24***	-56.76
P11	-46.21	-12.10	1.76	-14.36
P12	16.89*	43.91*	-80.63***	-76.75***
P13	-41.51***	138.49	53.24	38.24
P14	-10.592	2.27	30.68	-30.124
Mean	**-21.42* ± 11.1**	**2.89 ± 7.4**	**-16.47 ± 9.8**	**-21.48* ± 5.3**

Individual values of LICI were estimated in ECR and in FCR. Inhibitions were expressed in % of test MEP Significance was calculated using one-sample signed ranked test. Values with an asterisk indicate a significant P-value. Significance was set at $P < 0.05$ (* P<0.05; ** P<0.01; *** P<0.001). Mean values are shown ± SEM

ALS patients without LICI at baseline (n=8)



Box plot chart illustrating the distribution of the level of SICI expressed in % mean test MEP in a subgroup of ALS patient without LICI at baseline . Wilcoxon signed-rank test was used to compare the level of SICI estimated in FCR before and after PAS. Values with an asterisk indicate a significant P-value. Significance was set at $P < 0.05$

Conclusion

- The main finding is that PAS can enhance sICI and LICI evoked in the motor cortex in ALS patients .
- In patients who exhibited the more depressed inhibitions , PAS can help ICI to recover so as to counteract cortical hyperexcitability involved in motor neuron death.
- Variations of sICI induced by PAS depend on clinical profile of patients meaning that PAS may provide clue to forecast patients likely to respond to neuro-modulation methods.
- Further investigations are needed to shed light on potential of PAS paradigms to induce long term neuroplasticity to develop new therapeutic approaches in ALS.

References

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