INSPIRATORY- AND FINGER-FLEXION-RELATED CORTICAL POTENTIALS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Janez Zidar

Institute of Clinical Neurophysiology, University Medical Centre, Ljubljana, Slovenia

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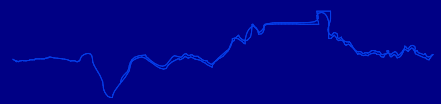
Amyotrophic lateral sclerosis

- Progressive and terminal neurodegenerative disease.
- Progression is relenting and leads to death in 2–4 years.
- Combination of the upper and lower motor neuron features.
- Any body part (e.g. limbs, bulbar muscles, and diaphragm) can be affected initially.
- A diagnosis relies on clinical symptoms and signs, and on the use of investigations to exclude other causes of impairment.



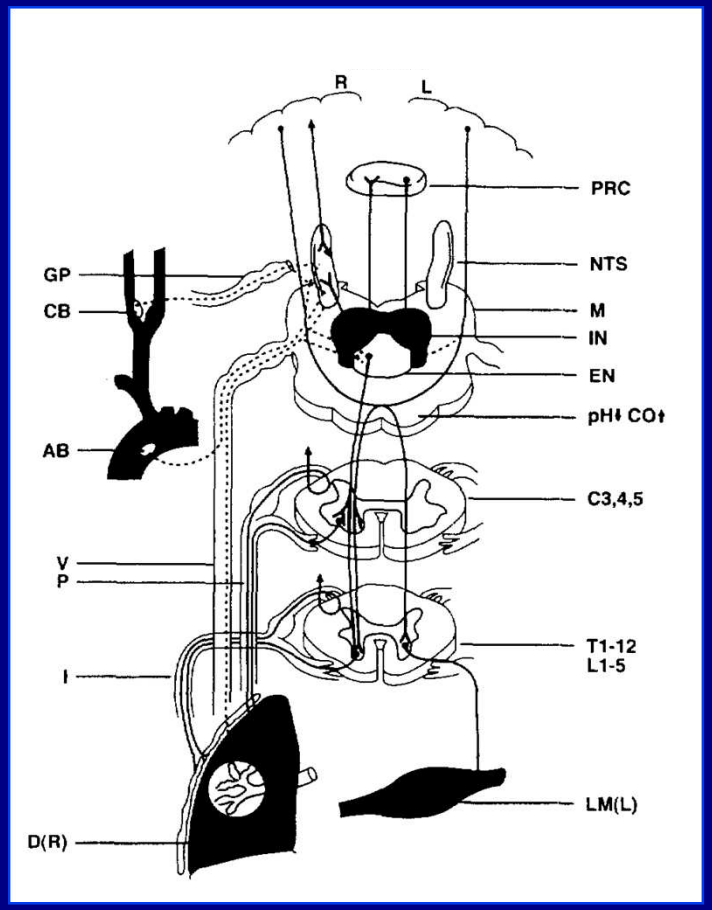
Neural control of breathing

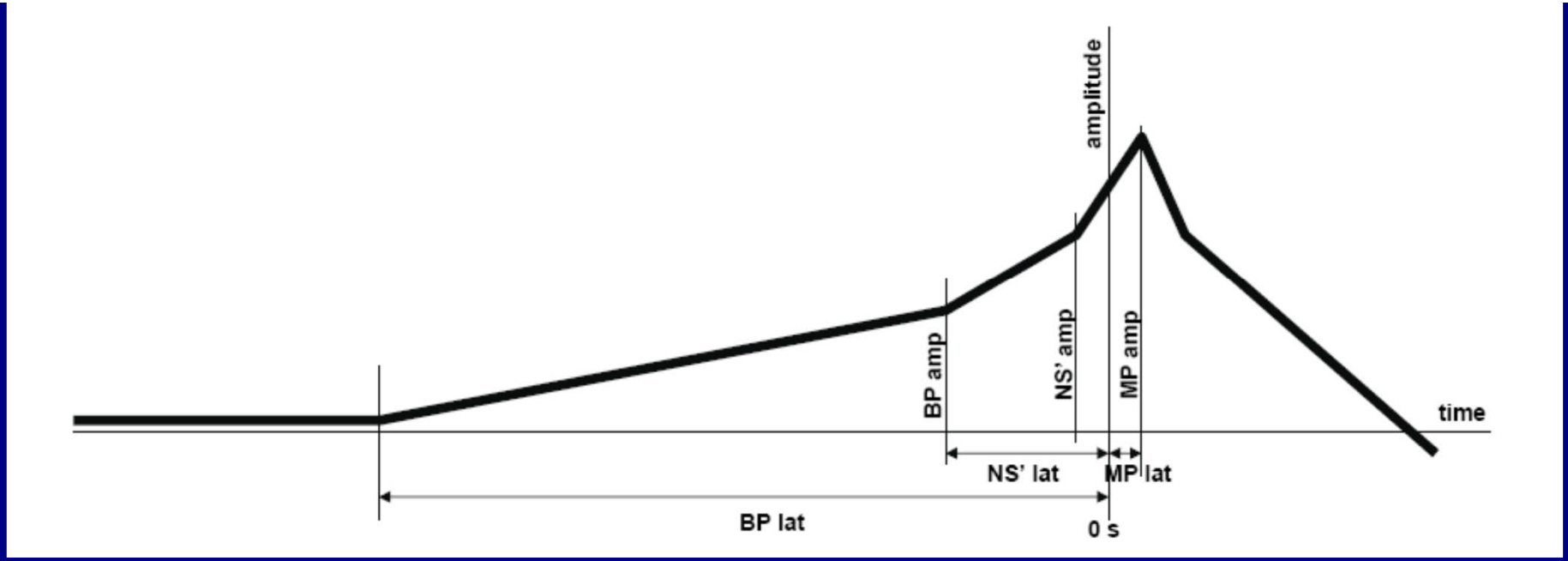
Three types of control:

Automatic
Originates in the ponto-medullary respiratory oscillator from which a descending projection connects to the cells in the spinal cord. Modulated by chemical and mechanical inputs. Controls breathing in sleep, anesthesia, in the presence of normal pCO2 and pH.

Voluntary
Allows voluntary modulation of breathing in response to speaking, singing, breath holding, and straining. Mediated by pathways descending from the motor cortex to the spinal cord.

Emotional
Modulation of breathing pattern by emotions. "Emotional" pathways connecting brain limbic areas and brainstem respiratory centres.

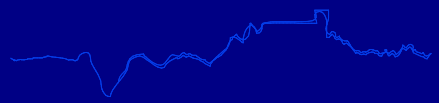




- MRCPs are negative scalp-recorded cortical potentials generated by voluntary movements.
- They begin 2.0 to 1.5 s prior to the onset of selfpaced movements.
- Result from excitatory post-synaptic potentials. Different successive components linked to the functioning of the supplementary (early Bereitschaftspotential component - BP1), pre-motor (late Bereitschaftspotential component - BP2), and primary motor areas (motor potential component - MP).
- Altered by disease or brain injury.

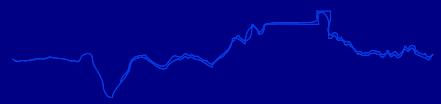
Sniffs

- Brief self-paced inspirations (sniffs) have been used as respiratory maneuvers in our studies.
- They are easy to perform, have a well defined electromyographic onset in the inspiratory muscles, and produce a rapid change in nasal air pressure..
- Sniff nasal-inspiratory pressure correlates well with the decline in the respiratory muscle strength and is a good predictor of the respiratory failure as well as of the prognosis in ALS.



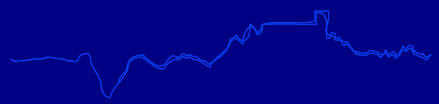
Topography of sniffing-related motor cortical potentials

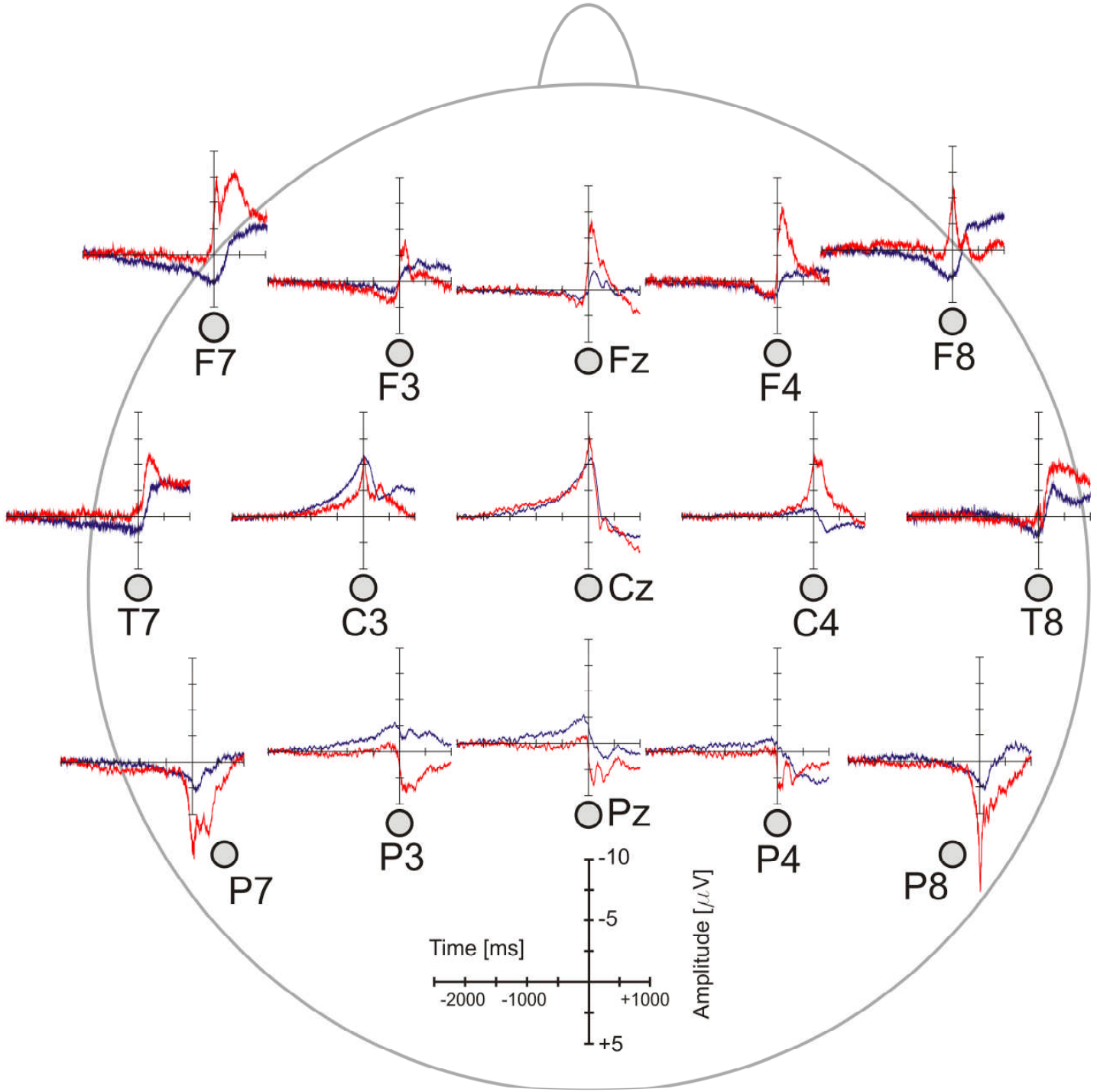
- MP component of MRCP precisely maps muscle representations in primary motor cortex.
- Several muscles active in sniffing (diaphragm, external intercostal and neck muscles (scalene and sometimes sternocleidomastoid), and muscles of the upper airway).
- Their representation spans nearly the whole primary motor strip.

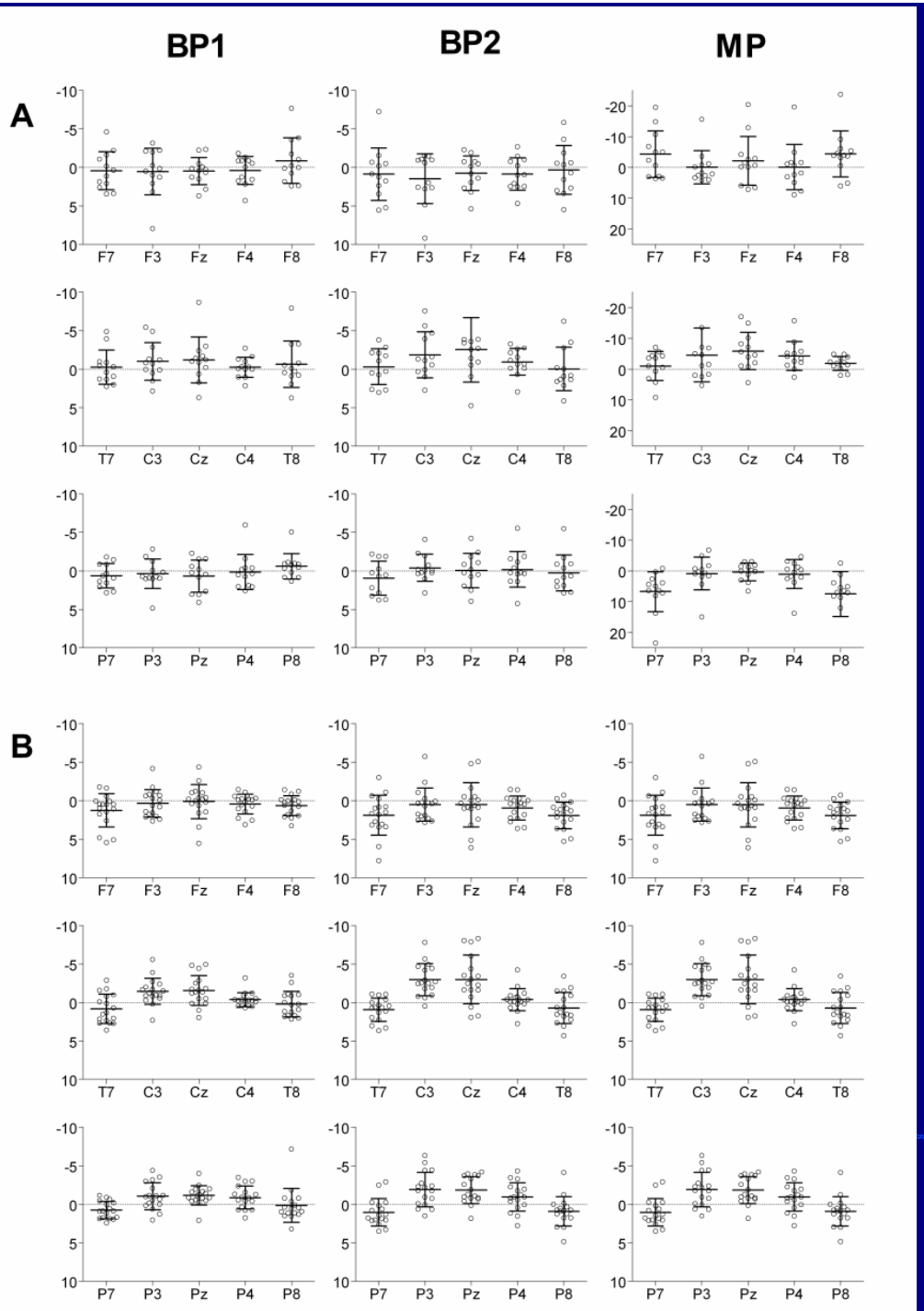


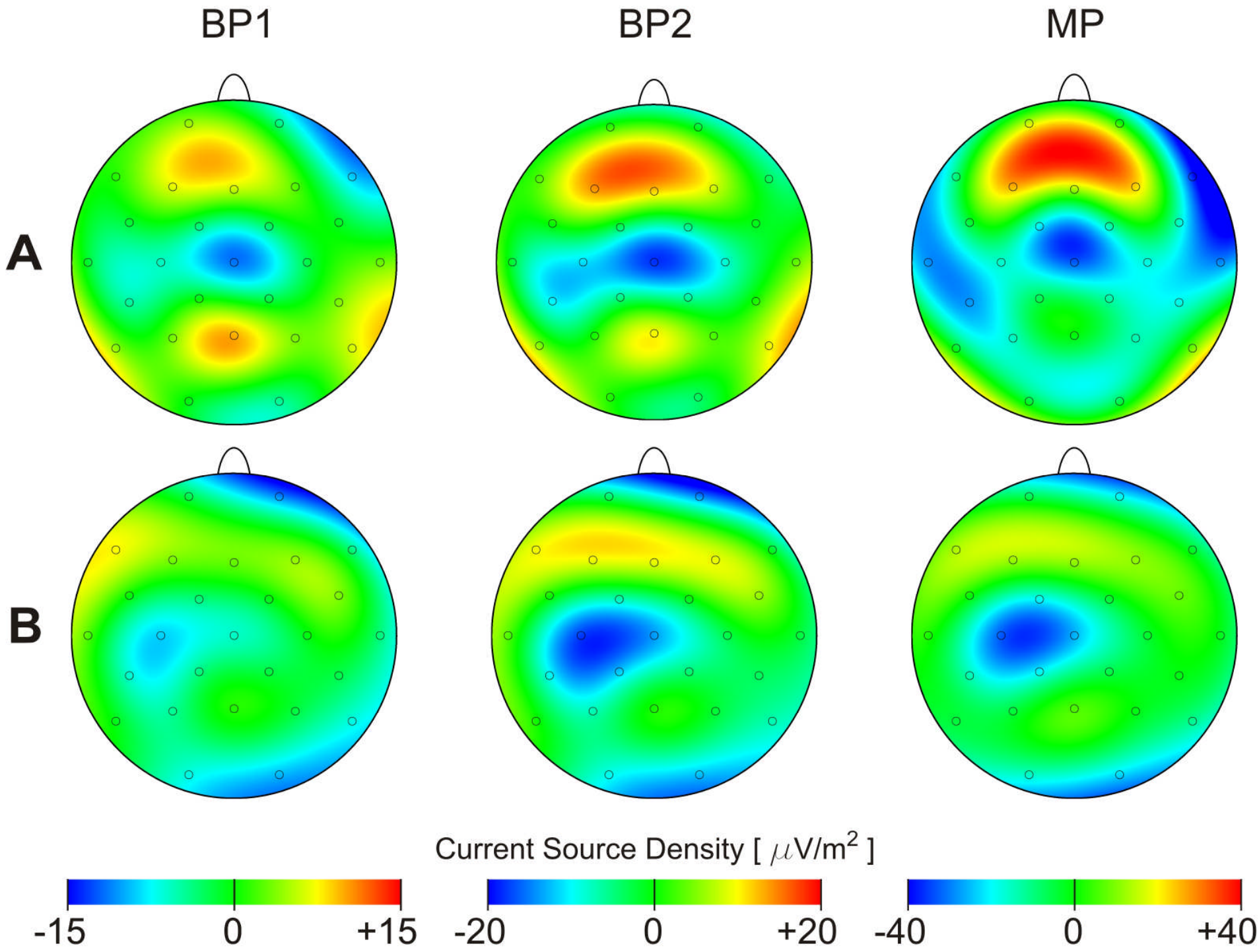
Aim

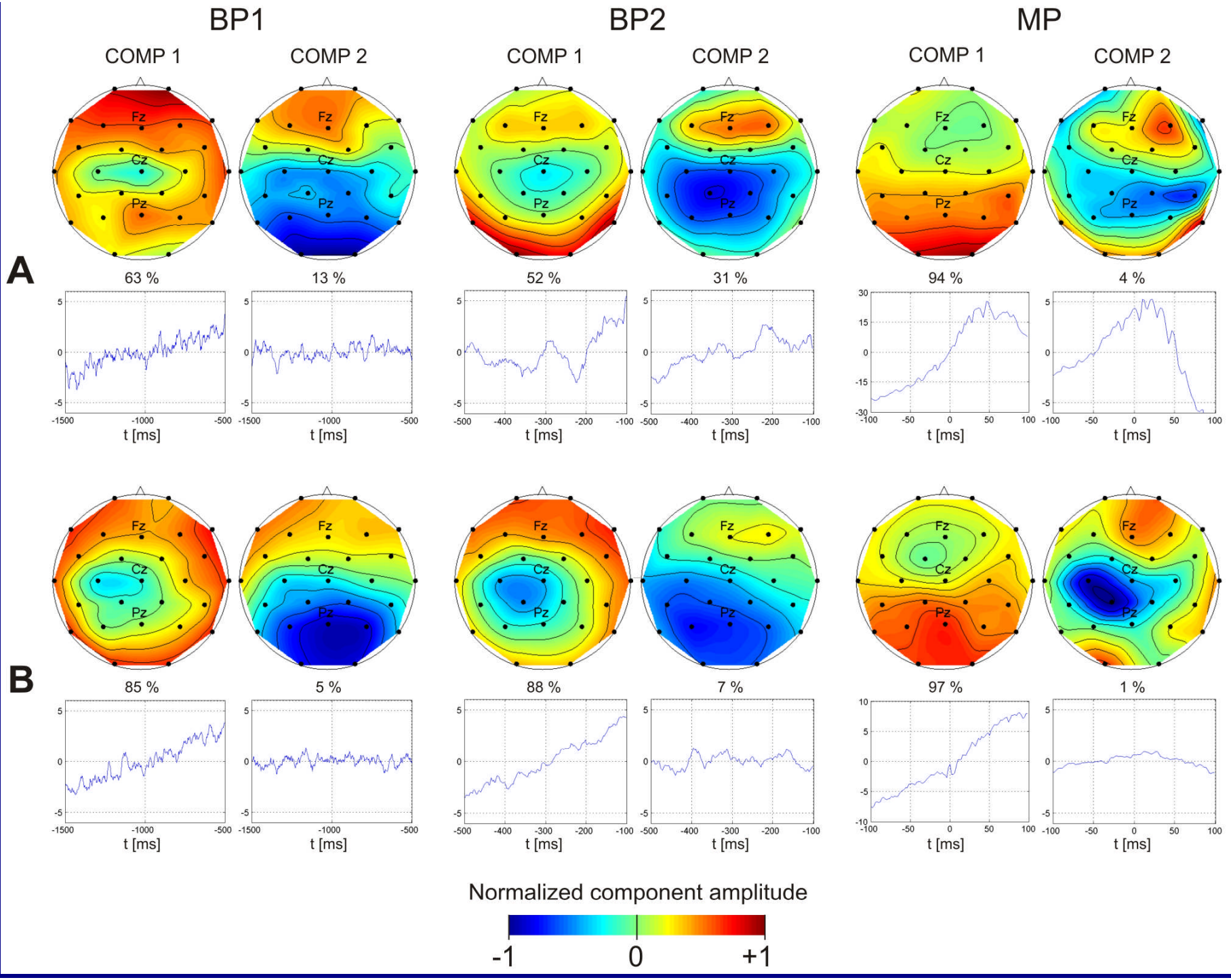
- To compare scalp topographies and PCA components of MRCP in sniffing and finger flexion to determine the differences in their spatial distribution.




F7
F3
Fz
F4
F8
T7
C3
Cz
C4
T8
P7
P3
Pz
P4
P8
Time [ms]
-2000
-1000
+1000
-10
-5
+5
Amplitude [μV]

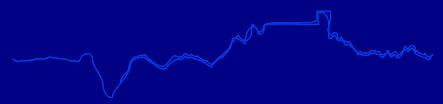

BP1
BP2
MP
A
B
F7 F3 Fz F4 F8
T7 C3 Cz C4 T8
P7 P3 Pz P4 P8


BP1
BP2
MP
A
B
Current Source Density [μV/m²]
-15
0
+15
-20
0
+20
-40
0
+40


BP1
BP2
MP
COMP 1
COMP 2
COMP 1
COMP 2
COMP 1
COMP 2
A
B
Fz
Cz
Pz
63 %
13 %
52 %
31 %
94 %
4 %
85 %
5 %
88 %
7 %
97 %
1 %
t [ms]
Normalized component amplitude
-1
0
+1

Conclusions

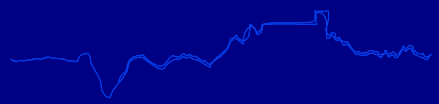
- Sequential cortical activation in preparation for sniffing is similar to other volitional movements. The current sources at sniff onset at the vertex likely reflect somatotopic motor representation of the diaphragm, neck and intercostal muscles, whereas current sources over fronto-temporal derivations likely reflect somatotopic representations of the orofacial muscles.



Respiratory failure is the main cause of death in patients with ALS and early respiratory dysfunction is associated with worse prognosis.
Respiratory symptoms, especially sleep-related, are easily over- looked.
Breathlessness is in patients with restricted mobility often a late feature. [1,2].

(1) Shoesmith CL. J Neurol Neurosurg Psychiatry. 2007 Jun;78(6):629-31.
(2) Spataro R. Acta Neurol Scand. 2010 Sep;122(3):217-23.

- It is still not known, whether the upper motor neuron loss contributes to the progressive respiratory failure in ALS.

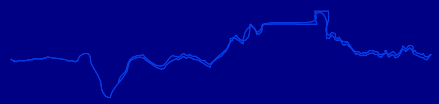


- Two studies, which investigated MRCPs in patients with ALS, showed the reduction of their amplitudes in those with more pronounced upper motor neuron involvement (1,2). Another study of patients with primary lateral sclerosis also described lowerMRCP amplitudes in patients. This was interpreted as a sign of the pyramidal motor neuron cellular death (3).

(1) Westphal KP et al. Acta Neurol Scand 1998;98:15–21.
(2) Inuggi et al. Brain Res 2011;1425:37–46.
(3) Bai et al. Ann Neurol 2006;59:682–90.

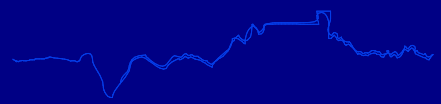
Aims

- Our aim was to explore, whether the SRCPs and index-finger- flexion MRCPs (FFRCPs) can be used as markers of cortical involvement in ALS patients. Quantifying possible changes of MRCP parameters in ALS might serve to further elucidate its complex pathophysiology. We hypothesised that patients with higher upper motor neuron burden(UMNB) would have reduced MRCPs due to neuronal loss in cortical motor areas.



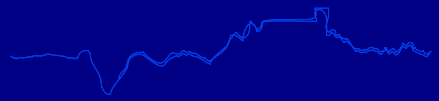
Methods

- Thirteen ALS patients and 15 healthy volunteers were assessed for their hand dexterity and strength, respiratory function,speech capacity,spasticity,electromyographic parameters and functional rating scales. EEG was recorded during self-paced sniffing and the right index finger.

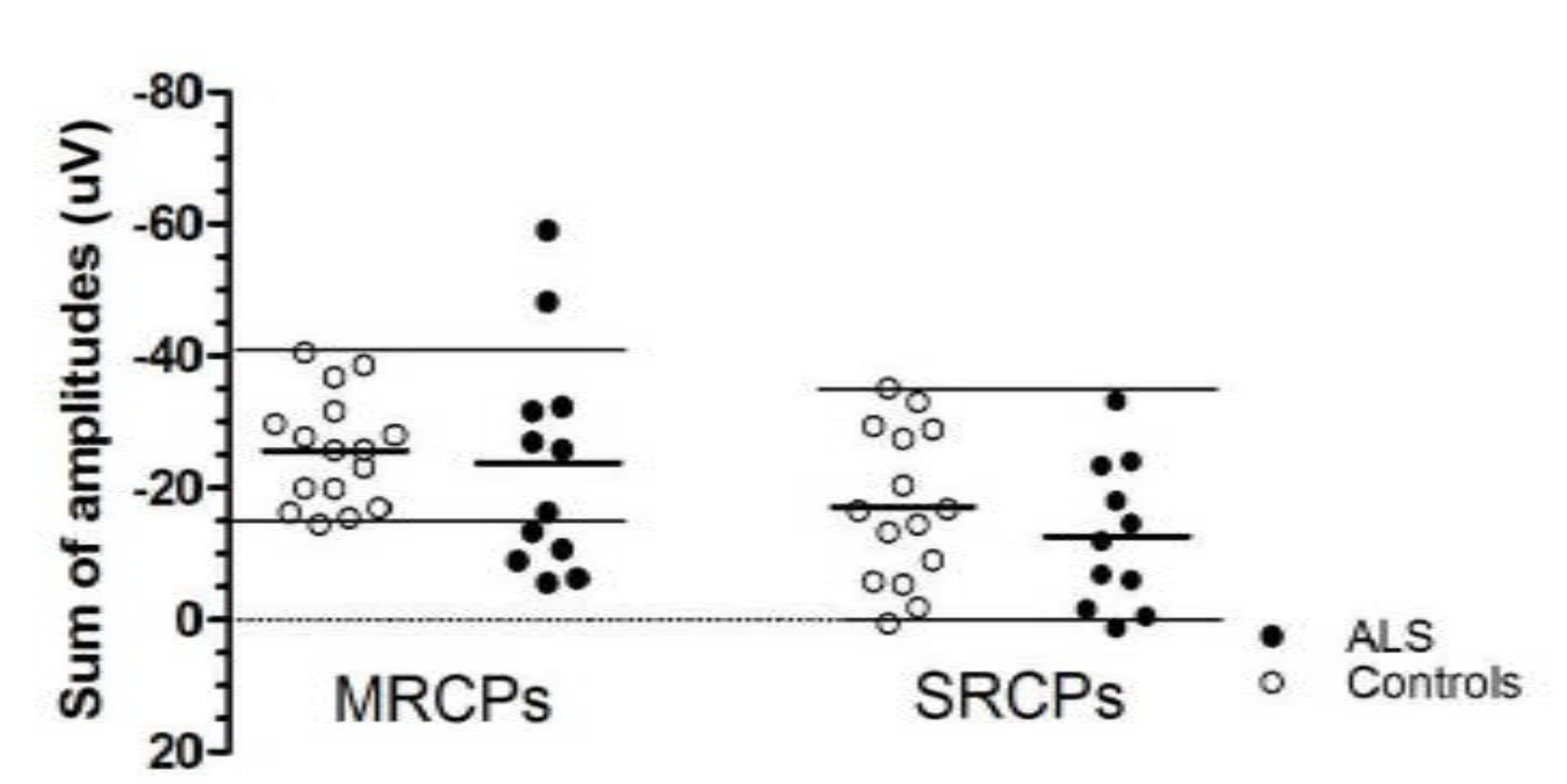


Methods

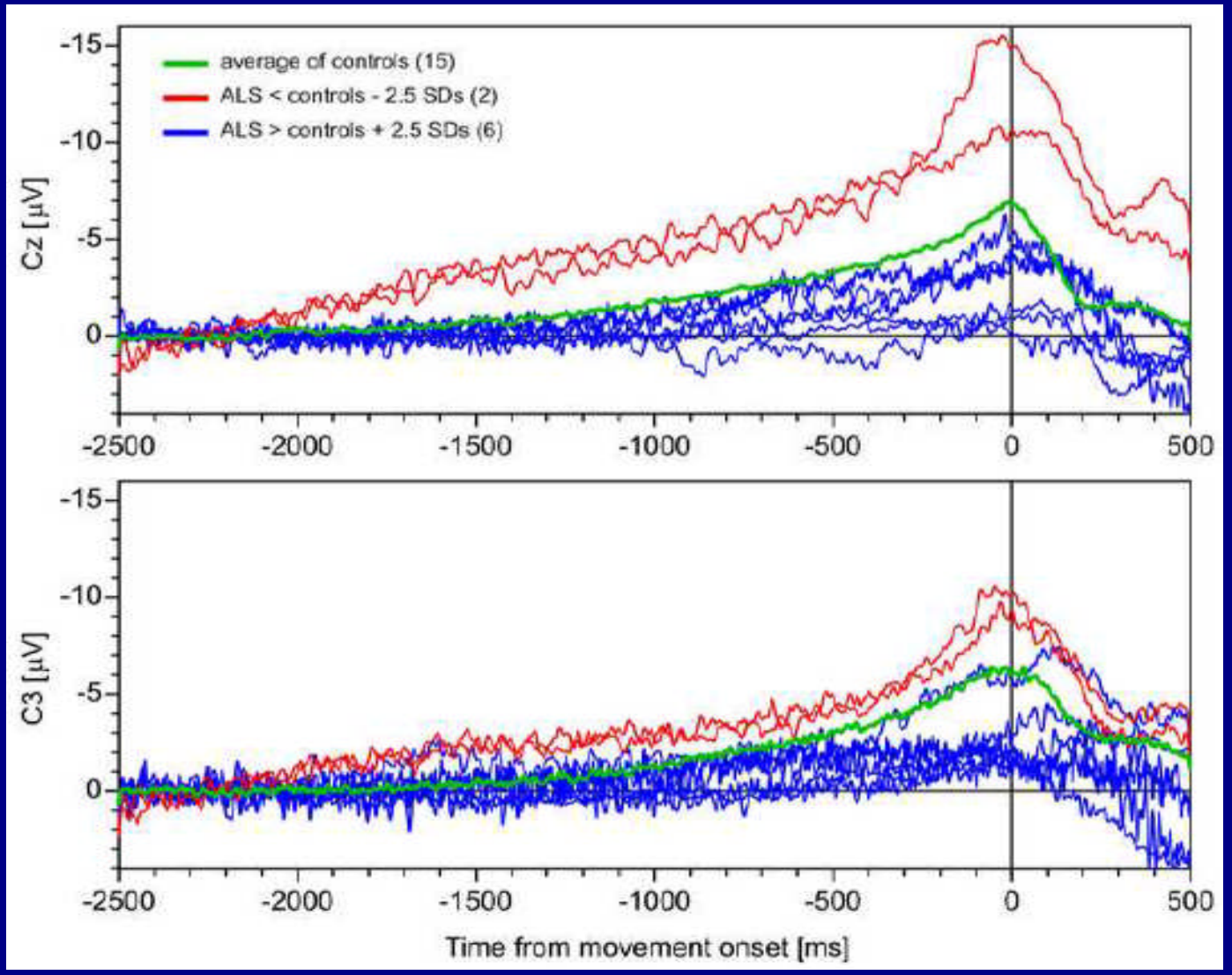
- Sniffing and right index finger flexions every 5 –10 s with 20% of individual maximal strengths.
- Amplitudes of cortical potentials measured at −500 ms, −100 ms and 0 ms at the representative scalp channels (finger flexion – Cz and C3 electrodes, sniffing – Cz ,FC5 and FC6 electrodes).
- Sums of BP1, BP2 and MP amplitudes at the representative scalp channels were calculated for each task.
- We specially focused on patients in whom the sum of BP1,BP2 and MP amplitudes were above or below 2.5 SD of the mean in controls.



Tests	ALS patients	Control group	p	Tests	ALS patients	Control group	p
	mean ± SD				mean ± SD		
Tapping board test [Hz]	1.5 ± 0.5	1.9 ± 0.5	0.009	Diadochokinetic syllable rate [Hz]	3.9 ± 1	4.4 ± 0,9	0.070
Nine-hole peg test [s]	26 ± 11	20 ± 2	0.019	VC [% of predicted normal]	84 ± 23	94 ± 14	0.105
Sequential finger-to thumb tapping rate [Hz]	1.9 ± 0.7	2.5 ± 0.6	0.006	FEV1 [% of predicted normal]	87 ± 24	92 ± 16	0.277
Hand grip strength [kg]	14 ± 12	30 ± 11	0.003	MIP [cm H_2O]	65 ± 36	82 ± 28	0.117
Hand pinch strength [kg]	3 ± 2	7 ± 2	0.000				
Right Neurophysiological index	2 ± 1.4	3.6 ± 0.9	0.002				
MEP [cm H_2O]	76 ± 38	113 ± 26	0.006				
SNIP [cm H_2O]	59 ± 22	77 ± 27	0.042				



FFRCP and SRCP amplitudes of individual patients and controls. Note that the sum of FFRCP amplitudes (BP1, BP2, MP) was above 2.5 SDs of the controls in 2 of 13 ALS patients and below 2.5 SDs in 6 patients. The thick horizontal line represents the respective mean and the two thin lines above and below indicate 2.5 SDs of the controls. Only one of the patients deviated from such limits regarding the SRCP amplitudes. Also one of the control subjects in each of the test paradigms set out of these limits.

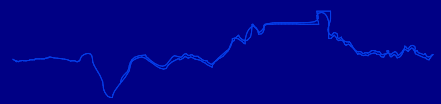


Mean FFRCPs from the two representative channels (Cz and C3) of patients that differed in their summed amplitudes from the control subjects. Traces in red are from patients with higher amplitudes, while those in blue represent patients with lower amplitudes. Green trace represents the grand average of the control group.

Functional test scores of patients with FFRCP amplitudes significantly above (>2.5 SD) or bellow (<2.5 SD) those of the control group.

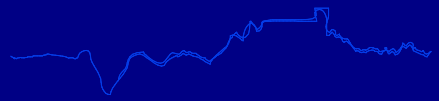
Tests	Mean value		
	ALS < 2.5th percentile	ALS > 97.5th percentile	Control
Tapping board test [Hz]	1.2	2.3	2.1
Nine-hole peg test [s]	27.2	20	20.3
Sequential finger-to-thumb tapping rate [Hz]	1.7	2.5	2.6
Upper motor neuron burden [Total sum]	10	12	0
Ashworth scale [Total sum]	5.6	2	0
ALSFRS-R [Total sum]	38.5	45	48
ALSFRS-R – upper arm [Total sum]	5.3	7.5	8
Norris scale [Total sum]	72.8	85	96
Norris scale – upper arm [Total sum]	18.7	24.5	27
Norris scale – spasticity [Total sum]	6.5	10.5	18

- The time between the onset of clinical symptoms and the EEG recording was shorter (409 days) for the ALS patients with higher amplitudes than for the subgroup of patients with lower FFRCP amplitudes (629 days).



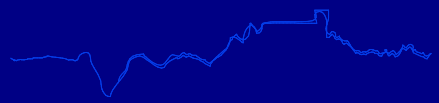
Correlation between the results of the upper limb and bulbar/respiratory functional testing with SRCP and FFRCP amplitudes of the patients.

SRCP amplitudes	Pearson R coeff.	p	FFRCP amplitudes	Pearson R coeff.	p
VC [% of predicted normal]	0.682	0.007	Tapping board test [Hz]	0.662	0.007
FEV1 [% of predicted normal]	0.524	0.045	Sequential finger-to thumb tapping rate [Hz]	0.521	0.046
ALSFRS-R – bulbar part [Total sum]	0.586	0.022			
Norris scale – bulbar part [Total sum]	0.636	0.011			
Diaphragm M-wave ampliude [mV]	0.649	0.022			



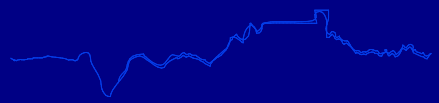
Conclusions

- The main finding was the correlation between the scores that measure some of the upper limb and respiratory functions depending on the cortical outflow and the SRCP and FFRCP amplitudes; worse functioning correlated with smaller amplitudes.
- Patients with rather preserved hand function generated FFRCPs with significantly larger amplitudes while those with most severe involvement generated potentials with significantly smaller amplitudes compared to controls.
- We thus demonstrated that MRCP may be a useful marker of the cortical involvement in ALS patients, including also a part of the cortex involved in the control of respiration.



Subjects

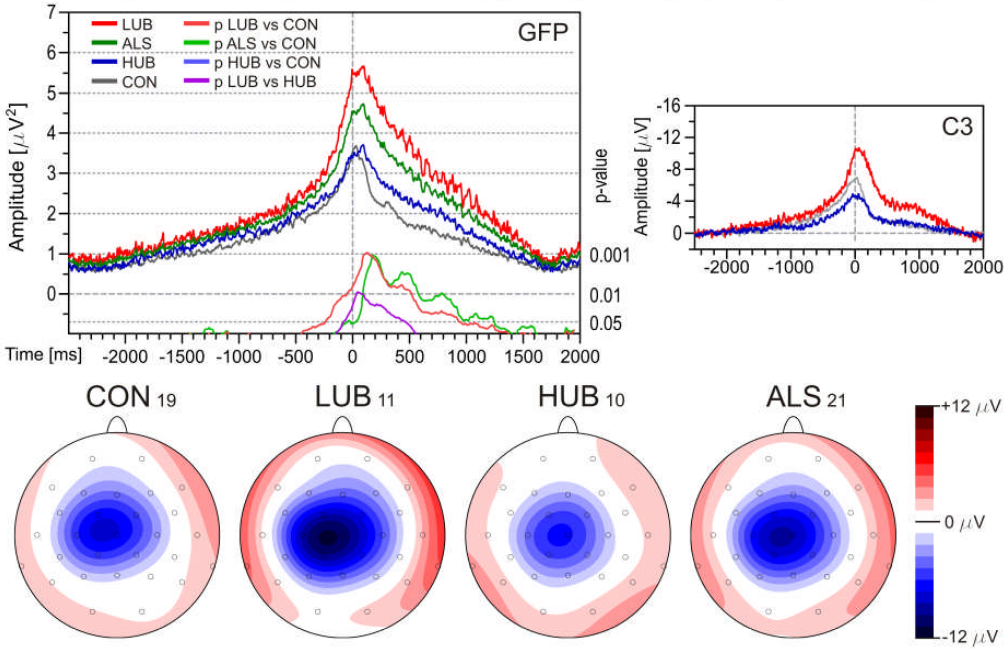
- 21 ALS patients and 19 controls.
- Flexions of the right index finger and brisk nasal inspirations (20% of individual maximal strength).
- The early (BP1), late (BP2) and motor potential (MP) components of MRCPs at the central electrodes were evaluated.
- Same functional tests as in the first study.
- ALS patients divided into a low UMNB score subgroup and high UMNB score subgroup.



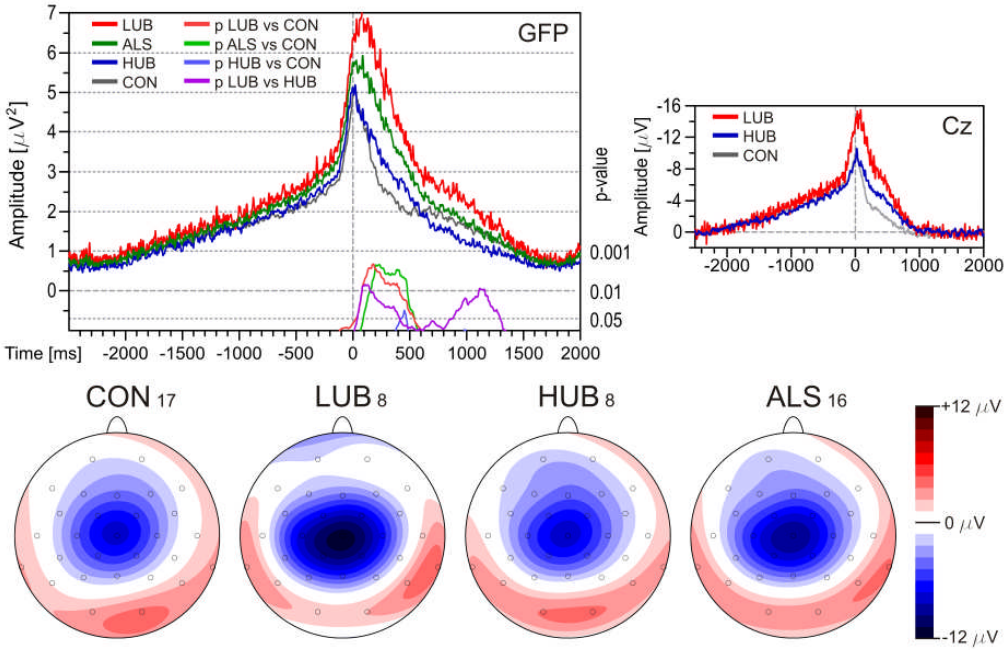
Performance on clinical tests

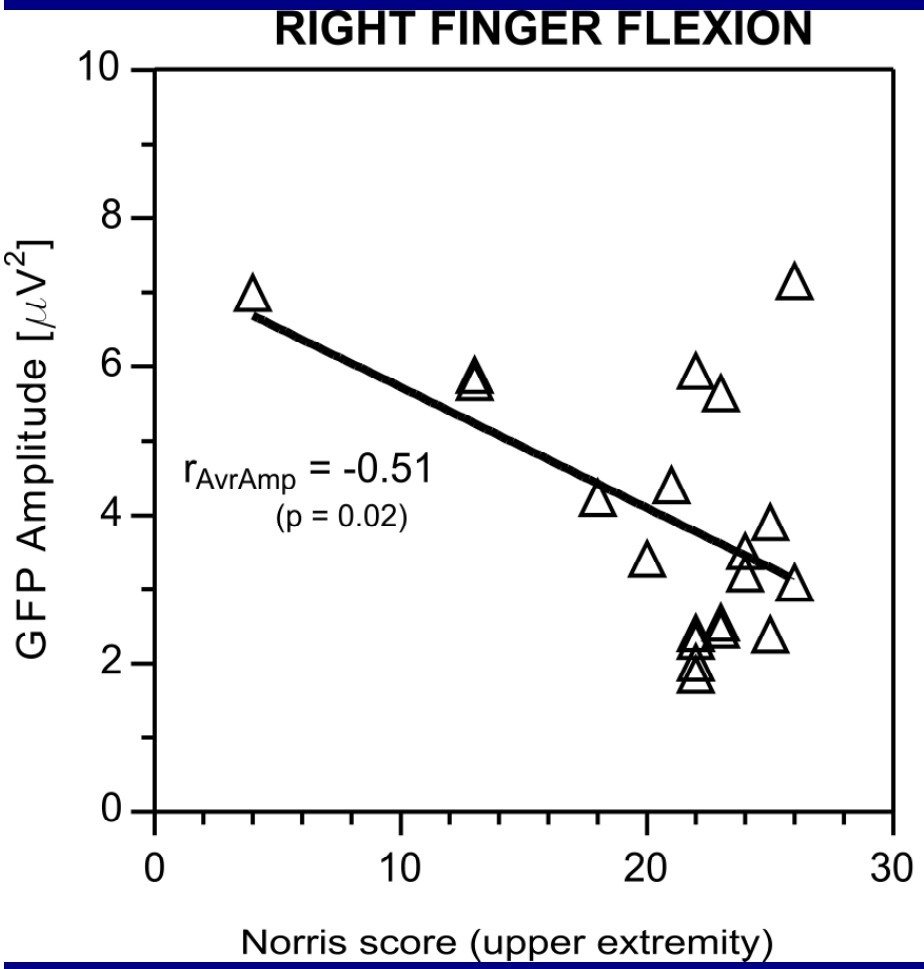
Tests		Controls	ALS	ALS vs. CON p-value *	LUB	HUB	LUB vs. HUB p-value *
		Mean (SD)			Mean (SD)		
Hand function	Tapping board test [Hz]	2.0 (0.5)	1.5 (0.5)	0.011	1.6 (0.5)	1.5 (0.4)	1.000
	Nine-hole peg test [s]	19.8 (2.1)	30.5 (13.2)	0.009	31.6 (16.7)	29.4 (9.5)	1.000
	Seq. finger tapping [Hz]	2.4 (0.6)	1.9 (0.7)	0.010	1.7 (0.6)	2.0 (0.68)	1.000
	Grip force [N]	353.5 (121.5)	134.3 (103.1)	<0.001	137.5 (121.2)	130.0 (84.0)	0.894
	Pinch force [N]	77.1 (18.5)	22.6 (21.4)	<0.001	21.6 (18.5)	24.0 (26.7)	1.000
	R-NPI	3.4 (0.9)	1.7 (1.4)	0.002	1.8 (1.4)	1.5 (1.5)	1.000
Respiratory function	MIP [cm H2O]	81.8 (27.1)	55.5 (32.7)	0.106	62.0 (30.3)	48.0 (36.5)	1.000
	SNIP [cm H2O]	83.5 (31.0)	54.5 (17.9)	0.034	56.0 (22.4)	52.7 (12.6)	1.000
	Vital capacity [% of normal]	93.2 (13.5)	80.0 (24.6)	0.216	82.6 (16.1)	77.0 (33.5)	1.000
	FEV1 [% of normal]	93.4 (14.6)	83.8 (24.0)	0.223	85.3 (19.1)	82.3 (29.6)	0.826

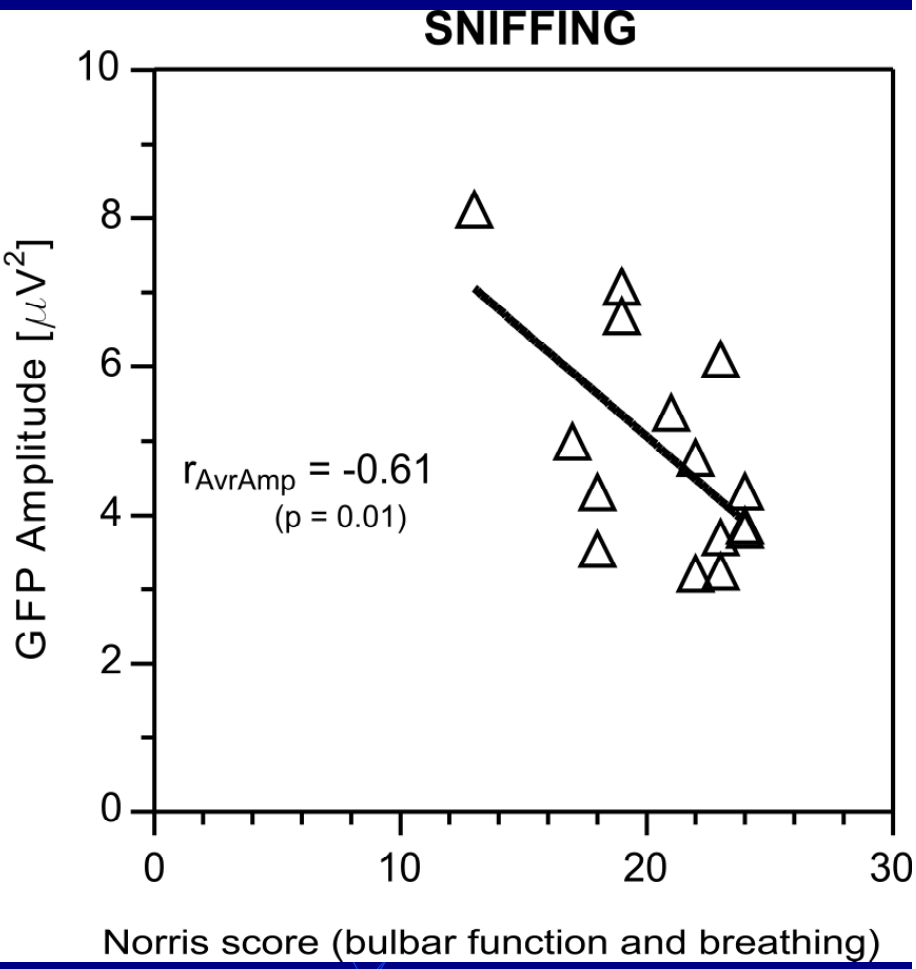
FINGER FLEXION RELATED CORTICAL MOTOR POTENTIALS

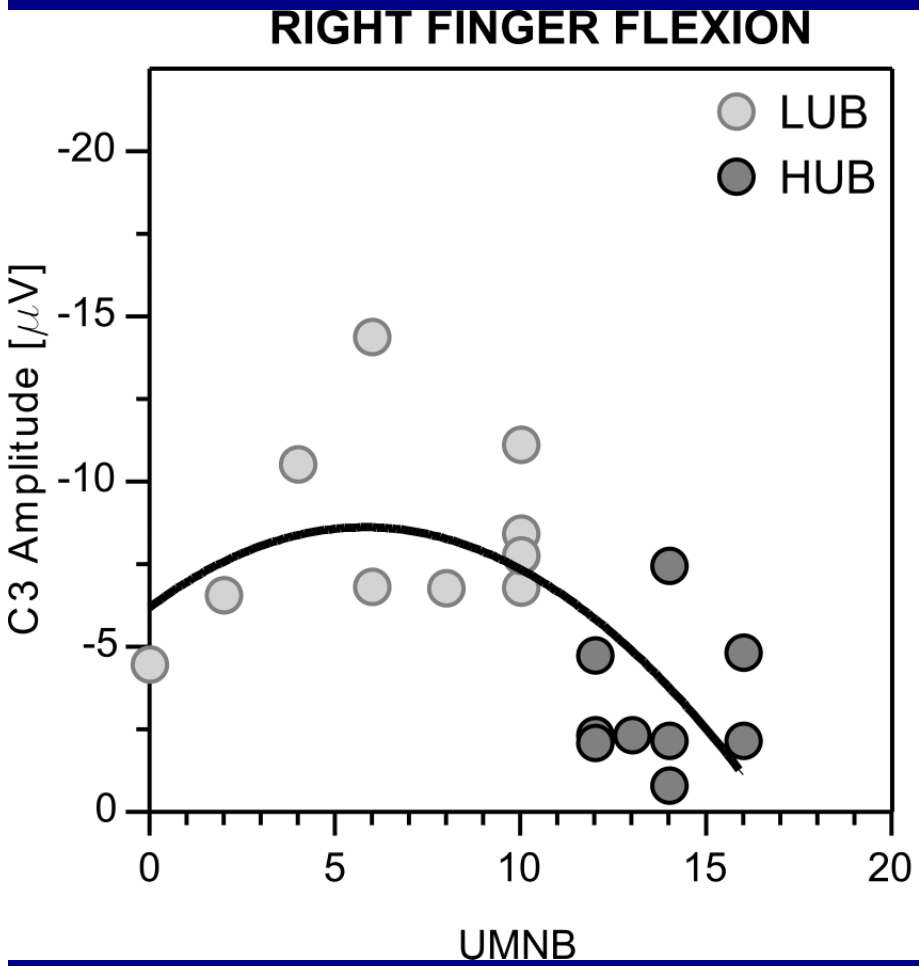


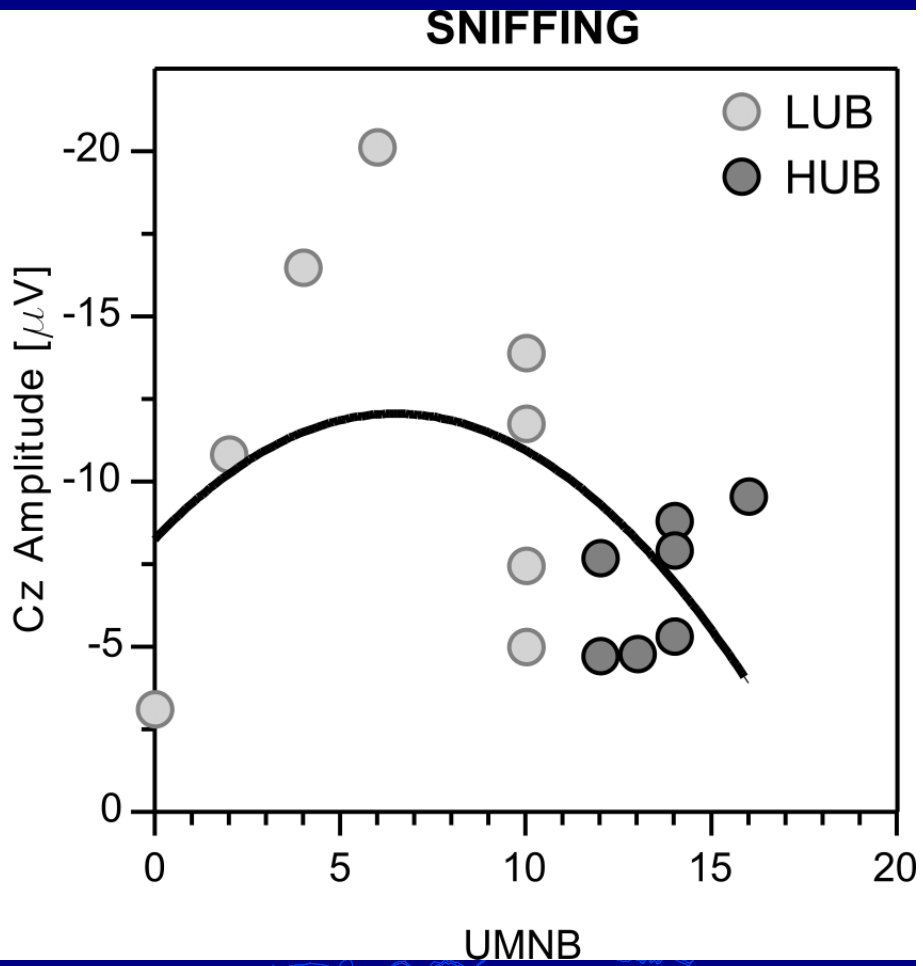
SNIFFING RELATED CORTICAL MOTOR POTENTIALS




RIGHT FINGER FLEXION
GFP Amplitude [μV^2]
r_{AvrAmp} = -0.51
(p = 0.02)
Norris score (upper extremity)
0
2
4
6
8
10
0
10
20
30

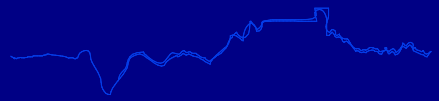

SNIFFING
GFP Amplitude [μV^2]
r_{AvrAmp} = -0.61
(p = 0.01)
Norris score (bulbar function and breathing)
0
2
4
6
8
10
0
10
20
30


RIGHT FINGER FLEXION
LUB
HUB
C3 Amplitude [μV]
-20
-15
-10
-5
0
0
5
10
15
20
UMNB


SNIFFING
LUB
HUB
Cz Amplitude [μV]
-20
-15
-10
-5
0
0
5
10
15
20
UMNB

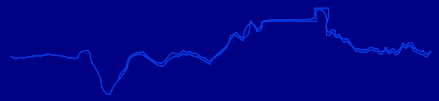
Comparison of motor potential (MP) parameters

Task	MP measure		LUB [µV]	HUB [µV]	CON [µV]	pANOVA*	pLUB vs HUB	pLUB vs CON	pHUB vs CON
			Mean (SD)						
FF	AvrAmp [-140, +100] ms	C3	-9.21 (2.97)	-4.34 (3.02)	-6.24 (2.08)	0.0004	0.0015	0.0098	0.0973
		GFP	4.98 (1.60)	3.26 (1.48)	3.19 (0.89)	0.0016	0.0194	0.0043	0.8858
SN		Cz	-12.25 (5.29)	-8.18 (2.05)	-8.14 (3.82)	0.0495	0.0727	0.0756	0.9737
		GFP	5.56 (1.42)	4.22 (1.04)	4.03 (1.16)	0.0186	0.0510	0.0216	0.6952



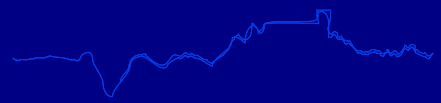
Movement execution

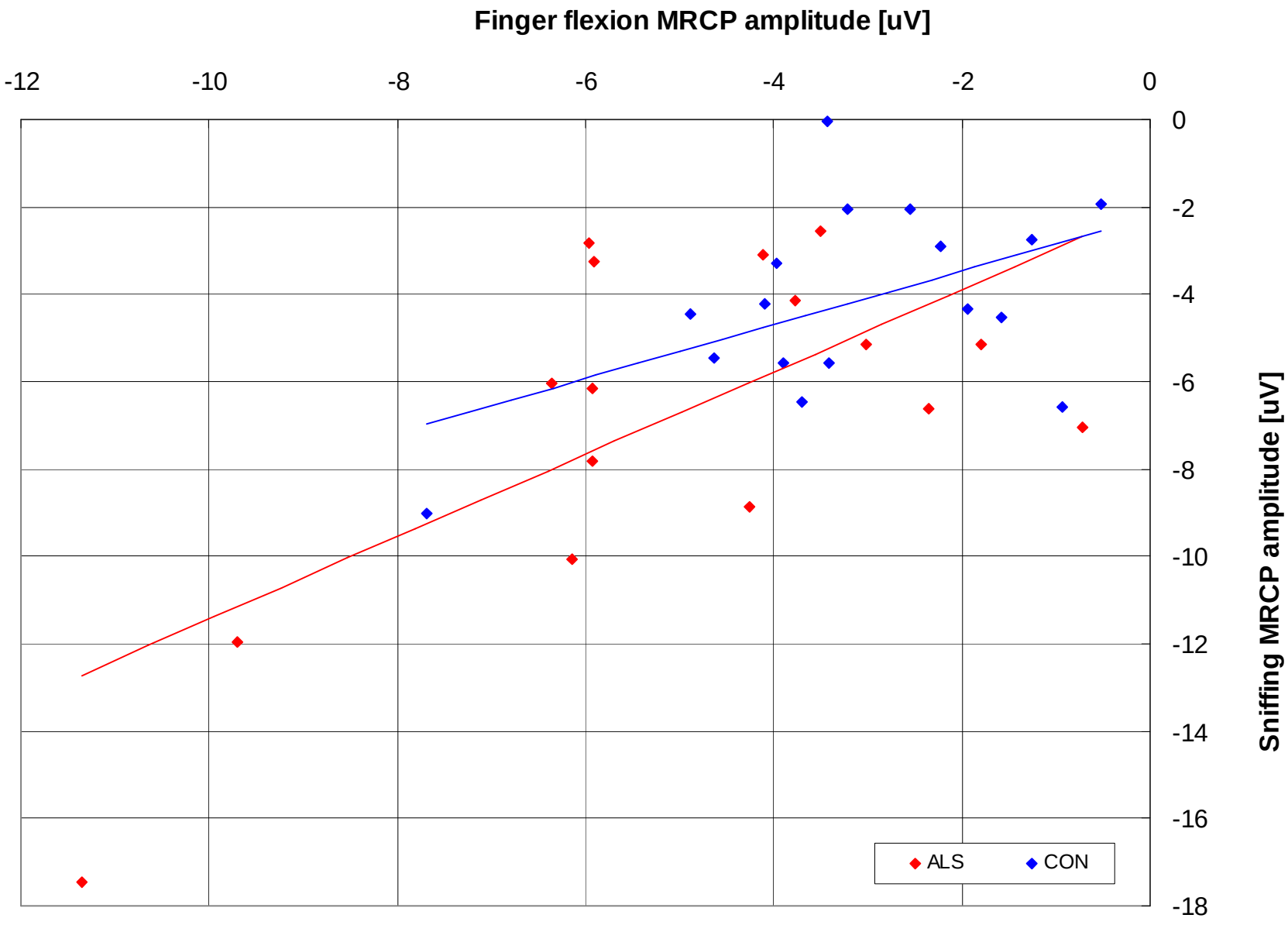
Tests	Controls	ALS	ALS vs. CON p-value *	LUB	HUB	LUB vs. HUB p-value *
	Mean (SD)			Mean (SD)		
EMG FF [μV^2]	57.5 (27.4)	52.0 (21.8)	0.980	52.1 (22.5)	51.8 (22.2)	0.974
FF pressure [mPa]	45.0 (25.4)	63.5 (38.2)	0.234	67.4 (45.5)	59.2 (30.2)	1.000
SN pressure [mPa]	18.2 (8.04)	19.6 (10.2)	0.674	21.3 (10.2)	17.8 (10.5)	1.000
MovDur FF [ms]	228 (96.4)	271 (99.5)	0.504	292 (97.9)	248 (101)	1.000
MovDur SN [ms]	258 (75.8)	277 (52.1)	1.000	286 (54.6)	269 (51.6)	1.000



Correlations between MPs and clinical measures of muscle strength

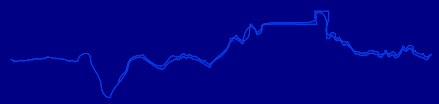
r (p)	FINGER FLEXION			SNIFFING		
	Channel	GRIP	PINCH	Channel	MIP	SNIP
LUB	C3	0.756 (0.030)	0.707 (0.050)	Cz	0.620 (0.138)	0.485 (0.270)
	GFP	-0.687 (0.060)	-0.548 (0.160)	GFP	-0.742 (0.056)	-0.539 (0.212)
HUB	C3	-0.088 (0.869)	-0.384 (0.452)	Cz	-0.474 (0.341)	-0.095 (0.857)




Finger flexion MRCP amplitude [uV]
-12
-10
-8
-6
-4
-2
0
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
Sniffing MRCP amplitude [uV]
ALS
CON

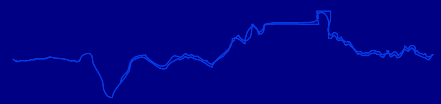
Conclusions

- The lack of difference between ALS patients and controls during the intervals of BP1 and BP2 might be explained by the fact that the earlier MRCP components are mostly generated in supplementary and premotor areas, which do not contain the Betz cells that are primarily affected in ALS.



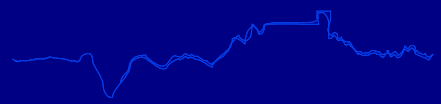
Conclusions

- Significantly increased LUB MPs in comparison to the control group and the tendency for LUB MPs to increase with the severity of the disease may be the result of pathologically increased cortical excitability and compensatory responses to ALS-related neuronal loss.
- Previous studies have linked increased motor activations in ALS with brain plasticity (compensating for neuronal degeneration) and processes resulting in pathologically increased cortical excitability (decreased intra-cortical inhibition).



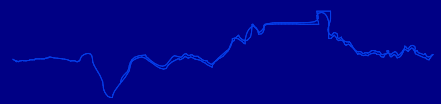
Conclusions

- The mechanism of decreased MP amplitudes in the HUB subgroup may be loss of neurons within the primary motor cortex. These neurons are known to contribute to MRCP generation. A
- Similar finding of reduced activation in the contralateral sensorimotor cortex over the course of the disease has been described using functional neuroimaging.



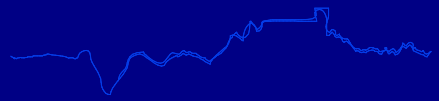
Conclusions

- The increased MRCPs in LUB compared to HUB indicate different phases of ALS pathophysiology that force opposing changes in MRCP amplitudes.



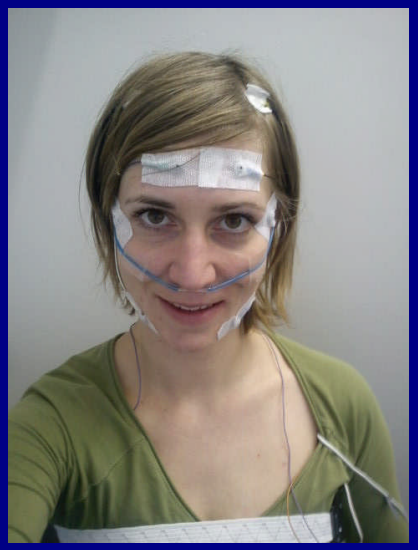
Conclusion

- The simplest explanation for the previously described results seems to be that there are two categories of concurrent pathophysiological processes in ALS that force opposing changes in MRCP amplitudes. The first category includes processes that tend to increase MRCPs and are most apparent in the LUB subgroup, while the second category includes processes that tend to reduce MRCPs and are most apparent in the HUB subgroup. The exact MRCP amplitude measured for a particular patient or subgroup is thus determined primarily by which of these two categories of processes is more pronounced at the time of the measurement.

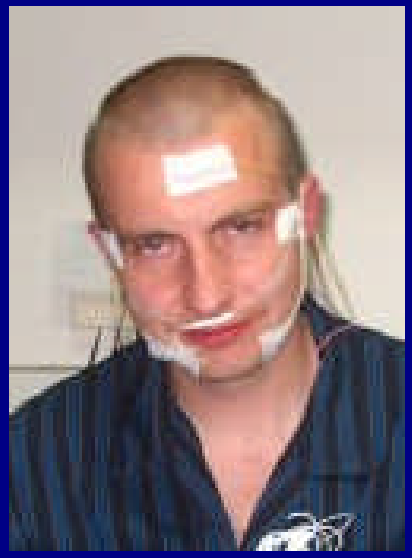


Collaborators

Ignac Zidar



Ditka Jeran



Aleš Belič

Nataša Bizovičar

Blaž Koritnik