Sonographic and 3T-MRI-based evaluation of the tongue in ALS

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Supplemental Material

Supplemental Table 1. Correlations of the tongue variables with the demographics of the sample under consideration

Sonography		Age		Height		Weight		Sex	
		r	*p*	*r*	*p*	*r*	*p*	*t/Z*	*p*
	Intensity	-0.1	0.5	**-0.4**	**0.001**	-0.2	0.2	**4.0****	≤ **0.001**
	Area	< 0.1	1.0	0.2	0.1	**0.3**	**0.007**	-0.9**	0.4
	Height	0.1	0.7	0.2	0.2	**0.3**	**0.03**	-0.7**	0.5
	Width	-0.1	0.4	0.2	0.2	**0.3**	**0.007**	-1.0**	0.4
	Ratio height / width	0.2	0.1	< 0.1	0.8	< 0.1	0.9	< 0.1**	1.0
MRI	Intensity	<-0.1	0.8	-0.1	0.3	-0.9	0.3	-0.7***	0.5
	Area	<-0.1	0.5	0.2	0.1	**0.3**	**0.001**	**-3.3*****	**0.001**
	Position	<-0.1	0.6	-0.3	0.7	-0.1	0.4	0.2**	0.9
	Shape	**0.2**	**0.012**	0.1	0.1	< 0.1	0.8	-1.7***	0.1

Correlation coefficient r, t-values**, Z-values*** and p-values of correlation analyses are given. Significant correlations are highlighted in grey. MRI, magnetic resonance imaging. P-values < 0.05 were deemed to be statistically significant.

Supplemental Table 2. Group and subgroup comparisons with respect to various sonographic and MRI tongue measures

		Sonography					MRI			
		Echo-intensity	Area (cm²)	Height (cm)	Width (cm)	Ratio height/width	Intensity	Area (cm²)	Position	Shape
1. ALS vs. CON	ALS	43.0 [7.0]	6.80 [1.28]	2.60 [0.30]	3.02 [0.30]	0.9 [0.1]	60.4 [25.6]	24.3 [3.9]	0.6 [0.04]	0.7 [0.1]
	CON	45.3 [7.9]	6.21 [1.62]	2.41 [0.43]	3.00 [0.30]	0.8 [0.1]	57.0 [18.2]	23.8 [3.1]	0.6 [0.04]	0.7 [0.1]
		p = 0.3	p = 0.1	p = 0.02	p = 0.5	p = 0.02	p = 0.3	p = 0.03	p = 0.9	p = 0.8
2. onset site	limb	43.3 [7.5]	6.83 [1.38]	2.62 [0.34]	3.02 [0.32]	0.9 [0.1]	65.3 [25.6]	24.5 [3.8]	0.6 [0.04]	0.7 [0.1]
	bulbar	41.8 [5.0]	6.68 [0.87]	2.55 [0.22]	3.02 [0.26]	0.9 [0.1]	50.4 [23.0]	23.4 [4.0]	0.6 [0.04]	0.7 [0.1]
	CON	45.3 [7.9]	6.21 [1.62]	2.41 [0.43]	3.00 [0.30]	0.8 [0.1]	57.0 [18.2]	23.8 [3.1]	0.6 [0.04]	0.7 [0.1]
		p = 0.2	p = 0.1	p = 0.1	p = 0.7	p = 0.1	**$p \leq 0.001$**	p = 0.1	p = 0.5	p = 0.9
3. assisted ventilation	required	42.0 [4.9]	6.52 [1.22]	2.47 [0.26]	3.02 [0.29]	0.8 [0.1]	62.1 [26.5]	24.9 [2.2]	0.6 [0.04]	0.7 [0.1]
	not required	43.0 [7.6]	6.94 [1.33]	2.65 [0.32]	3.03 [0.32]	0.9 [0.1]	60.9 [27.1]	24.2 [3.9]	0.6 [0.04]	0.7 [0.1]
		p = 0.6	p = 0.1	p = 0.1	p = 0.4	p = 0.2	p = 0.3	p = 1.0	p = 0.7	p = 0.3
4. gastrostomy	with	40.6 [5.5]	6.26 [1.34]	2.49 [0.29]	2.86 [0.32]	0.9 [0.1]	44.1 [22.0]	23.8 [4.4]	0.6 [0.05]	0.7 [0.05]
	without	43.3 [7.2]	6.88 [1.27]	2.62 [0.30]	3.05 [0.30]	0.9 [0.1]	61.6 [26.7]	24.3 [3.7]	0.6 [0.04]	0.7 [0.08]
		p = 0.4	p = 0.5	p = 0.6	p = 0.4	p = 0.6	p = 0.2	p = 0.4	p = 0.4	p = 0.9

Unless otherwise reported mean [SD] is given. For group and subgroup analyses ANOVA was conducted and adjustment for demographic data was performed, if appropriate (see Results). In detail, tongue variable [covariate adjustment]: echointensity [height, sex]; sonographic area [weight]; height [weight]; width [weight]; ratio height/width [none]; MRI intensity [none]; MRI area [weight, sex]; position [none]; shape [age]. ALS, amyotrophic lateral sclerosis; CON, controls; MRI, magnetic resonance imaging. Bonferroni-adjusted p-values of < 0.013 were deemed to be statistically significant.

Supplemental Table 3. Time interaction effects of tongue measures using mixed effects linear models

		ALSFRS-R total			ALSFRS-R bulbar		
Sonography		*e*	CI	*p*	*e*	CI	*p*
	Intensity	-0.01	(-0.26; 0.08)	0.3	**0.03**	(-0.02; 0.08)	**0.2**
	Area	**0.5**	(0.3; 0.6)	**< 0.001**	**0.2**	(0.1; 0.2)	**< 0.001**
	Height	**0.3**	(0.1; 0.4)	**0.002**	**0.1**	(0.1; 0.2)	**< 0.001**
	Width	**0.5**	(0.3; 0.6)	**< 0.001**	**0.2**	(0.1; 0.2)	**< 0.001**
	Ratio height/width	0.2	(0.004; 0.4)	0.05	0.05	(0.004; 0.1)	0.07
MRI	Intensity	0.06	(-0.03; 0.2)	0.2	0.002	(-0.03; 0.03)	0.9
	Area	0.04	(-0.06; 0.1)	0.4	**0.05**	(0.01; 0.08)	**0.004**
	Position	0.07	(-0.02; 0.2)	0.1	0.002	(-0.03; 0.03)	0.9
	Shape	**0.1**	(0.02; 0.2)	**0.015**	0.02	(-0.01; 0.1)	0.2

P-values and estimates e of time interaction effects are given. Significant values are highlighted in grey. ALSFRS-R, revised ALS functional rating scale; MRI, magnetic resonance imaging; Bonferroni-adjusted p-values of < 0.025 were deemed to be statistically significant.

Supplemental Table 4. Influence of studied sonographic parameters as additional inclusion parameters on power and sample size of a hypothetical study

	Whole sonographic ALS cohort	submedian sonographic tongue area	submedian sonographic tongue height	subgroup submedian sonographic tongue width
n per arm at P = 80 %	34	29	32	26
Power at n = 34	80 %	87 %	83 %	90 %

Calculation of the necessary sample size or obtainable power based on the characteristics of the whole sonographic cohort and, for comparison, those parameters for subcohorts selected to additionally show submedian sonographic tongue area, tongue height or tongue width.

Sample size calculations for a hypothetical, randomized, controlled trial with a 12-month observation period were conducted using a 2-sample t-test, assuming equal group means, a 50% treatment effect on ALSFRS-R decline, a linear ALSFRS-R decline, a 2-sided significance of 0.05, and a power of 0.8. Analysis was performed using nQuery winter 2019 release (ver 8.5.0) software (Statistical Solutions Ltd, Cork, Ireland).

Supplemental Table 5. Influence of studied MRI parameters as additional inclusion parameters on power and sample size of a hypothetical study

	Whole MRI ALS cohort	subgroup submedian MRI-based tongue area	subgroup submedian MRI-based tongue shape
n per group at P = 80 %	44	41	40
Power at n = 44	80 %	84 %	84

Calculation of the necessary sample size or obtainable power based on the characteristics of the whole MRI cohort and, for comparison, those parameters for subcohorts selected to additionally show submedian MRI-based tongue area or tongue shape parameter.

Sample size calculations for a hypothetical, randomized, controlled trial with a 12-month observation period were conducted using a 2-sample t-test, assuming equal group means, a 50% treatment effect on ALSFRS-R decline, a linear ALSFRS-R decline, a 2-sided significance of 0.05, and a power of 0.8. Analysis was performed using nQuery winter 2019 release (ver 8.5.0) software (Statistical Solutions Ltd, Cork, Ireland).