HHS Public Access

Author manuscript

Amyotroph Lateral Scler Frontotemporal Degener. Author manuscript; available in PMC
2021 February 01.

Published in final edited form as:

Amyotroph Lateral Scler Frontotemporal Degener. 2020 February ; 21(1-2): 34–41.
doi:10.1080/21678421.2019.1681454.

A speech measure for early stratification of fast and slow progressors of bulbar amyotrophic lateral sclerosis: Lip movement jitter

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Abstract

Objective: To assess the utility of novel measures derived from a rapid syllable repetition task (i.e., oral dysdiadochokinesis [DDK]) in early stratification of fast and slow progressive bulbar amyotrophic lateral sclerosis (ALS) and prediction of bulbar disease progression rate.

Methods: Fifty-four individuals with ALS were tracked longitudinally on their oral DDK and global bulbar/speech performance (i.e., bulbar subscore on the ALS Functional Rating Scale-Revised [ALSFRS-R]; articulation rate during passage reading) for a four-month average duration. Based on the bulbar deterioration rate over the tracked period, the participants were stratified as 14 fast bulbar progressors and 40 slow bulbar progressors using a posteriori classification approach. To determine if oral DDK performance predicts the differential bulbar disease progression

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Declaration of interest

The authors report no conflicts of interest. This work was supported by NIH-NIDCD under Grants R01DC009890, R01DC0135470, K24DC016312, the ALS Society of Canada under the Denise Ramsay Discovery Grant, and the CIHR Planning Grant no. FRN126682.

Data set statement

The data set will be made available in a de-identified format upon request.

trajectories in these individuals during the early stages of the tracked period (prior to significant bulbar/speech signs), twenty-two measures of lip motor performance in an oral DDK task were derived to (1) differentiate fast and slow bulbar progressors using the Receiver Operating Characteristic analysis and (2) predict bulbar disease progression rates across all individuals using linear regressions.

Results: Movement jitter, a measure of temporal variability of alternating lip movement during DDK, showed 80% sensitivity and 95% specificity in differentiating fast and slow bulbar progressors early in the disease, and outperformed the ALSFRS-R bulbar subscore and articulation rate. Movement jitter also predicted bulbar disease progression rates across participants.

Conclusions: Findings provided preliminary validation of the clinical value of movement jitter during oral DDK in patient stratification and bulbar disease prognosis.

Keywords

Bulbar amyotrophic lateral sclerosis; oral diadochokinesis; prognosis; patient stratification

Introduction

The progressive loss of speaking and swallowing abilities due to bulbar motor involvement in amyotrophic lateral sclerosis (ALS) has several significant consequences including social isolation, malnutrition, dehydration, and aspiration pneumonia, which significantly reduce the quality of life and shorten survival [1]. The rate of bulbar deterioration and the resulting speech and swallowing declines are known to vary significantly across individuals. This heterogeneity has challenged ongoing efforts to develop accurate prognostic models of bulbar and overall disease progression. There is a critical need for validated prognostic measures of bulbar dysfunction to advise patients about the impending loss of swallowing and communication, formulate timely management, and ensure early enrollment into therapeutic trials [2].

Due to the lack of bulbar biomarkers, the monitoring of bulbar dysfunction in ALS is currently based on combined symptom-based reports and clinician-based assessments of dysarthria and dysphagia [3]. Yet, it is now well-established that measurable changes in bulbar motor performance can be detected in ALS prior to the emergence of speech and swallowing symptoms [2, 4]. Establishing valid and reliable biomarkers (measures) for capturing such early subclinical bulbar changes is thus critical for improving diagnosis of ALS.

Speech, as a finely-controlled oromotor behavior requiring spatiotemporal coordination of up to 70 muscles [5], has shown early and progressive changes throughout bulbar ALS [2, 6, 7]. Among speech tasks, oral dysdiadochokinesis (DDK) tested via rapid syllable repetitions (e.g., repetitions of “ba” at a maximum rate on one breath) is particularly sensitive to early, subtle bulbar deficits in ALS [8] given its challenging nature as a “maximum performance” task. Moreover, due to the simplicity of the syllable structures, oral DDK tends to be less susceptible to cognitive-linguistic impairments.

Given the advantages of oral DDK, our group has recently developed a brief bulbar assessment tool based on the kinematic recording of oral DDK [8]. This tool automatically derives 22 measures that comprehensively assess the range of motion, speed, and spatial-temporal control of the lips, which are the primary effectors for the repetitions of “ba” during the DDK task. Of these measures, temporal variability in alternating lip movement (i.e., movement jitter) showed relatively early and progressive changes over the bulbar disease course [8].

Oral DDK has also shown promise in identifying patients exhibiting a faster versus slower rate of bulbar decline. In a preliminary study, we developed a posteriori classification approach, which stratified patients as fast and slow bulbar progressors based on their rates of speech intelligibility decline relative to speaking rate (i.e., words per minute [WPM]) during an extended time period in which speaking rate dropped from normal to below 100 WPM [9]. It was found that, compared to intelligibility, DDK performance distinguished between the fast and slow bulbar progressors at an earlier disease stage, when speaking rate remained normal (e.g., > 150 WPM) [9].

The current study extends our prior work by evaluating the clinical value of the DDK measures as derived by the tool in [8] in predicting the differential bulbar disease progression rates in fast and slow bulbar progressors as stratified using the a posteriori approach in [9]. Specifically, we addressed three research questions: (1) Do the DDK measures change progressively and differentially over the course of fast and slow progressive bulbar ALS; (2) How sensitive/specific are these DDK measures in differentiating fast and slow bulbar progressors at the early disease stages (i.e., speaking rate >150 WPM); (3) Can the early changes in these DDK measures predict the overall bulbar disease progression rate across individuals?

Materials and Methods

Participants

Fifty-four individuals with ALS were tracked longitudinally on their oral DDK and global bulbar/speech performance (i.e., bulbar subscore on the ALS Functional Rating Scale-Revised [ALSFRS-R] [10]; articulation rate in WPM during passage reading [11] [see Supplemental Material]) for an average length of 124 days (SD = 184). Using a previously-developed a posteriori classification approach [9], the participants were stratified as 14 fast bulbar progressors and 40 slow bulbar progressors based on their bulbar disease progression rates, which were indexed by the rate of speech intelligibility decline relative to speaking rate (i.e., % decrease in intelligibility when speaking rate drops by 1 WPM) over the tracked period. Methodological details of this approach were elaborated in [9] and summarized in Supplemental Material. Demographic information for all the participants is provided in Supplemental Material and summarized in Table 1.

Procedures

The participants repeated the syllable /ba/ at the maximum rate on one breath while their speech and three-dimensional (3D) movements of the upper and lower lips were recorded.

Lip movement data were first low-passed filter at 15 Hz; the 3D Euclidean distance between upper and lower lips was then calculated (i.e., lip distance). Based on the lip distance trace during the DDK task, 22 measures (see Table 2) were automatically extracted for each participant using the algorithmic approach in [8].

Statistical analysis

Changes in DDK measures over bulbar disease course—Given the considerable variability in the time of initial bulbar symptoms relative to the global disease onset [12], it is difficult to define a common bulbar disease timeline across participants. Thus, we used speaking rate to index bulbar disease progression given its linear and progressive decline with bulbar symptom duration [12, 13]. The disease-related changes in all the DDK and clinical measures (i.e., ALSFRS-R bulbar subscore and articulatory rate) were examined relative to speaking rate over the course of fast and slow progressive bulbar ALS.

Specifically, separate linear mixed-effects (LME) models were applied with the measures as the dependent variable, speaking rate $\times$ group (i.e., fast vs. slow) as the fixed effect, and subject as the random effect. Based on these models, a subset of measures showing significant between-group differences in slope of change as a function of speaking rate ($p < 0.05$) were identified for further analyses.

Early differentiation of fast and slow bulbar progressors using DDK measures

—To determine how well the DDK measures differentiated fast and slow bulbar progressors at the early disease stages prior to the presence of significant clinical bulbar/speech signs, we selected two time points (time 1, time 2) corresponding to the time when speaking rate just dropped below 175 WPM and 150 WPM, respectively, for each participant. These cutoffs were within the normal range of speaking rate, which roughly corresponded to the mean (175 WPM) and one standard deviation (26.53 WPM) below the mean of speaking rate in age-matched healthy speakers [8]. The participants whose speaking rate never dropped below these cutoffs were excluded (10 participants excluded at time 1 and 18 participants at time 2).

The values of the measures at time 1 and time 2 were used to differentiate fast and slow bulbar progressors using the Receiver Operating Characteristic (ROC) analysis. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff were obtained for each measure at each time point.

Early prediction of bulbar disease progression rates in fast and slow progressors

—Based on the ROC analysis, the measure with the largest AUC was selected to predict bulbar disease progression rate. Two linear regressions were applied with the pre-determined bulbar disease progression rate (i.e., % decrease in intelligibility per unit drop of speaking rate) as the dependent variable and the selected measure at time 1 and time 2, respectively, as the independent variable, across all individuals.

Results

Measures with significantly different slopes of change in fast and slow bulbar progressors

As shown in Figure 1, five DDK measures (*Ncyc*, *Dur*, *Sse2*, *Tsd*, *movJitter*), ALSFRS-R bulbar subscore (*Bulb_ALSFRS*), and articulation rate (*Artic_Rate*) showed significantly different slopes of change with speaking rate over the course of fast and slow progressive bulbar ALS. Among these measures, *movJitter* showed the largest between-group slope difference (see Table 3).

Early differentiation of fast and slow bulbar progressors

The ROC curves for the seven selected measures (*Ncyc*, *Dur*, *Sse2*, *Tsd*, *movJitter*, *Bulb_ALSFRS*, *Artic_Rate*) at each time point (time 1, time 2) are shown in Figure 2. The AUC, sensitivity, specificity, and optimal cutoff for each measure are provided in Table 4. Among all the measures, *movJitter* showed the largest AUC at both time points. Moreover, the value of *movJitter* at time 2 showed high sensitivity (i.e., 0.8) and specificity (i.e., 0.95) in differentiating fast and slow bulbar progressors.

Early prediction of bulbar disease progression rates in fast and slow progressors

As shown in Figure 3, the rate of bulbar disease progression was significantly correlated with *movJitter* at both time 1 ($r=0.44$, $p=0.003$) and time 2 ($r=0.72$, $p<0.001$) across the fast and slow bulbar progressors.

Discussion

The long-term goal of this research is to identify the best measures for diagnosing, staging, and prognosticating of bulbar dysfunction due to ALS. In this study, we screened the prognostic accuracy of multiple performance-based measures derived from lip movement during a commonly-used clinical diagnostic task – oral diadochokinesis [3]. Of the 22 DDK measures tested, movement jitter, which captures the cycle-to-cycle temporal variability of lip opening and closing movements, was found to be the most effective for (1) early differentiation of fast and slow bulbar progressors (80% sensitivity, 95% specificity) and (2) early prediction of bulbar disease progression rates across individuals. Movement jitter also outperformed two established clinical bulbar measures (i.e., ALSFRS-R bulbar subscore, articulation rate). Collectively, our findings provide preliminary validation of movement jitter in DDK as a bulbar measure for patient stratification and disease prognosis in ALS.

Measures of specific bulbar motor deficits capture the heterogeneous bulbar disease progression patterns in ALS

Among the seven measures showing significantly different slopes of change between fast and slow bulbar progressors (Figure 1 and Table 3), global bulbar declines were captured by both quantitative and clinical measures including *Ncyc*, *Dur*, *Artic_Rate*, and *Bulb_ALSFRS*. *Sse2*, *Tsd*, and *movJitter* captured the specific deficits related to the spatial or temporal control of lip movement that underlie the global bulbar declines. These measures were found to show overall larger differences in the slopes of change between fast and slow bulbar progressors than did global bulbar measures (Table 3). This finding

indicated a need for separate examinations of different aspects of bulbar motor performance to capture the heterogeneous progression patterns in ALS.

Among the three measures targeting specific bulbar motor deficits, *Sse2* decreased with disease progression, suggesting reduced spatial variability of lip closing, which may be secondary to motor neuron degeneration leading to an overall decrease of movement displacement and/or reduced movement flexibility [8, 14]. *Tsd* and *movJitter*, on the other hand, increased as the disease progressed, showing increased temporal variability of alternating lip movement resulting from degraded timing control of movement [8, 14]. In particular, cycle-to-cycle temporal variability (i.e., *movJitter*) showed the largest between-group difference in the slope of change with speaking rate. This finding suggested that the disruption of the regular temporal patterning of DDK as indicated by increased cycle-to-cycle temporal variability reflected the differential disease progression trajectories in fast and slow bulbar progressors.

Temporal variability of alternating articulatory movement as a bulbar measure for early patient stratification

Although all measures referenced in Figure 1 revealed differential patterns of change over the course of fast and slow progressive bulbar ALS, only movement jitter demonstrated robust changes during the early stage (i.e., time 2, defined as the time when speaking rate dropped below 150 WPM) that differentiated fast and slow bulbar progressors with relatively high sensitivity and specificity (Table 4). Early differentiation of fast and slow bulbar progressors may improve clinical trial design. Because the variability of disease progression rates has a substantial impact on the outcomes of clinical trials [15], stratifying patients based on movement jitter during DDK can reduce the heterogeneity of treatment groups and in turn, decrease the sample size to achieve appropriate statistical power and improve the reliability of the outcomes. Also, by recruiting patients with the fast-progressing form of bulbar ALS into clinical trials, the duration of the trials may be shortened to allow prompt evaluation of drug effectiveness.

Temporal variability of alternating articulatory movement predicts bulbar disease progression rate

In addition to patient stratification, movement jitter also predicted the overall bulbar disease progression rates across all individuals during relatively early disease stages (e.g., time 2) (Figure 3). Anticipating the rate of expected bulbar decline is the key to developing effective, timely management for bulbar dysfunction in ALS [12]. In previous studies, the ALSFRS-R score and its slope of decline have been most commonly used for disease prognosis in ALS [16, 17]. However, because ALSFRS-R assesses global motor disability of various origins, its power for predicting bulbar decline rate is limited until the disease has progressed substantially [9]. The current finding suggested that, by tracking the changes in temporal variability of alternating articulatory movement in oral DDK, it is possible to anticipate the rate of forthcoming bulbar decline at a much earlier stage.

Limitations & Future directions

Several limitations of this preliminary study include (1) the use of speaking rate to index bulbar disease progression due to the lack of a common bulbar disease timeline, (2) a relatively small sample size, particularly for the fast bulbar progressor group, and (3) variation in participation duration, which might potentially bias the results toward those who participated for a longer time. Because movement jitter showed early and progressive changes over time that captured the underlying disease progression trajectory in an individual, it may qualify as a prognostic biomarker. Future studies will focus on analytical and clinical validation of this measure to substantiate its validity as a prognostic biomarker in a larger cohort. Another future direction is to develop signal processing technologies for deriving cycle-to-cycle temporal variability of oral DDK from audio recordings, which will allow remote data acquisition and assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the patients and families for their participation. They also thank Brian Richburg and Hailee Reeves for their assistance with data collection and analysis.

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Figure 1.

Seven measures showing significantly different slopes of change with speaking rate for the fast and slow progressors of bulbar ALS. Dots and circles are the data points for the fast and slow progressors, respectively. Thin solid lines show the changes of the measures with speaking rate for each fast progressor. Thick solid lines show the group pattern of change of the measures with speaking rate across all fast progressors, which were derived from the linear-mixed effects (LME) models. Similarly, thin dashed lines show the changes of the measures with speaking rate for each slow progressor. Thick dashed lines show the group pattern of change of the measures with speaking rate across all slow progressors, as derived

from the LME models. Bulb_ALSFRS = bulbar subscore on the ALS Functional Rating Scaled-Revised; Artic_Rate = articulation rate in words in per minute (WPM) during passage reading; Ncyc = total number of cycles during DDK; Dur = total duration of DDK sequence in seconds; Sse2 = lip closing gestural variability in millimeters during DDK; Tsd = cross-cycle temporal variability in seconds during DDK; movJitter = movement jitter (i.e., cycle-to-cycle temporal variability) in seconds during DDK.

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(a) ROC curves for measures at time 1

(b) ROC curves for measures at time 2

Figure 2.

ROC curves for differentiating fast and slow bulbar progressors based on the seven selected measures at (a) time 1 (i.e., time point when speaking rate just dropped below 175 words per minute [WPM] for each participant) and (b) time 2 (i.e., time point when speaking rate just dropped below 150 WPM for each participant). Bulb_ALSFERS = bulbar subscore on the ALS Functional Rating Scaled-Revised; Artic_Rate = articulation rate in WPM during passage reading; Ncyc = total number of cycles during DDK; Dur = total duration of DDK sequence in seconds; Sse2 = lip closing gestural variability in millimeters during DDK; Tsd = cross-cycle temporal variability in seconds during DDK; movJitter = movement jitter (i.e., cycle-to-cycle temporal variability) in seconds during DDK.

Figure 3.

Relationship between bulbar disease progression rate (i.e., % intelligibility decrease per unit [words per minute] decrease in speaking rate) and *movJitter* (i.e., movement jitter) at (a) time 1 (i.e., time point when speaking rate just dropped below 175 WPM for each participant) and (b) time 2 (i.e., time point when speaking rate just dropped below 150 WPM for each participant) for fast (dots) and slow (circles) bulbar progressors. The lines correspond to linear regression fits.

Table 1.

Summary statistics for the demographic and clinical characteristics of the participants at the time of recruitment (i.e., 1st session). The first five rows list the number of participants for each sex/disease onset. The rest of the rows list the mean (standard deviation) for the following variables: Age = age in years; Disease duration = days since disease onset; Diagnostic delay = delay between the time of diagnosis and disease onset; Tot_ALSFRS = total score on the ALS Functional Rating Scale-Revised (ALSFRS-R); Bulb_ALSFRS = bulbar score on the ALSFRS-R; Intell = speech intelligibility in percentage of intelligible words during the Sentence Intelligibility Test (SIT) [Tice Technologies, Lincoln, NE]; SR = speaking rate in words per minute during the SIT. All = all participants; fast = fast bulbar progressors; slow = slow bulbar progressors.

		All	Fast	Slow
Sex	Male	32	8	24
	Female	22	6	16
	Bulbar	7	3	4
Onset	Spinal	42	8	34
	Mixed	4	2	2
Age		57.38 (10.08)	60.5 (10.14)	56.26 (9.96)
Disease duration		811 (602)	627 (544)	871 (615)
Diagnostic delay		565 (488)	489 (481)	584 (495)
Tot_ALSFRS		37.27 (6.5)	37 (8.67)	37.06 (6.41)
Bulb_ALSFRS		10.38 (1.99)	9.22 (3.11)	10.7 (1.47)
Intell		95.12 (10.97)	86.29 (18.86)	98.29 (2.03)
SR		149 (46)	138 (48)	153 (46)

Table 2.

Description of all DDK measures and their neuromotor underpinnings.

	Measures	Description	Neuromotor underpinning
<i>Spatial</i>	1. <i>Slp1 (mm)</i>	Lip opening endpoint change across repetitions during the vowel of /ba/: Slope of linear regression (LR1) fitted to the <i>peaks</i> of lip distance throughout all DDK cycles	Weakness: Time-dependent changes in movement amplitude
	2. <i>Slp2 (mm)</i>	Lip closing endpoint change across repetitions during consonant closure of /ba/: Slope of linear regression (LR2) fitted to the <i>troughs</i> of lip distance throughout all DDK cycles	
	3. <i>Slp_d (mm)</i>	Change in extent of mouth opening across the repetitions of /ba/: Slope of change in the distance between LR1 and LR2	
	4. <i>Sse1 (mm)</i>	Cross-cycle lip opening gestural variability: Root-mean-square (RMS) of residuals of LR1	Movement control: Spatial variability
	5. <i>Sse2 (mm)</i>	Cross-cycle lip closing gestural variability: RMS of residuals of LR2	
	6. <i>Sse (mm)</i>	Cross-cycle lip opening-closing gestural variability: RMS of the residuals of both LR1 and LR2	
	7. <i>Scanning_d1 (mm)</i>	Cycle-to-cycle lip opening variability: Mean of absolute differences of peaks in consecutive cycles	
	8. <i>Scanning_d2 (mm)</i>	Cycle-to-cycle lip closing variability: Mean of absolute differences of troughs in consecutive cycles	
	9. <i>Scanning_d (mm)</i>	Cycle-to-cycle lip opening-closing variability: Mean of absolute differences of peaks in consecutive cycles and absolute differences of troughs in consecutive cycles	
	10. <i>D_max_open (mm)</i>	Maximum lip opening distance	Weakness: Time-independent changes in movement amplitude
	11. <i>D_max_close (mm)</i>	Maximum lip closing distance	
	12. <i>D_mean (mm)</i>	Cross-cycle mean lip distance	
<i>Temporal</i>	13. <i>Freq (cycles/s)</i>	Frequency of syllable repetitions	Movement control: Temporal coordination
	14. <i>Tsd (s)</i>	Cross-cycle temporal variability: Standard deviation of cycle duration	Movement control: Temporal variability
	15. <i>Tsd_cv</i>	Normalized cross-cycle temporal variability: Ratio of Tsd to mean cycle duration	
	16. <i>movJitter (s)</i>	Movement jitter: Cycle-to-cycle temporal variability in duration	Movement speed
	17. <i>Max_vel (mm/s)</i>	Maximum velocity of lip movement across all cycles	
<i>Spatiotemporal</i>	18. <i>STI</i>	Spatiotemporal variability index	Movement control: Spatiotemporal variability
	19. <i>D_dtw</i>	Dynamic time warping (DTW) distance: Index of dissimilarity between lip distance time series and a sinusoidal template (i.e., sine wave with the same frequency and average magnitude as the lip distance time series)	
overall	20. <i>Dur (s)</i>	Total duration of the DDK sequence	Overall oromotor capacity
	21. <i>Ncyc (cycles)</i>	Total # of cycles	

Table 3.

Statistics for seven measures showing significantly different slopes of change with speaking rate for fast and slow bulbar progressors. Mean slope = mean slope of change of the measure per unit decrease (i.e., 1 word per minute [WPM]) of speaking rate. Bulb_ALSFRS = bulbar subscore on the ALS Functional Rating Scaled-Revised; Artic_Rate = articulation rate in WPM during passage reading; Ncyc = total number of cycles during DDK; Dur = total duration of DDK sequence in seconds; Sse2 = lip closing gestural variability in millimeters during DDK; Tsd = cross-cycle temporal variability in seconds during DDK; movJitter = movement jitter (i.e., cycle-to-cycle temporal variability) in seconds during DDK.

Measure	Mean slope		Between-group slope comparison	
	Fast progressors	Slow progressors	z-score for slope difference	p-value
<i>Bulb ALSFRS</i>	0.046	0.014	3.17	0.0023
<i>Artic Rate</i>	0.77	0.27	2.81	0.006
<i>Ncyc</i>	0.450	0.13	2.36	0.02
<i>Dur</i>	0.072	0.007	2.36	0.02
<i>Sse2</i>	0.004	0.0005	3.20	0.0018
<i>Tsd</i>	-5.75e-4	7.57e-5	-3.32	0.0012
<i>movJitter</i>	-0.002	-0.0004	-5.61	< 0.001

Table 4.

Area under the curve (AUC), sensitivity, specificity and optimal cutoff for all measures showing significantly different slopes of change with speaking rate for fast and slow bulbar progressors at time 1 and time 2. Time 1 = time point when speaking rate just dropped below 175 words per minute (WPM) for each participant; Time 2 = time point when speaking rate just dropped below 150 WPM for each participant. Bulb_ALSFERS = bulbar subscore on the ALS Functional Rating Scaled-Revised; Artic_Rate = articulation rate in WPM during passage reading; Ncyc = total number of cycles during DDK; Dur = total duration of DDK sequence in seconds; Sse2 = lip closing gestural variability in millimeters during DDK; Tsd = cross-cycle temporal variability in seconds during DDK; movJitter = movement jitter (i.e., cycle-to-cycle temporal variability) in seconds during DDK.

Measure	Time 1				Time 2			
	AUC	Sensitivity	Specificity	Cutoff	AUC	Sensitivity	Specificity	Cutoff
<i>BulbALSFRS</i>	0.40	0.44	0.5	11	0.24	0.17	0.61	12
<i>Artic Rate</i>	0.26	0.25	0.57	254	0.29	0.29	0.72	265
<i>Ncyc</i>	0.38	0.39	0.71	58	0.18	0.1	0.9	83
<i>Dur</i>	0.49	0.46	0.68	15.65	0.51	0.6	0.55	10.62
<i>Sse2</i>	0.4	0.46	0.55	0.63	0.35	0.5	0.45	0.46
<i>Tsd</i>	0.61	0.46	0.84	0.067	0.67	0.6	0.75	0.067
<i>movJitter</i>	0.71	0.54	0.87	0.36	0.9	0.8	0.95	0.37