

# Effects of different cognitive functions on acoustic voice parameters in young adults

## Genç yetişkinlerde farklı bilişsel işlevlerin akustik ses parametrelerine etkisi

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### ABSTRACT

**Objectives:** The aim of this study was to investigate the effect of different cognitive functions on acoustic voice parameters by recording the use of cognitive functions during extended /a/ phonation in young adults.

**Patients and Methods:** This study was conducted with a total of 31 participants (8 males, 23 females, mean age: 22.3±1.1 years; range, 18 to 30 years) between June 14, 2023 and August 23, 2023. The mean fundamental frequency (F0), jitter (local), jitter (rap), shimmer (local), shimmer dB, and mean harmonics-to-noise ratio values were analyzed as acoustic voice parameters in a total of 186 voice recordings taken in six tasks, including normal and other five tasks (visual attention, language, auditory memory, visual memory, and working memory).

**Results:** A statistically significant difference was found between the acoustic parameters of the six tasks (p<0.001). Shimmer dB showed a statistically significant difference between the auditory memory task and normal state, visual attention and normal state, and working memory and normal state (p<0.05).

**Conclusion:** Different cognitive functions, especially auditory memory, visual attention, and working memory, may have an effect on acoustic voice parameters. Therefore, cognitive functions can be evaluated to identify deficiencies in the relevant cognitive area, and working on these cognitive functions together with voice therapy may shorten the therapy process.

**Keywords:** Acoustic, cognitive, shimmer, voice, young adult.

### ÖZ

**Amaç:** Bu çalışmada, genç yetişkinlerde uzatılmış /a/ fonasyonu sırasında bilişsel işlevlerin kullanımını içeren ses kayıtları alınarak farklı bilişsel işlevlerin akustik ses parametreleri üzerindeki etkisi araştırıldı.

**Hastalar ve Yöntemler:** Bu çalışma, toplam 31 katılımcı (8 erkek, 23 kadın; ort. yaş: 22.3±1.1 yıl; dağılım, 18-30 yıl) ile 14 Haziran 2023 - 23 Ağustos 2023 tarihleri arasında gerçekleştirildi. Normal ve diğer beş görev (görsel dikkat, dil, işitsel bellek, görsel bellek ve çalışma belleği) olmak üzere altı görevde alınan toplam 186 ses kaydında akustik ses parametreleri olarak ortalama fundamental frekans (F0), jitter (lokal), jitter (rap), shimmer (lokal), shimmer dB ve harmonik/gürültü oranı değerleri analiz edildi.

**Bulgular:** Altı görevin akustik parametreleri arasında istatistiksel olarak anlamlı bir fark bulundu (p<0.001). Shimmer dB, işitsel bellek görevi ile normal durum, görsel dikkat ile normal durum ve çalışma belleği ile normal durum arasında istatistiksel olarak anlamlı farklılık gösterdi (p<0.05).

**Sonuç:** İşitsel hafıza, görsel dikkat ve çalışma hafızası başta olmak üzere farklı bilişsel işlevler akustik ses parametreleri üzerinde etkili olabilmektedir. Bu nedenle, bilişsel işlevler değerlendirilerek ilgili bilişsel alandaki eksiklikler tespit edilebilir ve ses terapisi ile birlikte bu bilişsel işlevler üzerinde çalışmak terapi sürecini kısaltabilir.

**Anahtar sözcükler:** Akustik, biliş, shimmer, ses, genç yetişkin.

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According to the latest regulation of the World Health Organization in 2017, the group between the ages of 18 to 65 was reported as young adults.<sup>[1]</sup> The rate of voice disorders in young adults is estimated to be 6%.<sup>[2]</sup> The most common diagnoses among adults with voice disorders include functional dysphonia (20.5%), acid laryngitis (12.5%), and vocal polyps (12%).<sup>[3,4]</sup> There is currently no clear consensus on the etiology of voice disorders.<sup>[5]</sup> However, risk factors include voice hygiene, voice use habits, psychological factors, personality traits, and disorders of the autonomic nervous system.<sup>[6,7]</sup> Research on disorders in the autonomic nervous system uses questionnaires that include questions to determine the symptoms that occur as a result of these disorders.<sup>[5]</sup> However, there are also studies showing that autonomic nervous system arousal and cognitive load affect some aspects of motor speech processes.<sup>[8,9]</sup>

The term cognitive is a set of functions involving the processing, perception, and understanding of stimuli from the environment.<sup>[10]</sup> According to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), cognitive functions are discussed under six main headings: attention, memory, language, executive function, perceptual-motor, and social cognition.<sup>[11]</sup> In two studies, the terms cognitive load and mental load were used when a task requiring the use of task-specific cognitive functions was given.<sup>[12,13]</sup> The sympathetic part of the autonomic nervous system responds to tasks that use cognitive functions.<sup>[14]</sup> The autonomic nervous system influences different features of speech during different cognitive functions, such as the timing and stability of speech production,<sup>[15]</sup> lip kinematics,<sup>[8]</sup> and rate.<sup>[16]</sup> The human voice represents an important alternative measure of cognitive load, and there are studies showing that cognitive load also affects acoustic voice parameters.<sup>[5,12,13]</sup>

There are different results in the literature regarding the relationship between cognitive functions and acoustic voice parameters. For example, fundamental frequency (F0) has been found to increase,<sup>[12]</sup> decrease,<sup>[17]</sup> or remain unchanged<sup>[5]</sup> with cognitive load. In addition, different results were found in sound pressure level<sup>[5,16]</sup> and perturbation measurements.<sup>[12]</sup> These inconsistencies stand out when the results of studies on voice and cognitive functions are compared.

Knowing the acoustic parameters most sensitive to cognitive load can improve the performance of automatic voice recognition systems. In addition, determining the acoustic parameters associated with cognitive functions may lead to rapid progress in the therapy of voice disorders that have occurred or may occur by applying voice therapy together with the task

for the associated cognitive function. Therefore, in this study, we aimed to investigate the effect of different cognitive functions on acoustic voice parameters in young adults by taking voice recordings, including the use of cognitive functions during extended vowel phonation. In addition, the participants' performance on the task without normal cognitive functioning was compared with their performance on the task with cognitive functioning, and which parameters in the acoustic voice assessment would be affected by different cognitive functions were determined.

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## PATIENTS AND METHODS

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The study was conducted with healthy young adults who were undergraduate students of the speech and language therapy department between June 14, 2023 and August 23, 2023. Inclusion and exclusion criteria were determined to eliminate factors that may directly affect cognitive functions and voice in the participants. The inclusion criteria were as follows: being at least a third-year undergraduate student of speech and language therapy (to be at a similar educational level), having taken the assessment course in voice disorders (to master the appropriate position distance effect on the voice), having a score of 30 on the Mini-Mental State Examination (MMSE; to have the same general cognitive level), never having smoked before (due to its effect on voice), not having known attention deficit and cognitive impairment (to have no effect on cognitive functions), not being in the menstrual period for females (to have no effect on voice), and being able to phonate the /a/ vocal for at least 15 sec (to be able to maintain phonation in the given cognitive task). The exclusion criteria were as follows: having any vocal disease and pathological or physiological problems that may disrupt the formation of the voice, neurological disease, lung disease, having an upper respiratory tract infection during voice recording, having received treatment or undergone surgery for any vocal disease, having neuropsychiatric disease, as it may affect cognitive functions, having a diagnosis of attention deficit, and having a sleep time of less than 7 h during the evaluation. Students from the principal investigator's institution were invited to participate in the study using the snowball method. Within one month, 49 people volunteered to participate in the study. However, three people were excluded from the study since their MMSE result was below 30, five people were excluded because they had smoked before, two people were excluded because their maximum phonation time was below 15 sec, three people were excluded because they had upper respiratory tract infection during the evaluation, four people were

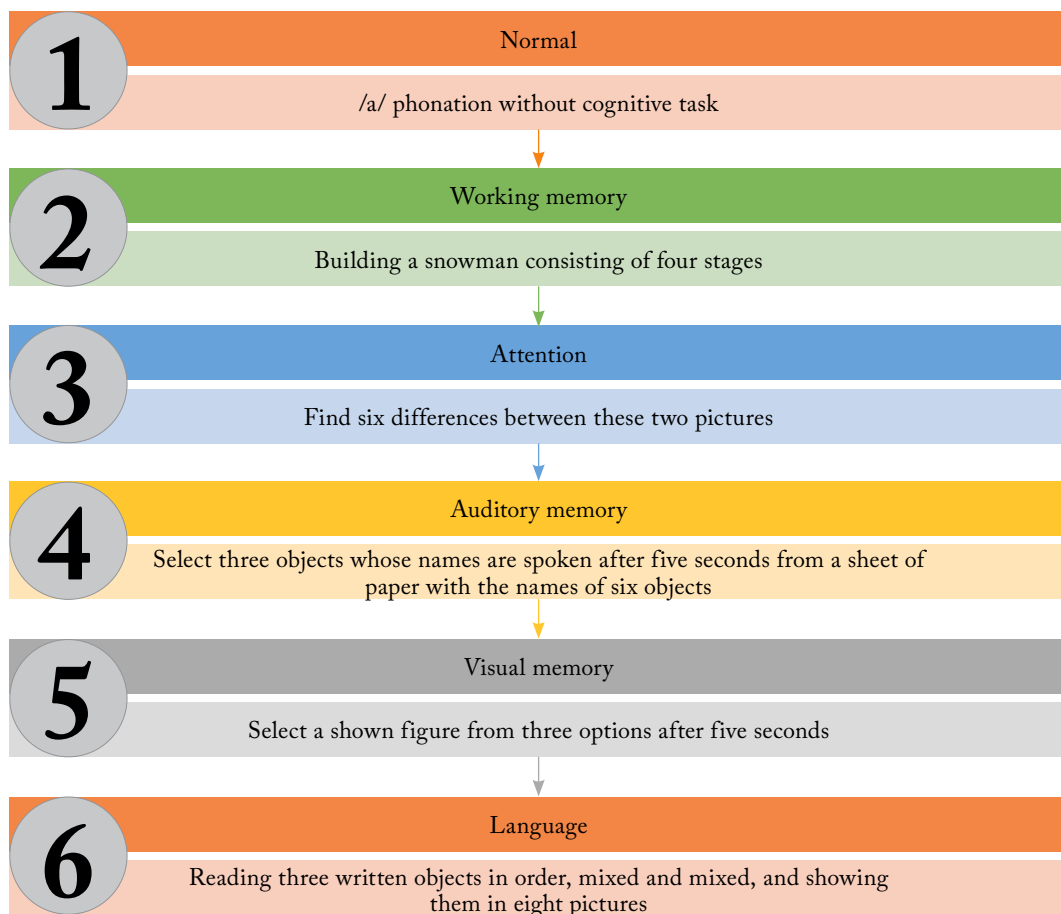
excluded because they were menstruating during the evaluation, and one person was excluded due to taking medication for attention deficit. Finally, this study was conducted with a total of 31 participants (8 males, 23 females; mean age:  $22.3 \pm 1.1$  years; range, 18 to 30 years).

For the study, task questions were prepared according to cognitive functions. Afterward, a pilot study was conducted, and the opinions of the participants were obtained. During the cognitive tasks, which were finalized according to the opinions of the participants, voice recordings were taken while the participants were phonating /a/. The last audio recordings were analyzed and interpreted.

Before data collection, sample questions were prepared by the researchers for four areas of basic cognitive functions: executive functions, language, memory, and attention. Cognitive tasks were determined in a way that they would not require voice from the external environment and there would be no external noise not to affect the voice recording. The questions in

the ready-made tests used in the clinic and explained in the course content were not used in the evaluation. This is to familiarize people with the question and not to prevent us from clearly observing the effect of cognitive load. In addition, all pictures were printed in black and white. Thus, the visual cue and visual stimulus factor were tried to be minimized.

One of the two questions originally designed for visual attention was removed to prevent people's voices from being affected by fatigue due to too many consecutive tasks. Only the memory section had two tasks to ensure that auditory and visual memory were evaluated separately, while the other sections had one task. A pilot study was conducted with seven people for the functionality of these tasks and the comprehensibility of the questions. Since six of them stated that they could not understand the baklava (traditional Turkish dessert) picture in the language section, this picture was removed, and the language task was performed in the real application with 31 people. These tasks are as follows and are shown in Figure 1.



**Figure 1.** Different tasks where voice recordings are taken.

Working memory functions (task 1) are included among executive functions in the current literature, and it is stated that event sequencing is a function that requires working memory. The task of building a snowman consisting of four stages was given to the graphic designer to assess this function.

Language (task 2) is a cognitive function and has its own subfields. In this study, a task was created to demonstrate reading comprehension. For this task, while there were eight pictures on a page, the students were asked to read the three objects written above in order and show them among the mixed pictures.

Attention (task 3) is considered the basis of all cognitive functions, and in this study, the task of showing the difference between two pictures, frequently used in therapies for visual attention, was chosen. To evaluate this function, the graphic designer was asked to draw a new image that people were not familiar with before. Participants were asked to find six differences between these two pictures.

As a capacity for memory, two tasks were created for short-term memory assessment. One of these tasks was for auditory (task 4) and the other for visual memory (task 5). In these tasks, three object names were spoken in auditory memory. After 5 sec, the participant was asked to choose the names of the objects from a paper with the names of six objects. In visual memory, a shape was shown. After 5 sec, the participant was asked to choose the same shape from three options.

Audio of all participants was recorded in the same room where the ambient noise was not above 35 dB by Praat software version 5.1.37 (Paul Boersma and David Weenink, University of Amsterdam, Amsterdam, The Netherlands). Even though all participants were students of speech-language pathologists, they were informed about the position they should assume during the assessment and explained how to perform the task before each task was performed. The papers with the relevant cognitive task were attached to the phone mount on the desktop microphone stand, and the participant was adjusted so that the paper was at their eye level.

Each task was performed during /a/ phonation. It was recorded as a WAV (Waveform Audio File Format) file using the Praat software, which is one of the objective methods in voice analysis. In the voice analysis, the recording was taken after the participants took a deep breath and were asked to phonate the /a/ vowel while showing the required action for the given cognitive task on the screen. Six voice recordings of each participant were taken, including five cognitive

tasks and normal states without tasks. During voice recordings, the distance between the patient and the microphone was set to 15 cm. A Shure SM48 microphone (Shure Inc., Niles, IL, USA) and Shure MVI audio interface (Shure Inc., Niles, IL, USA) were used. A pop filter was installed on the microphone to minimize noise.

The mean fundamental frequency (F0), jitter (local), jitter (rap), shimmer (local), shimmer (dB), mean harmonics-to-noise ratio (HNR) values were analyzed as acoustic voice parameters in a total of 186 voice recordings (six recordings per participant) taken in a total of six tasks, including the normal state and other five tasks.

### Statistical analysis

Data were analyzed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The conformity of the variables to normal distribution was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since it was determined that the variables did not conform to normal distribution, the Friedman test was used to compare the values between six groups consisting of the normal state and five task records. The Wilcoxon signed-rank test was used for pairwise comparisons between groups. *P* The statistical significance level was set at  $p < 0.05$ .

## RESULTS

Of the participants, 9.68% ( $n=3$ ) were third-year students, and 90.32% ( $n=28$ ) were fourth-year students. The mean F0 of all participants in the normal state was  $189.34 \pm 54.13$ . The mean values of jitter (local), jitter (rap), shimmer (local), shimmer dB, and HNR were  $0.33 \pm 0.16$ ,  $0.18 \pm 0.10$ ,  $3.89 \pm 1.89$ ,  $0.34 \pm 0.17$ , and  $23.48 \pm 16.27$ , respectively (Table 1).

According to the results of the Friedman test, there was a statistically significant difference between the groups ( $\chi^2=661.114$ ,  $p=0.000$ ) in the comparison, including F0, jitter (local), jitter (rap) shimmer (local), shimmer dB, and HNR for all cognitive tasks (total of six groups) for cognitive normal /a/ phonation (Table 2).

Shimmer dB showed a statistically significant difference between the auditory memory task and the normal state ( $p=0.01$ ). Shimmer dB increased from  $0.343 \pm 0.167$  in the normal condition to  $0.415 \pm 0.193$  in the auditory memory task. In the visual attention task, shimmer (local) increased statistically significantly from  $4.889 \pm 1.887$  to  $5.036 \pm 2.924$ , and shimmer dB increased to  $0.454 \pm 0.259$ . In the working memory task, shimmer dB increased statistically significantly compared to the normal condition (mean shimmer dB =  $0.438 \pm 0.223$ ,

**Table 1**  
Voice analysis results in normal and different cognitive tasks (n=31)

	Mean±SD	Median	Min-Max
<b>Normal</b>			
F0	189.34±54.13	212.32	95.35-276.15
Jitter (local)	0.33±0.16	0.30	0.07-0.68
Jitter (rap)	0.18±0.10	0.17	0.03-0.41
Shimmer (local)	3.89±1.89	3.47	1.77-10.39
Shimmer (dB)	0.34±0.17	0.30	0.16-0.93
HNR	23.48±16.27	20.36	14.66-108.74
<b>Attention task</b>			
F0	186.06±53.31	192.60	102.44-281.83
Jitter (local)	0.36±0.28	0.31	0.11-10.65
Jitter (rap)	0.19±0.19	0.16	0.04-10.08
Shimmer (local)	5.04±2.92	3.78	1.72-11.52
Shimmer (dB)	0.45±0.26	0.34	0.15-10.06
HNR	20.17±5.29	20.09	8.19-31.94
<b>Auditory memory task</b>			
F0	186.46±58.79	206.54	94.42-274.46
Jitter (local)	0.36±0.24	0.34	0.14-0.62
Jitter (rap)	0.19±0.14	0.17	0.06-0.32
Shimmer (local)	4.46±1.99	3.69	1.96-12.64
Shimmer (dB)	0.42±0.19	0.36	0.18-1.12
HNR	19.89±4.07	19.29	11.17-28.05
<b>Visual memory task</b>			
F0	186.0006±51.53342	206.5420	94.42-274.46
Jitter (local)	0.3380±0.12178	0.3350	0.14-0.62
Jitter (rap)	0.1729±0.06376	0.1740	0.06-0.32
Shimmer (local)	4.4741±2.35058	3.6860	1.96-12.64
Shimmer (dB)	0.412±0.217	0.356	0.175-1.119
HNR	19.5010±4.01578	19.2900	11.17-28.05
<b>Language task</b>			
F0	193.44±53.98	210.27	103.27-279.83
Jitter (local)	0.35±0.18	0.30	0.9-0.75
Jitter (rap)	0.18±0.11	0.15	0.03-0.45
Shimmer (local)	4.41±2.72	3.27	1.83-11.70
Shimmer (dB)	0.40±0.24	0.30	0.16-1.13
HNR	20.53±4.52	19.63	12.47-29.94
<b>Working memory task</b>			
F0	184.54±54.14	107.37	278.89-204.73
Jitter (local)	0.35±0.20	0.12	0.96-0.30
Jitter (rap)	0.18±0.11	0.06	0.57-0.16
Shimmer (local)	4.76±2.50	1.96	11.93-3.86
Shimmer (dB)	0.43±0.22	0.18	1.06-0.38
HNR	19.59±4.29	11.25	28.16-19.31

SD: Standard deviation; HNR: Harmonics-to-noise ratio.

Table 2

Comparison of six voice parameters in six tasks (n=31)

Total acoustic parameters	
Chi-square	661.114
Df	23
Asymptotic significance	0.000
Df: Degrees of Freedom; Friedman test.	

$p=0.24$ ), while HNR decreased statistically significantly from  $23.480 \pm 16.273$  to  $19.593 \pm 4.291$  ( $p=0.039$ , Table 3). In visual memory and language tasks, no statistically significant difference was found in any voice parameter compared to the normal condition ( $p>0.05$ , Table 3).

## DISCUSSION

The main aim of the study was to investigate the effect of different cognitive functions on acoustic voice parameters in young adults. The mean voice parameters of the participants were within the normal values of their age group when asked to perform /a/ phonation without a cognitive task.<sup>[18]</sup> Moreover, differences in F0, jitter (local), jitter (rap), shimmer (local), shimmer dB, and HNR were found for /a/ phonation with and without all cognitive tasks (normal condition). These findings show that cognitive functions influence

voice. Voice is a speech component, and cognitive processes are necessary in speech. During cognitive tasks, prosodic features, another component of speech, may also change.<sup>[19]</sup> Prosodic features reflect changes in the control of vocal fold vibration (vibrations, standard deviation of F0) and glottal resistance (shimmer). The F0 provides information about the number of glottal opening/closing cycles and is also related to laryngeal muscle tension. The frequency of amplitude modulation of glottal pulses during vowel phonation can be linked to the control of airflow in the glottis. The HNR reflects speech activity, while others indicate the effects of holistically coupled vocal tract resonators and voice emitted from the lips. Therefore, physiological changes may occur during the cognitive task and may be linked to acoustic voice parameters.<sup>[12]</sup> Moreover, the common involvement of autonomic nervous system activity in speech activity and cognitive process may explain our findings.<sup>[5]</sup>

Another aim of this study was to determine which parameters in acoustic voice evaluation would be affected by different cognitive functions. Accordingly, the most important finding of our study was that there was a difference in shimmer dB between the normal state and the paired cognitive tasks of auditory memory, visual attention, and working memory. Shimmer dB was found to be higher in the cognitive tasks compared to the normal condition task. In addition, some of

Table 3

Pairwise comparison of voice analysis results in cognitive tasks and the normal state

	F0	Jitter (local)	Jitter (rap)	Shimmer (local)	Shimmer (dB)	HNR
Normal-attention						
Z	-0.627 <sup>c</sup>	-0.745 <sup>c</sup>	-0.088 <sup>b</sup>	-20.136 <sup>c</sup>	-20.312 <sup>c</sup>	-0.314 <sup>b</sup>
p	0.531	0.456	0.930	<b>0.033*</b>	<b>0.021*</b>	0.754
Normal-auditory memory						
Z	-0.196 <sup>b</sup>	-0.441 <sup>c</sup>	-0.196 <sup>b</sup>	-1.578 <sup>c</sup>	-2.489 <sup>c</sup>	-1.333 <sup>b</sup>
p	0.845	0.659	0.845	0.115	<b>0.013*</b>	0.183
Normal-visual memory						
Z	-0.051 <sup>c</sup>	-0.679 <sup>c</sup>	-0.082 <sup>c</sup>	-0.812 <sup>c</sup>	-1.419 <sup>c</sup>	-1.697 <sup>b</sup>
p	0.959	0.497	0.934	0.417	0.156	0.090
Normal-language						
Z	-0.216 <sup>b</sup>	-0.648 <sup>c</sup>	-0.262 <sup>c</sup>	-0.566 <sup>c</sup>	-0.586 <sup>c</sup>	-1.162 <sup>b</sup>
p	0.829	0.517	0.793	0.572	0.558	0.245
Normal-working memory						
Z	-0.627 <sup>b</sup>	-0.237 <sup>c</sup>	-0.247 <sup>b</sup>	-0.1882 <sup>c</sup>	-2.252 <sup>c</sup>	-2.067 <sup>b</sup>
p	0.530	0.813	0.805	0.060	<b>0.024*</b>	<b>0.039*</b>

Wilcoxon signed-rank test; b: Based on negative ranks; c: Based on positive ranks; \* Considered statistically significant for  $p<0.05$ .



the students who participated in our study provided feedback after the test. It was generally stated that the most difficult sections were visual attention, working memory, and auditory memory, respectively. These views are also common for the increase in shimmer dB, which is common in these sections of voice analysis. Shimmer is a short-term variability in amplitude and reflects the amplitude stability of the acoustic signal from one period to another.<sup>[20]</sup> Shimmer is altered by decreased glottal resistance and mass lesions in the vocal folds and is associated with the presence of noise emission and breathy voice quality.<sup>[21]</sup> In our study, the increase in the shimmer value in different cognitive tasks suggests that glottal resistance control may be affected by the cognitive task. Our results are in parallel with Mendoza and Carballo's<sup>[22]</sup> study. In addition, two studies have reported an increase in perturbation in the voices of older individuals.<sup>[23,24]</sup> Our results suggest that some cognitive tasks may impair amplitude stability and increase shimmer dB, even if there is no age-related effect on voice. Cognitive tasks may cause stress in individuals, and vocal muscle tension may increase. This may affect the vibration regularity of the vocal folds, leading to a possible increase in jitter and shimmer.<sup>[22]</sup>

In the study of Boyer et al.,<sup>[12]</sup> the number of periods and jitter were found to be the strongest predictors of memory load. However, shimmer (local) and HNR were not found to significantly contribute to the multiple regression model.<sup>[12]</sup> In our study, however, F0 did not change significantly in any of the cognitive tasks, and shimmer dB was the apparent co-significant affect parameter. The reason why we found different results with Boyer et al.'s study may be that we used different cognitive tasks. In addition, the fact that verbal tasks were not used in our study may also have led to this difference. Our study is similar to the studies by MacPherson et al.<sup>[5]</sup> and Dahl and Stepp.<sup>[13]</sup> An increase in F0 under cognitive load may be associated with an increase in longitudinal strain.<sup>[13]</sup> The reason why F0 did not change in our results may be that the cognitive tasks we used did not affect longitudinal tension enough to increase F0.

A recent study reported that HNR was not a significant predictor of cognitive load.<sup>[13]</sup> In our study, the change in HNR was only in working memory. Harmonics-to-noise ratio decreased in the working memory task. This decrease in HNR was found to be inconsistent with a study in the literature.<sup>[12]</sup> The reason for this inconsistency may be the differences in the cognitive tasks and voice-speech production of the two studies. In our study, waiting time for thinking during sequencing in the working memory task may have reduced the HNR. However, the decrease in HNR

indicates an increase in the level of extra-audible noise in the voice. This result suggests that the decrease in the HNR parameter in the working memory task should be taken into account.

This study has some limitations. The questions we prepared were not standardized. Although there were orientation and other cognitive tasks among cognitive functions, there were no tasks specific to visual-spatial functions. Another limitation is the small number of participants. In future studies, the number of participants can be increased, participants can be divided into age groups, or long-term memory can also be evaluated. Determining the relationships between different cognitive functions and voice for each age group may be more effective in conducting voice therapy with these cognitive functions in therapies.

Nonetheless, there are some strengths to this study. The strongest aspect of our study is that the participants were homogeneous for the age and education factors of the group that may affect cognitive functions and voice. Another strength of our study is that the participants were exposed to cognitive tasks that they had not encountered before. Sample questions for four areas of basic cognitive functions, namely executive functions, language, memory, and attention, were determined by the researchers. It is thought that the prepared sample questions will be useful for future research.

In conclusion, this study demonstrated that different cognitive functions had an effect on acoustic voice parameters. It was determined that the cognitive tasks affecting the voice in young adults were auditory memory, visual attention, and working memory; during these cognitive tasks, there was an increase in the basic voice parameter shimmer dB and difficulty in maintaining the loudness. Therefore, deficiencies in the relevant cognitive area can be determined by evaluating cognitive functions, particularly in individuals who cannot maintain the intensity of the voice. In young adults with voice disorders, working on these cognitive functions together with voice therapy may shorten the therapy process. In addition, we speak with many cognitive tasks during the day. Cognitive loads can cause breaks in the voice. For example, an increase in shimmer for a long time can cause voice disorders in people. Therefore, the increase in the shimmer dB parameter during vocal tasks should not be overlooked. Future research could focus on identifying sensitive voice parameters for speech disorders and cognitive processes.

**Ethics Committee Approval:** The study protocol was approved by the Üsküdar University Ethics Committee (date: 14.04.2023, no: 61251342). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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