Methylphenidate mediated change in prosody is specific to the performance of a cognitive task in female adult ADHD patients

YUVAL BLOCH1,2,3, SHAI AVIRAM1,4, RONNIE NEEMAN1,4, YORAM BRAW1,5, URIEL NITZAN1,3, HAGAI MAOZ1,2,3 & AVIVA MIMOUNI-BLOCH1,3,6

1The Emotion-Cognition Research Center, Shalvata Mental Health Care Center, Hod-Hasharon, Israel, 2Child and Adolescent Outpatient Clinic, Shalvata Mental Health Care Center, Hod-Hasharon, Israel, 3Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, 4Department of Psychology, Haifa University, Haifa, Israel, 5Department of Behavioral Sciences, Ariel University Center of Samaria, Ariel, Israel, and 6The Pediatric Neurology and Developmental Unit, Loewenstein Rehabilitation Hospital, Raanana, Israel

Abstract

Objectives. Prosody production is highly personalized, related to both the emotional and cognitive state of the speaker and to the task being performed. Fundamental frequency (F main) is a central measurable feature of prosody, associated with having an attention deficit hyperactive disorder (ADHD). Since methylphenidate is an effective therapy for ADHD, we hypothesized that it will affect the fundamental frequency of ADHD patients. Methods. The answers of 32 adult ADHD patients were recorded while performing two computerized tasks (cognitive and emotional). Evaluations were performed at baseline and an hour after patients received methylphenidate. Results. A significant effect of methylphenidate was observed on the fundamental frequency, as opposed to other parameters, of prosody. This change was evident while patients performed a cognitive, as opposed to an emotional, task. This change was seen in the 14 female ADHD patients but not in the 18 male ADHD patients. The fundamental frequency while performing a cognitive task without methylphenidate was not different in the female ADHD group, from 22 female controls. Conclusions. This pilot study supports prosodic changes as possible objective and accessible dynamic biological marker of treatment responses specifically in female ADHD.

Key words: ADHD; pharmacotherapy; gender; main frequency; prosody

Introduction

Prosody has been defined as the melody and intonation of speech (Aziz-Zadeh et al. 2010). It is created through the variability of the frequencies, times, and intensities of phonation (García-Toro et al. 2000; Aziz-Zadeh et al. 2010). Prosody production is a specialty of the premotor cortex, in particular of the inferior frontal gyrus (I FG; Aziz-Zadeh et al. 2010). It serves to relay linguistic and emotional information from one individual to another. Prosody production is to a large extent unconscious and is strongly related to the emotional state of the speaker, as well as the emotional and cognitive tasks that he faces at the time. Thus it is not surprising that research into potential biomarkers of central nervous system disorders such as schizophrenia, affective disorder, autistic spectrum disorder and Parkinson’s disease have explored prosody and other speech characteristics as possible physiologically based indicators of disease progression, severity or treatment efficacy (García-Toro et al. 2000; Alpert et al. 2002; Cannizzaro et al. 2004; Harel et al. 2004; Reilly et al. 2004; Aziz-Zadeh et al. 2010; Nadig and Shaw 2012). Voice production typifies the specific person. Prosody like other voice features is effected by multiple variables including age (Dilley et al. 2012), gender (Rymarczyk and Grabowska 2007), oral and laryngeal characteristics (Hoffman et al. 2012). Thus, some of the recent studies have focused on the study of voice production of treatment efficacy using a within subject
ADHD is a common neurobehavioral disorder in which the clinical manifestations are suspected to have evolved from difficulties in attention and executive functions (Willcutt et al. 2005; Kessler et al. 2006). Neuroanatomical and neuroimaging studies in patients with ADHD point to fronto-striatal circuit abnormalities. ADHD is defined as a clinical entity, diagnosed and evaluated using questionnaires and clinical assessments (Willcutt et al. 2005; Kessler et al. 2006; Wilens et al. 2009). However, the limitations of subjective reports for diagnosing ADHD have been emphasized in recent adult ADHD literature (Manor et al. 2012). Since core symptomatic difficulties relate to coping with sustained mental efforts, performing cognitive tasks has been suggested as objective measures in ADHD research (Willcutt et al. 2005; Kessler et al. 2006; Wilens et al. 2009). Tests that evaluate continuous attention (CPT) and other executive functions, do not find a recognizable deficit in more than 15% of ADHD patients (Chhabildas et al. 2001; Willcutt et al. 2005; Wang et al. 2011; Bloch et al. 2012). Also, approximately 10–30% of healthy subjects cannot be distinguished from ADHD patients based on cognitive tests alone (Kessler et al. 2006). For many patients, methylphenidate therapy ameliorates both the symptoms and the deficits found in CPT’s (Swanson et al. 2011). Performance on a CPT achieved by methylphenidate is not an unequivocal predictor of the clinical utility of the medication (Chhabildas et al. 2001; Willcutt et al. 2005; Wang et al. 2011; Bloch et al. 2012). Performance on these tests is possibly effected by motivation and basic cognitive abilities (Chhabildas et al. 2001; Willcutt et al. 2005; Wang et al. 2011). Imaging and electrophysiological assessments present significant and valuable findings, but their sensitivity and specificity in assessing ADHD patients is equivocal (Willcutt et al. 2005; Swanson et al. 2011). Possibly part of the limitations relate to diversity in ADHD (Westerberg and Spencer 2009). It is therefore important to have objective and easy-to-attain physiological markers to substantiate the diagnosis of ADHD and to predict the benefits of therapy.

The few existing studies related to prosody production among ADHD patients point to the fundamental frequency of prosody as an acoustic measure that is potentially correlated with ADHD (Hamdan et al. 2009). Two additional phenomena of fundamental frequency support its potential utility in ADHD research; first, ADHD patients are described clinically as noisy (Willcutt et al. 2005; Kessler et al. 2006; Hamdan et al. 2009; Wilens et al. 2009), and fundamental frequency is related to pitch and thus to how loud speech is perceived by others (Hamdan et al. 2009; Aziz-Zadeh et al. 2010). Second, control of fundamental frequency is highly correlated with feedback loops that convey acoustic emotional and social precepts. Therefore, prosody in general, and fundamental frequency in particular, demand attention and control (Parkinson et al. 2012).

Prosody is affected by the task performed. Difficulties in coping with boring cognitive efforts typify ADHD patients. Thus, we hypothesized that the production of specific voice characteristics (i.e., fundamental frequency) would be influenced by methylphenidate therapy while the patient was performing a cognitive task but not while performing an emotional task.

**Method**

Thirty-six patients diagnosed with ADHD were recruited. Due to technical difficulties only 32 had voice recordings. Fourteen were females and the mean age of the participants was 30.75 years (SD ± 5.9).

ADHD patients were recruited via advertisements and the outpatient clinic of the Shalvata Mental Health Care Center. They were required to be between 18 and 45 years of age, with a diagnosis of adult ADHD. Exclusion criteria included mental retardation, substance abuse (with the exceptions of nicotine and caffeine), any major medical disorder (emphasizing neurological disorders), schizophrenia spectrum disorder, bipolar disorder, autistic spectrum disorder, a depressive episode or an active anxiety disorder within the last year. The diagnosis of ADHD was based on thorough clinical interviews conducted by a psychiatrist experienced in adult ADHD diagnosis and was assisted by the Adult ADHD Self Report Scale (ASRS; Adler et al. 2006) and the Wender-UTah Adult ADHD Scale (WUAAS; Ward et al. 1993). After signing an informed consent form, all participants underwent an evaluation: their voices were recorded while they performed two computerized tasks. Tasks were presented onscreen and thus were standardized. Participants received onscreen instructions and were recorded while performing the tasks. The tasks included the following: (a) “Neutral task”: participants were recorded while providing general information about themselves, i.e., their names, ages, home addresses, etc. This task was used for calibration. (b) “Emotional task”: highly emotionally laden pictures from “The International Affective Picture System” (IAPS), including one picture of a dying man and one picture of a woman breastfeeding, were used (Aldhafeeri et al. 2012). The examinees were recorded while they expressed and described their feelings about the pictures.
was approved by the local Institutional Review Board (IRB) committee.

Results

ADHD group

The voice analysis parameters (LVA) were analysed using paired-samples *t*-tests using a within-subjects factor of time (before and one hour after receiving methylphenidate, while participants performed the different tasks).

Voice parameters while performing a cognitive task: there was a significant difference in the F main variance (voice concentration measure) pre–post methylphenidate (*P* < 0.05). No difference was found in the variance of the other LVA parameters, except JQ (comprehensive stress) which was marginal (*P = 0.0501*) (see Table I).

Emotional task: in the pre–post methylphenidate none of the LVA parameters changed (Table I).

Gender difference: to eliminate possible gender effect, the F main effect that was found during cognitive test was tested separately for ADHD males and females. In the female ADHD group, a similar F main effect was found. There was a significant decrease in the F main variance while performing a cognitive task before (M = 16.05, SD = 5.64) and after (M = 12.60, SD = 3.27) methylphenidate; *t*(13) = 2.44, *P* < 0.05. Such difference was not found in the male group (*P* > 0.1).

ADHD control comparison

Since the effect on F main was in female patients only, all analysis were performed by comparing the 14 ADHD female patients to the 22 control females.

A two-way ANOVA with repeated measure with group (Female ADHD/Female Control) as between

| Table I. Voice analysis parameters before (a) and after (b) methylphenidate. |
|-----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Tasks                      | Voice measure | Mean ± SD(a) | Mean ± SD(b) | *t* | df | *P* |
| Cognitive task             | F main       | 13.39 ± 5.51 | 11.43 ± 2.88 | 2.138 | 31 | 0.041* |
|                            | JQ           | 14.27 ± 4.61 | 16.36 ± 5.21 | -2.039 | 31 | 0.05 |
|                            | SPT          | 118.52 ± 50.16 | 100.90 ± 44.10 | 1.703 | 31 | 0.099 |
|                            | AVJ          | 15.02 ± 5.80 | 16.20 ± 8.25 | -0.721 | 31 | 0.476 |
|                            | SPJ          | 68.85 ± 24.88 | 68.59 ± 18.12 | 0.047 | 31 | 0.963 |
| Emotional task             | F main       | 11.49 ± 5.05 | 11.77 ± 4.36 | -0.262 | 31 | 0.795 |
|                            | JQ           | 14.39 ± 6.14 | 16.50 ± 7.22 | -1.525 | 31 | 0.137 |
|                            | SPT          | 82.54 ± 41.01 | 88.72 ± 47.70 | -0.784 | 31 | 0.439 |
|                            | AVJ          | 17.52 ± 11.19 | 14.68 ± 8.05 | 1.48 | 31 | 0.149 |
|                            | SPJ          | 66.07 ± 31.52 | 67.67 ± 33.88 | -0.234 | 31 | 0.817 |

Notes: *P* < 0.05; For all measurement “a” relates to the result at baseline, “b” after a single dose of Methylphenidate; 1F main-concentration; 2JQ to comprehensive stress 3SPT to the emotional load; 4AVJ to the thinking load; 5SPJ to cognitive load.
subject and time (pre–post methylphenidate/recess) analysis was conducted. A significant interaction effect was found; $F(1,34) = 6.16$, $P < 0.05$) see Figure 1. Further analysis reveals that when controlling for group, a previously reported significant effect for pre–post methylphenidate/recess was found for female ADHD group ($t(15) = 2.44$, $P < 0.05$). This effect was not found for female control group ($t(21) = -0.308$, $P > 0.1$). When controlling for time (pre–post), no significant difference were found between the groups before treatment ($t(34) = -1.08$, $P > 0.1$) or after ($t(34) = 1.53$, $P > 0.1$). Figure 1 demonstrates this interaction.

Discussion

In this pilot study a hypothesis-based paradigm (an effect while performing a cognitive task) supports the use of prosody production to study the effect of stimulants in ADHD female patients.

In the quest to find new markers for ADHD the study of prosody has an interesting and important potential. The study of prosody provides a feasible and inexpensive tool to complement both research and clinical evaluations. Voice characteristics such as being too talkative or being too loud are qualitative and clinical evaluations. Voice characteristics such as being too talkative or being too loud are qualitative measures present in many ADHD patients (Willcutt et al. 2005; Kessler et al. 2006; Hamdan et al. 2009; Wilens et al. 2009). Thus the study of prosody is based on some of the clinical features of ADHD. Prosody production involves similar neuronal networks to those studied in attention (Alpert et al. 2002; Willcutt et al. 2005; Aziz-Zadeh et al. 2010; Cortese et al. 2012; Nadig and Shaw 2012). In imaging studies of ADHD patients, decreased activity in the frontal cortex is one of the repeated findings. The production and comprehension of prosody involves the left inferior frontal gyrus (Broca’s area), as well as networks involving the right hemisphere (Garcia-Toro et al. 2000; Aziz-Zadeh et al. 2010).

When compared to neurocognitive assessments, the production of prosody is unconscious and thus less affected by an intentional bias of the examinee (Garcia-Toro et al. 2000; Alpert et al. 2002; Cannizzaro et al. 2004; Reilly et al. 2004; Willcutt et al. 2005; Aziz-Zadeh et al. 2010).

Since prosody (like many of the possible markers of ADHD) is affected by multiple confounders, the use of prosody as a marker of the short-term effect of methylphenidate is a strength. It enables us to analyse a within-subject comparison, within a short time frame, thus avoiding many of the confounders. In this pilot study we did not use placebo, and multiple methylphenidate dosage, these would have strengthened the validity of the effects we observed on prosody. Still, the fact that the effect was observed specifically while performing the cognitive and not the emotional tasks strengthens the validity of our results. The unique occurrence in female patients but not in males is possibly in line with current awareness that female ADHD differs from male ADHD. Females diagnosed with ADHD may present with lower ratings of hyperactivity, inattention, impulsivity and externalizing problems (e.g., aggression and comorbid conduct disorders) than ADHD males, but greater intellectual impairments and more internalizing problems (e.g., affective, eating and somatization disorders) (Gershon 2002). In accord with that a meta-analysis of stop-signal studies found a borderline effect of gender, whereby behavioural inhibition in male ADHD patients (compared with male healthy controls) was more severely impaired than in female ADHD patients (compared with female healthy controls) (Lipszyc and Schachar 2010).

There is evidence that support gender differences in functional neuroanatomy. Male but not female adults with ADHD showed significantly altered patterns of neural activity during performance on a verbal working memory task. Males and females showed different associations between neural activity and ADHD symptoms (Valera et al. 2010). The results of the presented study support the use of the fundamental frequency as a putative marker in female but not in male ADHD patients. If replicated and substantiated, this might contribute to the evaluation and conceptualization of sex differences in ADHD.

The use of a hypothesis based paradigm i.e., a control task (emotional) that is presumed to be less affected by methylphenidate substantiates the presumed validity of the presented findings.

Study limitations include the lack of placebo, and the fact that the female control group did not receive methylphenidate. Future studies are needed focusing on the fundamental frequency in female ADHD patients.

![Figure 1. F main Measure – Group × Time Interaction. Notes: *$P < 0.05$; Second evaluation was done after administration of methylphenidate for the ADHD group and a recess for the control group.](image-url)
If these findings are replicated in the future, analysis of prosody could complement questionnaires and neurocognitive tests in the evaluation of adult ADHD patients. Specifically, they would provide an additional objective evaluation of the effects of pharmacotherapy.

Acknowledgments
We wish to thank Nemesysco for allowing us to use the LVA software free of charge. We wish to thank Eve Horowitz Leibowitz for her editorial assistance.

Statement of Interest
None to declare.

References