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Effects of Auditory Training on Electrophysiological Measures in Individuals with Autism Spectrum Disorder

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Abstract

Background: Identifying objective changes following an auditory training program is central to the assessment of the program's efficacy.

Purpose: This study aimed (1) to objectively determine the efficacy of a 12-week auditory processing training (APT) program in individuals with autism spectrum disorder using auditory evoked potentials (AEPs) and (2) to identify the top central AEP predictors of the overall score on the Test of Auditory Processing Skills-3 (TAPS-3), the primary behavioral outcome measure of the APT program published in our earlier article.

Research Design: A one-group pretraining, posttraining design was used.

Study Sample: The sample included 15 children and young adults diagnosed with autism spectrum disorder. Participants underwent the APT program consisting of computerized dichotic training, one-on-one therapist-directed auditory training, and the use of remote microphone technology at home and in the classroom.

Data Collection and Analysis: All participants underwent pre- and posttraining auditory brain stem responses (ABRs), complex auditory brain stem responses (cABRs), and auditory late responses (ALRs). Test results from ABRs and ALRs were grouped based on scores obtained in their dominant and nondominant ears. Paired *t*-tests were used to assess the efficacy of the training program, and least absolute shrinkage and selection operator regression was used to assess the relationship between ALRs and the TAPS-3 overall summed raw score reported in our earlier article.

Results and Conclusions: When compared with pretraining results, posttraining results showed shorter ABR latencies and larger amplitudes. The cABRs showed decreased latencies of the frequency following waves, a reduction in pitch error, and enhancement of pitch strength and phase shift. ALR results indicated shorter latencies and larger amplitudes. Our earlier article showed that the TAPS-3 overall score was significantly higher after training. This study showed that the top three ALR predictors of TAPS-3 outcomes were P1 amplitude in the dominant ear, and N1 amplitude in the dominant and nondominant ears.

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This article and the article by Schafer et al (2019) are part of a complementary pair. Portions of this manuscript have been presented at the American Academy of Audiology conference (2018), American Speech-Language-Hearing Association conference (2017), and the Educational Audiology Conference (2017).

Key Words: ABR, ALR, auditory training, autism spectrum disorder, cABR, LASSO

Abbreviations: ABRs = auditory brain stem responses; AEPs = auditory evoked potentials; ALRs = auditory late responses; APT = auditory processing training; ASD = autism spectrum disorder; BIC = Bayesian information criterion; cABRs = complex auditory brain stem responses; LASSO = least absolute shrinkage and selection operator; TAPS = Test of Auditory Processing Skills

INTRODUCTION

Auditory processing is a cognitive function wherein the auditory system uses, manipulates, and integrates concurrent or sequential auditory input into definite patterns that can be used purposefully for various tasks, including for developing spoken language (Lasky and Katz, 1983). Neurophysiological studies of auditory processing in individuals with autism spectrum disorder (ASD) suggest atypical neural activity in this population (Marco et al, 2011). Aberrant neural network connectivity leading to a deficit in integration of information in individuals with ASD has been widely recognized and is thought to contribute toward their social, communication, cognitive, and behavioral characteristics (Just et al, 2007, Anderson et al, 2011; Cauda et al, 2014; Linke et al, 2018). Compromised interhemispheric connectivity of temporal regions can lead to deficits in dichotic listening and abnormal cortical processing of auditory information, a central deficit found in ASD (Edelson et al, 1999).

Altered corpus callosum is considered an anatomical substrate of processing and integration deficits found in ASD (Just et al, 2007). Interhemispheric connectivity, mainly between secondary auditory areas, was significantly weaker in ASD and was associated with auditory sensory processing deficits (Linke et al, 2018). Because basic auditory perceptual and processing abilities are essential for language learning (Mueller et al, 2012), interventional strategies aimed at enhancing auditory listening and integration abilities in individuals with ASD are highly desirable.

Auditory evoked potentials (AEPs) are noninvasive objective tests that provide information on the central auditory pathways. Evoked potentials provide quantitative brain measures that can be used as possible biomarkers of sensory processing (Modi and Sahin, 2017). Furthermore, they can be used for objectively assessing treatment/training outcomes as they provide quantitative data that permit evaluation and comparison of the same participants across different times. The human brain has an amazing capacity to learn. Practice-induced plasticity in the white matter tracts following cognitive and motor training are reported in normal children (Skare et al, 2005) and in poor readers (Keller and Just, 2009). Auditory training programs are proposed as a way of leveraging neural plasticity to enhance processing skills in various populations, including ASD (Edelson et al, 1999; Hayes et al, 2003; Russo et al, 2005; 2010; Krishnamurti et al, 2013). Although only a handful of studies used both physiological and behavioral outcomes to assess the efficacy of auditory training programs, positive results were obtained in those studies (Sokhadze et al, 2016), thus indicating beneficial effects of training reflected as enhanced neural firing and processing at the brain stem level, cortical level, or both. These findings provided the impetus for the intensive dichotic listening training used in this study to strengthen network connectivity. Our 12-week auditory processing training (APT) program consisted of computerized dichotic training, one-on-one therapist-directed auditory training, and the use of remote microphone technology at home and in the classroom. Furthermore, as AEPs can be used as an objective tool to assess the flow of auditory information processing (Marco et al, 2011), they were used in this study to probe the underlying neural processes to assess the efficacy of our training. We selected AEP measures that would not be overly challenging to obtain, yet allow us to assess changes at various levels of the auditory pathway. Auditory brain stem responses (ABRs) and complex auditory brain stem responses (cABRs) were chosen to enable us to assess changes at the brain stem level and auditory late responses (ALRs) to assess changes at the thalamocortical level. There is evidence to suggest that individuals with ASD have abnormal physiological encoding of auditory stimuli in quiet and noisy listening conditions from the level of the brain stem to the cortex (Russo et al, 2009a,b). Studies on individuals with ASD have documented prolonged ABR peaks and interpeak latencies (Rosenhall et al, 2003; Kwon et al, 2007; Magliaro et al, 2010; Dabbous, 2012; Roth et al, 2012; Azouz et al, 2014; Ververi et al, 2015; Miron et al, 2016). Several studies have also reported prolonged latency, diminished amplitude, or both for ALR peak N1 in individuals with ASD (Bruneau et al, 1999; Seri et al, 1999; Bruneau et al, 2003; Azouz et al, 2014; Sokhadze et al, 2016), and for ALR peaks P1 and N2 (Donkers et al, 2015).

PURPOSE

We proposed that the 12-week APT would strengthen the underlying neurophysiological substrates and the overall auditory processing skills reflected objectively as an enhancement of AEP amplitude and latency measures. A detailed description of the training is provided in the earlier article (Schafer et al, 2019). The goals of this study were to (a) quantify the efficacy of the APT program using AEPs and (b) identify the top central AEP measures that predict the overall summed raw score on the *Test of Auditory Processing Skills*—Third Edition (TAPS-3; Martin and Brownell, 2005). The TAPS test is a behavioral test, and the participants' overall summed raw score on TAPS conceptualizes auditory processing capabilities based on the scores obtained from the nine subtests within TAPS-3.

METHODS

Participants

AEP data were obtained from the same 15 individuals with ASD who were used in our earlier article (Schafer et al, 2019). We grouped the ABR and ALR data based on the dominant versus nondominant ear scores (as determined by the two-pair dichotic digit test in the earlier article). Because cABR scores were obtained only from the right ear, no such classification was made for cABRs.

Protocols

Electrophysiological Testing

All testing was performed while the participant sat in a comfortable chair and watched a silent movie with captions, with breaks provided as needed. Recordings were made using the Intelligent Hearing Systems SmartEP module in a soundproof and electrically shielded room. Surface electrodes were placed on the high forehead (FPz/active), low forehead/ground, and right and left earlobes (A1/reference and A2/reference). Stimuli were presented using ER-3A shielded insert earphones (Etymotic Research Inc., Elk Grove Village, IL) . Two rounds of testing were conducted: (a) pretraining testing, conducted just before starting the training, and (b) posttraining testing, conducted immediately after the training.

Parameters

ABR: 70-dB nHL monaural alternating clicks, 21.1/s, gain =100,000, filter settings =100–3000 Hz, three repetitions, and n = 1,024. Absolute latencies and amplitudes for peaks I, III, and V were obtained.

cABR: /ba/ and /ga/ to right ear, 80-dB nHL, alternating polarity, rate = 4.35/sec, n = 1,024, four blocks for each syllable, and for a total of 4,096 presentations. Intelligent Hearing Systems acquired the stimulus and analyses files from the Auditory Neuroscience Laboratory at Northwestern University. Absolute latencies of transition and frequency following response waves, as well as pitch error and strength, and phase shift measures were obtained.

ALR: 70-dB nHL monaural 1000 Hz tone pips, 1.1/sec, gain = 100,000, filter settings = 1–30 Hz, three repetitions, and minimum of 150 sweeps. Absolute latencies and amplitudes for peaks P_1, N_1, and P_2 were obtained.

STATISTICAL ANALYSES

All waveforms were analyzed by two trained researchers who were blinded to each other's analysis and to the behavioral test measures. Latency and amplitude differences between pre- and posttraining sessions were calculated to identify change. Paired *t*-tests were used to assess the efficacy of the training program. To identify the top ALR measures that predicted the behavioral outcome of training (TAPS-3 score), we used the least absolute shrinkage and selection operator (LASSO) technique for feature extraction (Tibshirani, 1996). The LASSO is a shrinkage and selection method for regression models and is best described as a constraint on the sum of the absolute values of the model parameters, where this sum has a specified constant as an upper bound. One of the advantages of LASSO is a clear hierarchy of the predictors for model selection. Each predictor variable enters the model in order of importance and never leaves the model as the constraint is relaxed. The advantages of using LASSO regression are that it selects an appropriate set of predictor variables when there are a large number of potential predictors relative to the sample size and there are no distributional assumptions needed. Based on our success of using LASSO in identifying AEP predictors (Gopal et al, 2017), ALR measures representing cortical activity were selected for LASSO analysis in this study.

RESULTS

Table 1 provides demographic information about the 15 participants, identifies the dominant ear, and provides the change in the summed TAPS-3 raw scores following training (as reported in Schafer et al [2019]).

ABR Results

Table 2 depicts the average pre- and posttraining ABR measures for peaks I, III, and V. ABR latencies showed a nonsignificant decrease in posttraining measures for peaks I, III, and V, except for peak I in the dominant ear, which stayed the same. Posttraining amplitude measures were not as consistent across peaks; however, when a one-sided paired *t*-test was used, peak V showed a significant increase ($p < 0.05$) in both dominant and nondominant ears.

Table 1. Participant Data

Participant	Gender	Age (years;months)	Dominant Ear	TAPS Summed Raw Score Post − Pre Difference
1	F	9;6	L	29
2	M	21;9	R	29
3	M	7;5	R	30
4	M	7;11	R	−4
5	M	14;7	R	36
6	M	10;3	L	1
7	F	12;0	L	44
8	M	20;6	R	19
9	F	16;4	R	35
10	F	21;8	L	3
11	F	21;5	L	21
12	M	10;2	L	10
13	M	15;10	R	9
14	M	9;5	R	33
15	M	15;7	R	10

Note: Dominant ear was based on the two-pair dichotic digit test reported in Schafer et al (2019).

cABR Results

The cABR measures reported in this article include changes between pre- and posttraining for waves C (representing transition to the periodic portion of the stimulus), D, E, and F (frequency following response), and for pitch error, pitch strength, and phase shift. Averaged posttraining latency data for both /ba/ and /ga/ showed a nonsignificant latency decrease for waves C, D, and E, with no change in F (Table 3). Pitch-related measures (Figure 1) showed positive changes following training: pitch error decreased marginally for /ba/, but significantly for /ga/ ($p < 0.02$), pitch strength increased for /ba/ and /ga/, and the phase shift depicted a slightly better lead for /ga/.

ALR Results

Averaged pre- and posttraining ALR measures for peaks P_1, N_1, and P_2 are shown in Figure 2. All latencies decreased following training, except for peak P_1 in the dominant ear. One-sided paired *t*-test without correction for multiple testing showed the following results: P_1, N_1, and P_2 latencies in the nondominant ear and P_2 latency in the dominant ear decreased significantly after training ($p < 0.05$). P_1, N_1, and P_2 amplitudes showed enhancement in dominant and nondominant ears, with all peaks but one (peak P_1 in the nondominant ear) showed a significant increase ($p < 0.05$). After correcting for multiple testing using Holm's sequential correction, only N_1 amplitude in the dominant ear was considered significant ($p = 0.0009$). However, the findings are stronger than nominally suggested by adjusted statistical significance. Irrespective of the calculated *p*-values, the changes in mean scores have been found to be in the positive direction for 11 of the 12 ALR measures. This reflects remarkable consistency. Overall, it appears that the amplitude scores offer bigger changes than the latency changes. In fact, all six amplitude scores exhibited changes in the positive direction.

Data collected in the earlier study (Schafer et al, 2019) showed a significant improvement on the summed TAPS-3 raw scores following training ($p = 0.0001$). In this study, to explore the predictive ability of the changes in ALR scores for change in the TAPS-3 behavioral score, we used LASSO regression. Because of the comparatively small sample size relative to the number of predictors, and because the predictors may be highly correlated, LASSO was preferred instead of conventional regression. The difference scores obtained

Table 2. Mean ABR Latencies and Amplitudes Obtained Pre- and Posttraining in Dominant and Nondominant Ears

	Dominant Ear		Nondominant Ear	
	Pretraining	Posttraining	Pretraining	Posttraining
Wave I latency (msec)	1.76 ± 0.1	1.76 ± 0.12	1.76 ± 0.13	1.72 ± 0.12
Wave I amplitude (μV)	0.2 ± 0.13	0.19 ± 0.13	0.18 ± 0.12	0.22 ± 0.09
Wave III latency (msec)	3.99 ± 0.21	3.95 ± 0.21	4.01 ± 0.22	3.96 ± 0.19
Wave III amplitude (μV)	0.21 ± 0.09	0.19 ± 0.1	0.23 ± 0.13	0.21 ± 0.09
Wave V latency (msec)	5.79 ± 0.24	5.77 ± 0.24	5.74 ± 0.29	5.71 ± 0.26
Wave V amplitude (μV)	0.38 ± 0.15	0.46 ± 0.13*	0.37 ± 0.13	0.45 ± 0.16*

*$p < 0.05$.

Table 3. Pre- and Posttraining Mean cABR Wave Latencies for /ba/ and /ga/

	Peak C		Peak D		Peak E		Peak F	
	/Ba/	/Ga/	/Ba/	/Ga/	/Ba/	/Ga/	/Ba/	/Ga/
Pre	16.4 ± 1.2	16.9 ± 1.0	24.5 ± 1.4	24.1 ± 1.1	34.6 ± 1.4	34.0 ± 1.1	44.1 ± 1.3	44.2 ± 1.1
Post	16.2 ± 1.1	16.3 ± 1.5	24.0 ± 1.6	23.6 ± 1.4	34.3 ± 1.3	33.9 ± 0.8	44.1 ± 1.4	44.2 ± 0.9

between post- and pretraining in dominant and nondominant ears for latency and amplitude measures were used as predictor variables. Table 4 shows the 12 ALR measures used in the LASSO analyses as possible predictors of TAPS-3 outcomes.

We used the commonly used Bayesian information criterion (BIC) for model selection. BIC is an objective criterion that can be used to choose the best model among several competing ones by striking a balance between the quality of model fit and the number of parameters. Using BIC, the LASSO technique selected the following predictors in order of importance: V7, V10, V9, V2, V8, V6, V3, V5, V12, and V4. The selected model offered a high adjusted R^2 value of 0.9. In other words, the proportion of the variance in the dependent variable that is predictable from the independent variables is rather high, thus reflecting an excellent overall fit. However, further scrutiny revealed that the top three predictors, V7, V10, and V9, accounted for half of the variability, thus indicating that amplitude increases in ALR peaks P_1 and N_1 may by far be the most important measures depicting the overall improvement from training.

DISCUSSION

Atypical auditory processing and the underlying language impairment seen in individuals with ASD can be attributed to the functional disconnectivity of networks important for sensory information integration (Brandwein et al, 2015; Sokhadze et al, 2016). Compared with neurotypical peers, individuals with ASD exhibit weaker neural network connectivity across various regions in the brain, including interhemispheric connectivity of the auditory regions, which is associated with auditory processing deficits (Anderson et al, 2011; Cauda et al, 2014; Linke et al, 2018). Although there is evidence that auditory processing, especially dichotic listening, can be enhanced with training (Tremblay et al, 2009; Denman et al, 2015; Kozou et al, 2018), there is limited research relating physiological changes to behavioral changes in ASD following auditory training.

This study assessed the efficacy of the 12-week APT program (program described in Schafer et al [2019]) using electrophysiological measures. The program focused on dichotic listening training to strengthen the interhemispheric integration of auditory information. The changes in electrophysiological recordings were evaluated by comparing AEPs before and after training in dominant and nondominant ears, rather than the traditional right- and left-ear comparison. Our earlier study (Schafer et al, 2019) showed that the APT program significantly enhanced multiple areas of auditory processing skills as measured by various behavioral tests, including TAPS-3.

In this study, we used the TAPS-3 (Martin and Brownell, 2005) overall score as our behavioral all-encompassing outcome measure against which the AEP measures were compared. Results of this study indicated high variability among ASD participants in AEP latency and amplitude measures. Nevertheless,

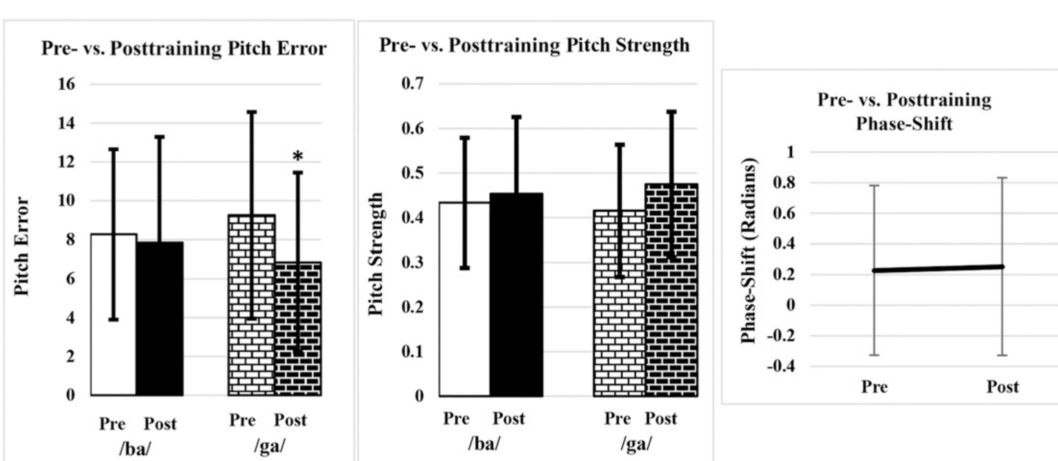

Figure 1. Pre- and posttraining cABR measures. Left: pitch error, middle: pitch strength, right: phase shift for /ba/ and /ga/.

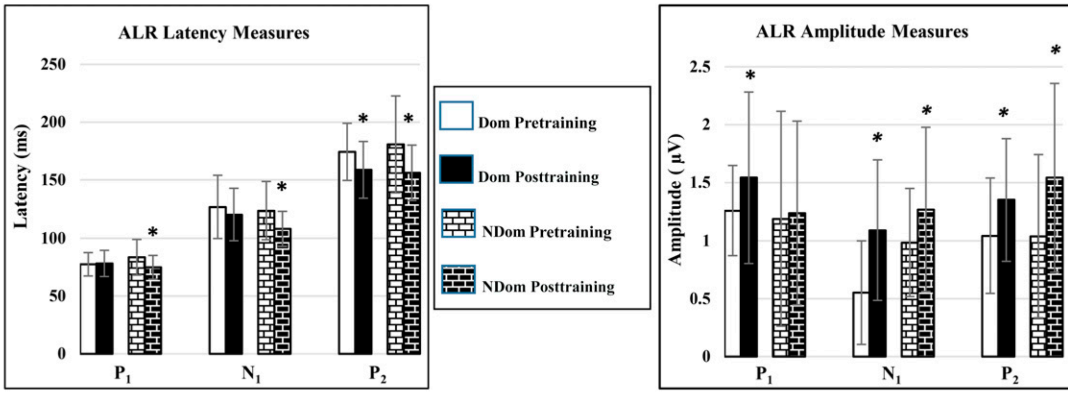

Figure 2. Pre- and posttraining ALR P1, N1, and P2 peak measures. Left: latency, right: amplitude. Dominant (Dom) and nondominant (NDom) ears.

following APT, group averages showed positive changes in both dominant and nondominant ears. ABR latency for peak V decreased following training; however, the difference between pre- and posttraining was not significant, consistent with the findings of earlier publications on auditory training in children with learning or processing disorders (Yencer, 1998; Hayes et al, 2003). Conversely, the present study found a significant increase in the amplitude of ABR peak V in dominant and nondominant ears following training, unlike a previous study which reported no changes in amplitude (Krishnamurti et al, 2013). Analogous to results reported by Russo et al (2005; 2010) and Krishnamurti et al (2013), the cABR results in this study showed improved subcortical representation of speech sounds after training. At the group level, there was a decrease in the latencies for waves C, D, and E, depicting positive changes in transition to the periodic portion of the stimulus and the sustained frequency following response. In addition, there was a reduction in the pitch error, an increase in pitch strength, and a positive phase shift between /ba/ and /ga/, depicting increased precision of pitch encoding, phase locking, and response timing.

Table 4. Twelve ALR Measures Used in LASSO Analysis

Variable/Predictor	Test Measure (Post − Pre Difference)
V1	P1 latency—dominant ear
V2	P1 latency—nondominant ear
V3	N1 latency—dominant ear
V4	N1 latency—nondominant ear
V5	P2 latency—dominant ear
V6	P2 latency—nondominant ear
V7	P1 amplitude—dominant ear
V8	P1 amplitude—nondominant ear
V9	N1 amplitude—dominant ear
V10	N1 amplitude—nondominant ear
V11	P2 amplitude—dominant ear
V12	P2 amplitude—nondominant ear

Although these changes seen at the brain stem level were not all significant or sufficient to support the idea of using brain stem measures as probable biomarkers in ASD (Miron et al, 2018), or as an index of auditory training, it is encouraging to see that the changes are all in the positive direction.

ALRs provide a window at the cortical level to explore the underlying neurophysiological changes following auditory exposure and training (Cheour-Luhtanen et al, 1995; Koravand et al, 2017; Key et al, 2018). In this study, at the level of ALRs, we found a significant decrease in N_1 and P_2 latencies after training in the dominant and nondominant ears, in addition to P_1 latency decrease in the nondominant ear. These results support earlier studies that reported reduction in latency following auditory training (Hayes et al, 2003; Warrier et al, 2004; Russo et al, 2010). In addition to the shortened latencies, the increase in ALR amplitudes in dominant and nondominant ears seen in this study provides evidence of a holistic improvement in these individuals' abilities to process acoustic signals following training. Our results indicate that intensive auditory training alters neural activity in the central auditory system, and ALR peaks P_1 and N_1 may be the most important measures depicting the overall improvement from training. These positive changes in ALR latencies and amplitudes following training can be attributed to one or more of the underlying processes as outlined by earlier investigators: increased neuronal response to auditory signals, improved neural synchrony, and enhanced organization and strengthening of neural network connections (Tremblay et al, 2009; Kozou et al, 2018).

The central auditory nervous system is shown to exhibit behavioral perceptual enhancements and neurophysiological changes, demonstrating transfer of learning and plasticity in underlying physiological processes (Tremblay et al, 1997; 2001). Nevertheless, directly attributing specific electrophysiological changes to auditory processing skills as measured by TAPS-3 can be very challenging. Earlier research has shown that spectral and temporal cues in speech are reflected in ALR N_1-P_2 potentials (Tremblay et al, 2001), but these potentials may not explicitly reflect changes in processes or skills such as auditory working memory, reasoning, or sequencing captured by behavioral tests. In this study, to examine if direct relationships exist between posttraining improvements on TAPS subtests and posttraining changes in electrophysiological measures, Pearson's product moment correlations were calculated. No significant correlations were obtained, but this could be due to several reasons, including insufficient statistical power from the small sample size used in this study and the wide age range of our participants. However, it is also highly likely that the lack of significance is related to the fact that a one-to-one change in ALR measures and specific behavioral measures from TAPS subtests may not be meaningful because ALRs target several cognitive processes, including learning and memory (Key et al, 2018), and would not be limited to or representative of individual processes or skills that the TAPS subtests would be targeting. Nevertheless, it is noteworthy that when the overall TAPS score (a composite of all subtests) was used, electrophysiological measures were highly predictive as demonstrated by LASSO with an adjusted R^2 value of 0.9. Furthermore, P_1 and N_1 changes were found to be the dominant predictors of the TAPS score.

To assess long-term effects, participants were encouraged to return for electrophysiological testing at 12 weeks following cessation of training (posttraining2). However, data were successfully obtained from only five participants because of lack of commitment for yet another round of electrophysiological testing. We compared ABR and ALR measures between immediate posttraining and posttraining2 in the five participants to see if the performance had changed. Results from the paired samples t-test did not show significant differences between the two rounds ($p > 0.05$), indicating no further changes. In addition, two participants went through two rounds of pretreatment testing. Comparison of these measures using the Wilcoxon signed-rank test showed no significant changes ($p > 0.05$) between the two pretreatment rounds. However, it is not meaningful to reach any conclusion based on the small data set. A future longitudinal study with a larger participant pool is necessary to reach conclusions about the pretraining variability and long-term effects of training.

Based on the averaged pretraining versus posttraining performance scores from behavioral and electrophysiological tests, APT was found to be beneficial, although there was variability among participants supporting the concept of heterogeneity in this disorder (Kozou et al, 2018), or just a difference in the activation pattern of the underlying processes among individuals (Tremblay et al, 2009). Participants did not show improvement in all AEP measures in the study, but showed noteworthy improvements in several AEPs derived from the brain stem and cortical levels substantiating enhanced subcortical and cortical processing following training. Because the final sound processing is performed at the cortical level, we used LASSO to select the most probable cortical measure (ALR) that could objectively predict the behavioral outcome as measured by TAPS-3. Results indicated that the top predictors of the overall TAPS-3 outcome were amplitude measures for the ALR peak P1 in the dominant ear and ALR peak N1 for nondominant and dominant ears.

LIMITATIONS AND FUTURE DIRECTIONS

The limitations of this study include (a) small sample size, (b) a wide range of age and test scores among participants, (c) varying comorbidity among participants, (d) unquantified maturational effects, and (e) lack of a control group consisting of individuals with ASD who did not receive auditory training. Difficulty with participant commitment to 12 weeks of training led to the small sample size and inability to form subgroups. Further research calls for shorter yet effective training periods, larger sample size, better subgrouping, using control groups, and evaluating long-term effects of training.

SUMMARY

This study incorporated behavioral (earlier article [Schafer et al, 2019]) and electrophysiological findings (present article) to understand the underlying neural integration of sensory processing. It quantified the efficacy of training on auditory processing skills as it relates to brain plasticity by understanding the relationship between behavioral performance and neural substrates. We have demonstrated that intense auditory training in individuals with ASD results in a significant decrease in their ear advantage score, suggesting a reduction in the interaural asymmetry. Higher score on the overall TAPS-3 test following training was associated with a decrease in ALR latencies and enhancement of ALR amplitudes, especially in the nondominant ear. We attribute these changes to brain plasticity illustrated as posttraining enhancement of signal conduction and neuronal connectivity at the brain stem and cortical levels, leading to a more efficient propagation and processing of signals in the central auditory pathways.

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