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Electrophysiological and Behavioral Outcomes of Berard Auditory Integration Training (AIT) in Children with Autism Spectrum Disorder

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Abstract Autism is a pervasive developmental disorder of childhood characterized by deficits in social interaction, language, and stereotyped behaviors along with a restricted range of interests. It is further marked by an inability to perceive and respond to social and emotional signals in a typical manner. This might due to the functional disconnectivity of networks important for specific aspects of social cognition and behavioral control resulting in deficits of sensory information integration. According to several recent theories sensory processing and integration abnormalities may play an important role in impairments of perception, cognition, and behavior in individuals with autism. Among these sensory abnormalities, auditory perception distortion may contribute to many typical symptoms of autism. The present study used Berard's technique of auditory integration training (AIT) to improve sound integration in children with autism. It also aimed to understand the abnormal neural and functional mechanisms underlying sound processing distortion in autism by incorporating behavioral, psychophysiological and neurophysiological outcomes. It was proposed that exposure to twenty 30-min AIT sessions (total 10 h of training) would result in improved behavioral evaluation scores, improve profile of cardiorespiratory activity, and positively affect both early [N1, mismatch negativity (MMN)] and late (P3) components of evoked potentials in auditory oddball task. Eighteen children with autism spectrum disorder (ASD) participated in the study. A group of 16 typically developing children served as a contrast group in the auditory oddball task. Autonomic outcomes of the study reflected a linear increase of heart rate variability measures and respiration rate. Comparison of evoked potential characteristics of children with ASD versus typically developing children revealed several group difference findings, more specifically, a delayed latency of N1 to rare and frequent stimuli, larger MMN; higher P3a to frequent stimuli, and at the same time delayed latency of P3b to rare stimuli in the autism group. Post-AIT changes in evoked potentials could be summarized as a decreased magnitude of N1 to rare stimuli, marginally lower negativity of MMN, and decrease of the P3a to frequent stimuli along with delayed latency and higher amplitude of the P3b to the rare stimuli. These evoked potential changes following completion of Berard AIT course are in a positive direction, making them less distinct from those recorded in age-matched group of typical children, thus could be considered as changes towards normalization. Parental questionnaires clearly demonstrated improvements in behavioral symptoms such as irritability, hyperactivity, repetitive behaviors and other important behavioral domains. The results of the study propose that more controlled research is necessary to document behavioral and psychophysiological changes resulting from Berard AIT and to provide explanation of the neural mechanisms of how auditory integration training may affect behavior and psychophysiological responses of children with ASD.

Keywords Autism spectrum disorder · Auditory integration · Heart rate · Respiration · Auditory evoked potentials · Mismatch negativity

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Background

It is well recognized that autism spectrum disorders (ASD) are identified by various levels of deficits in reciprocal social interactions, communication and stereotypical play/behaviors. Sensory stimuli also cause inappropriate responses with some individuals exhibiting over-stimulation, others showing under-stimulation, and some exhibiting both conditions at various times (Powers 2000). These sensory challenges may actually be a cause for some of the unusual behaviors that are characteristic of the disorder (Bluestone 2004; McKean 1994; Kraus et al. 1996; O'Connor 2012). Many treatments and interventions have focused on methods to reduce the deficits or facilitate improved function and performance in the developmental areas affected by this disorder (Ayres 2005; Brown 1999; Bundy et al. 2002; Schoeneck 2012). However, there has been limited scientific research on many of the sensory dysfunctions, particularly auditory hypersensitivity and auditory processing. In spite of limited rigorous research, a variety of interventions directed at reducing sound sensitivity and related auditory problems are currently used by practitioners and parents, with reported positive results in many cases. The Berard method of auditory integration training (AIT) is of particular interest for several reasons. There are some research studies that do provide behavioral and some physiological data (Berard and Brockett 2011; Brockett et al. 2014; Edelson et al. 1999; Rimland and Edelson 1994, 1995) to document efficacy. In addition, this particular method requires the least amount of listening time (a total of 10 h) for the patient (Berard and Brockett 2011). It is also easily adapted to be applied in a laboratory/clinic setting that will enable physiological data to be collected to measure change. Dr. Berard originally developed his method of AIT to rehabilitate disorders of the auditory system, such as hearing loss or hearing distortion. AIT uses filtered and modulated frequencies imbedded in pleasant music to help re-train the auditory system and normalize the way the brain processes information. It seems very likely that if a child with autism could hear and process sounds more accurately, he/she could understand and speak more accurately and clearly, thus improving many related areas such as social skills and social communication. The Berard AIT program is based on theory that the use of electronically modulated, and on occasion, selectively filtered music retrains the ear and auditory system to work properly.

Auditory Processing Abnormalities in Autism

Auditory Evoked Potentials

There is increasing evidence that abnormal cortical processing of auditory stimuli is one of the core deficits in autism (Bomba and Pang 2004). Auditory evoked potentials (AEP), or event-related potentials (ERP), reflect activation of neural structures in auditory cortex, auditory association areas, and areas related to higher order cognitive processes (Bomba and Pang 2004; Rosentall et al. 2003). They can be approximately divided into short-latency (exogenous) and long-latency (endogenous) ERPs, where the long-latency responses reflect more cognitive, higher-level, less modality-specific processing (e.g., P3) and the short-latency ERPs (e.g., N1) reflect modality-specific processing.

The N1 is a short-latency ERP specific to the auditory modality that reflects basic auditory processing (Näätänen and Picton 1987 The N1 measured at the vertex (Cz) and generated in the supra-temporal cortex, reflects changes in stimulus presentation and the physical properties of a stimulus. Studies have generally reported differences in N1 amplitude and latency (Kemner et al. 1995), such as amplitude increases (Oades et al. 1988) and decreases (Courchesne et al. 1985) in autism as compared to controls. These findings of short latency potentials along with other similar studies were interpreted as an indication that autism is related to ineffective regulation of auditory sensory input (Bruneau et al. 1997, 1999; Buchwald et al. 1992).

Mismatch Negativity (MMN)

One of the auditory event-related potentials important for the understanding of atypical processing of sound and deficits of auditory perception is mismatch negativity ([MMN], Jeste and Nelson 2009). MMN is a difference waveform that reflects the processing required to compare a different incoming stimulus with the neural representation already stored in transient auditory memory. This waveform is only evident when the frequently occurring stimuli are subtracted from the rare stimuli; without this subtraction, the MMN would not be detectable. The MMN is thought to be a pre-perceptual measure of central auditory function. The MMN has generators on both supratemporal planes of the auditory cortices (Alho 1995) and in frontal cortex (Giard et al. 1990).

Mismatch negativity (i.e., differential evoked potential) is thought to reflect an automatic electrocortical response to a change in auditory input and has been studied extensively and employed as an index of processes related to auditory discrimination and auditory sensory memory (Näätänen 1990; Näätänen and Alho 1997; Näätänen et al. 2005; Picton et al. 2000). In laboratory settings, MMN is most commonly elicited by a rare "deviant" auditory stimulus in a train of repetitive, homogeneous stimuli (so called "frequents" or "standards"). A comparison of the ERPs elicited by the frequent standard and rare deviant stimuli reveals a potential that is larger for the deviant stimuli, and

is negative at the midline frontal and fronto-central EEG sites MMN usually peaks between 100 ± 50 ms and 200 ± 50 ms post onset of the deviant physical characteristic of the auditory stimulus (Picton et al. 2000). In most studies, MMN has been elicited by changes in a variety of acoustic features, such as intensity, frequency, duration, and location of the sound, as well as by changing auditory stimulation patterns (Kraus, et al. 1996; Näätänen et al. 2005; Picton et al. 2000; Sams et al. 1985) MMN appears to be caused by a neuronal mismatch between the deviant auditory input and a sensory-memory trace representing the standard stimuli (Alho 1995; Giard et al. 1990)

Mismatch Negativity in Autism Research

The mismatch negativity is an important measure for better understanding of the pre-attentive detection of rule violations in auditory stimuli (Schall 2015). and offers the possibility to identify abnormal functioning in the neural system involved in generation of the MMN that occurs in autism. Children with autism often exhibit abnormalities in auditory processing and consequently receptive language functioning (Bomba and Pang 2004). They are frequently under-reactive and/or hypersensitive to sound, and there is often poor auditory processing in contrast to a significantly better visual-spatial processing (Courchesne et al. 1985; Dunn et al. 2008; Gomot, et al. 2002; Ornitz 1989). The consistent findings in clinical observations of children with autism are their under-reactivity to sound and failure to notice important auditory information in the environment. Deficits in processing auditory information automatically, especially auditory information outside the spotlight of attention, missing prompt to shift, may have negative implications for social communication and certain aspects of practical language development. Obviously, deficient attentional processing of important auditory information may contribute to various clinical features of autism (Goldstein et al. 2001; Ornitz 1989; Sams et al. 1985).

Kemner et al. (1995) reported normal latency and amplitude of the MMN in high functioning children with autism. Another study examining MMN in children with autism (Gomot et al. 2002) found that left hemisphere MMN peak latency was earlier in the autistic compared to the control group and the topography of the MMN was different. In the autistic group, the right hemisphere showed the supratemporal MMN component, whereas the left temporal MMN was shortened by the appearance of an abnormal deviance-related positivity in left pre-frontal cortex, generated by non-primary thalamo-cortical projections. It has been suggested that this thalamo-cortical pathway results in a higher cerebral reactivity to the deviancy that allows children with autism to become hypersensitive to acoustic changes. Further support for this idea stems from a study by Ferri et al. (2003) who compared the MMN in males with a diagnosis of autism to healthy controls. They found that the MMN amplitude of the autistic group was significantly enhanced and occurred at a shorter latency, but only to the deviant stimuli, thus, their results support a dysfunction that influences the pre-perceptual processing of auditory sensory information. On the other hand, Seri et al. (1999) found a significantly lower MMN amplitude with longer latency in the children with autism. Based on these results, they suggested that it is likely that children with autism have some difficulty encoding information into transient memory.

Late potentials (P3) in Autism Research

The P300, P3, or P3b (Katayma and Polich 1996; Picton 1992) is a large positive waveform that occurs at approximately 300 ms after stimulus onset in adults and appears to originate in the association cortex of the parietal lobes. In general, the P3b is elicited at the centro-parietal and parietal sites by cognitive parameters such as stimulus probability, meaningfulness and task relevance (Donchin 1981). At the frontal and fronto-central regions P3 is of larger magnitude to non-target distracter stimuli, is labeled as P3a, and is considered as a marker of attention orienting to a novel stimulus. In individuals with autism the most consistent, and frequently reported, abnormality is a P3b amplitude attenuation with auditory stimulus presentation. Amplitude decreases have been reported with clicks (Lincoln et al. 1993; Oades et al. 1988), phonemes (Dawson et al. 1988), and novel distracters (Courchesne et al. 1985). P3b latency in autism has been reported unaffected (Ciesielski et al. 1990; Courchesne et al. 1985; Dawson et al. 1988; Lincoln et al. 1993;Novick et al. 1980; Oades et al. 1988). The P3b is thought to reflect a limited capacity mechanism whereby attention is consciously allocated to specific information in the environment (Picton 1992).Thus, the reduced P3b may reflect either a failure to allocate appropriate attention to stimuli or, a misallocation of attentional resources to less important stimuli (Dawson et al. 1988). A smaller P3b may reflect either a difficulty in attaching significance to unexpected stimuli (Oades et al. 1988) or a defect related to the modification of expectancies based on previous experience (Lincoln et al. 1993). This may explain why individuals with autism, who have rigid expectations and thus difficulty extracting information in a way that leads to a re-integration of previously learned information (Lincoln et al. 1993), have smaller P3b. To date, results from MMN and P3 studies that have controlled for diagnostic and developmental issues are very promising. Furthermore, MMN and P3 studies suggest that children with autism may have difficulty encoding information in transient memory (Gomot et al. 2002; Seri et al.

1999) and deficits in selective attention (Ciesielski et al. 1990). This body of literature does indicate that the examination of cortical auditory ERPs (i.e., N1, MMN, P3) holds great potential for contributing to our knowledge of autism, and eventually, for shedding light on understanding of the pathogenesis and etiology of this disease. However, another important aspect of MMN, specifically usefulness of it's application as an intervention outcome measure has not been investigated in children with autism spectrum disorder.

Autonomic Dysfunctions in Autism

Many children with autism exhibit symptoms associated with autonomic dysfunction. Skin conductance level (SCL) studies in autism have shown a lack of the normal habituation in the skin conductance responses (SCR) and respiratory pause to the same stimulus over time (Barry and James 1988; Van Engeland 1984). Children with autism had blunted, poorly dissociated heart rate (HR) and SCR responses to visual or auditory social stimuli. Higher basal tonic electrodermal activity as well as larger responses to sounds were observed in autistic children compared to controls (Palkovitz and Wiesenfeld 1980). All these are indications of increased basal sympathetic and reduced parasympathetic tone in autism (Hirstein et al. 2001; Ming et al. 2005). Reduced cardiac vagal tone, decreased baroreflex sensitivity, and labile respiratory rhythm in autism spectrum disorder was reported by Julu et al. (2001). Heart rate variability (HRV) measures represent reliable assessment of cardiac autonomic responses (Berntson et al. 1997) and are reported to be attenuated in ASD (Porges 1995, 2003). Reduced HRV indicative of limited psychophysiological flexibility is not a specific marker for autism, as it was found in various psychopathologies, for example anxiety disorders, depression, etc. (Movius and Allen 2005).

Goals and Aims of the Study

In this pilot research study we administered auditory tests prior to Berard AIT training and post-AIT to investigate changes in the individual's auditory response pattern using electroencephalographic (EEG) responses. Auditory evoked potentials (AEP) and event-related potentials (ERP) were recorded in 20 children with autism diagnosis twice (pre- and post-AIT) and in 16 typically developing children only once at baseline test. For evaluation of behavioral changes we used several parent questionnaires and surveys (Aberrant Behavior Checklist [ABC, Aman and Singh 1986, 1994], Repetitive Behavior Scale-Revised [RBS-R, Bodfish et al. 1999, 2000]) and also Comprehensive Performance Index (CPI) questionnaire (Brockett 2012). In addition we recorded heart rate, respiration and skin conductance level during AIT to monitor autonomic changes resulting from the auditory integration training course. The AIT group was tested at the beginning of the AIT sessions and at the end of the 10 days of AIT. Results of the auditory oddball tasks in the ASD group were compared with results obtained from typically developing children (TD group). During the AIT procedure several autonomic measures (heart rate, skin conductance, and respiration) were monitored on-line in all children with ASD to investigate whether AIT will have effect on these physiological variables.

Methods

Subjects and Enrollment

Participants with autism spectrum disorder (ASD) (age range 8–14 years) were recruited through the University of Louisville Weisskopf Child Evaluation Center (WCEC) and Kosair Charities Autism Center. The candidates for the study were also recruited from the pool of individuals with autism spectrum disorder seeking treatment with assistance of Louisville Chapter of FEAT (Families for Effective Autism Treatment) and Louisville Home of Innocents. The study was advertised in a form of flyers with invitations and preliminary screening form mailed along with self-addressed return envelope to families at the FEAT. In addition to this recruitment effort there was arranged a lecture by Berard AIT certified specialist and university-based investigators at the Home of Innocents to explain goals of the AIT study to be conducted at the university lab. The timing of the study was specifically set at summer vacations at schools allowing children to get enrolled for the 2 week long daily intense training course. Parents were requested to confirm their commitment to have at least 3 h break between morning and afternoon AIT sessions. Majority of subjects ($N = 14$) were enrolled at the first year's summer, while remaining ($N = 6$) were trained at the second year's summer of the study. Selection of holidays period for AIT course was determined by the recommendation of Berard's AIT procedure manual, and in addition by availability of undergraduate students at their research practice at the laboratory.

Confirmation of autism diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA 2000) and further ascertained with the Autism Diagnostic Interview—Revised (ADI-R) (Le Couteur et al. 2003). All subjects had normal hearing based on past hearing screens. Participants either had normal vision or wore corrective lenses. Participants with a

history of seizure disorder, significant hearing or visual impairment, a brain abnormality conclusive from imaging studies or an identified genetic disorder were excluded. All participants were children with ASD with full-scale IQ > 70 assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV, Wechsler 2003) or the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler 1999). Prior records of IQ test of eligible subjects were acceptable. Typically developing (TD) children were recruited by advertisement, and before enrolling into the study were screened using interview with them and their parents to rule out any neurological or psychiatric disorders history. Children in TD group were compensated for their time. The study complied with all relevant national regulations and institutional policies and was approved by the University of Louisville Institutional Review Board (IRB). Participating subjects and their parents (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local IRB. The consent and assent forms approved by the IRB were reviewed and explained to all families who expressed interest to participate. All questions were answered before consent signature was requested. If the individual (and their parents/guardians) agreed to participate, she/he signed and dated the informed consent/assent form and received a copy countersigned by the investigator who obtained consent.

Berard AIT Procedure

All children with ASD at the lab participated in a standard protocol of Berard AIT following exactly the same procedure provided by the same experimenter trained by a certified Berard instructor. The standard Berard AIT protocol consists of two 30-min sessions of listening each day within a 12 day period. In our study, subjects were not trained on the weekend, but rather had a 2 week-long course consisting of 10 sessions on the 1st week and another 10 sessions on the 2nd week, i.e., was conducted in 2 five days sets. The listening sessions were separated by a mandatory 3-h interval to allow a break from the auditory stimulation. After leaving the morning session, children usually participated in activities chosen by the families. These activities included but were not limited to excursions to the nearby Ohio riverside park and playground, river beach, science museum, mall, etc. Some local children returned home during the break. It was, however, recommended that stressful activities be avoided between morning and afternoon AIT sessions.

Music for Berard AIT represented a variety of light rock, reggae, and jazz, selected specifically to assure that it contains a wide range of frequencies from 20 Hz to 20 kHz. Sony CD changer (Model CDP-CE500) was used to program the sequence of preselected music pieces. Music was modulated by an electronic device called the Earducator^{TM}/6F (Hollagen Designs CC, Western Cape, South Africa).The processed music did not exceed an average output of 85 dB. The Earducator/6F intermittently emphasized low and high sound frequencies in the music (called gating or modulation). Children listen to the music through closed, high fidelity headphones (Beyerdynamic DT250-80). The protocol for Berard AIT recommends quiet listening without engagement in cognitive activities. Most children were able to listen quietly, and frequently preferred to sit on a leather recliner chair. Some required small, passive sensory fidget toys to keep their hands away from the headphone cord. Reading, writing, assembling puzzles, and other cognitively stimulating activities were not provided. Several children opted to watch video with nature scenes with sound turned off (e.g., "March of Penguins", National Geographic Society movies, "Life" and "Planet Earth" series by BBC, etc.).

Audiologists collaborating in the study tested the child's hearing profile before AIT beginning and after five days of intervention. In some cases, the low functioning children were not able to cooperate with the audiometry test procedure, or behaviors interfered with the testing. In these cases, the audiologist reported that the test could not be completed, or that the data obtained may not be highly accurate or reliable. When a reliable audiogram was obtained, it was analyzed using a computer program available to all Berard practitioners to determine if specific sound frequencies should be filtered from the child's music program. Based on the analysis, specific, narrow-band Earducator filters were activated to reduce the stimulation of selected frequencies. When no reliable audiogram was obtained or when the analysis indicated none was needed, no Earducator filters were used. No additional sensory support activities were given to the children during this listening process and no changes were made in sensory support activities for home programs. If the children already participated in home program activities before participating in the AIT, they continued with those recommendations to avoid additional changes in behavior that may occur with changes in the home program.

Procedure of Autonomic Function Recording

Electrocardiogram (ECG), photoplethysmogram (PPG), pneumogram (PNG) and electrodermal activity (EDA) were acquired by a portable 10 channel physiological monitoring system (NeXus10, Mind Media, Netherlands) with BioTrace+ software. Three Ag/AgCl electrodes (pregeled with Signa Crème, NJ) were attached for measurement of Lead II ECG, PPG was recorded from the index

finger, and PNG was recorded with a strain gauge transducer. EDA was recorded by Ag/AgCl electrodes attached to the distal phalanx of index and middle fingers of the left hand to measure skin conductance level (SCL in μS, Boucsein 2012). Following cardiovascular measures were recorded during each AIT session: Average heart rate (HR) extracted both from ECG and PPG, the standard deviation of the HR (SDEV-HR, time domain HRV measure), spectral power of high frequency (HF, 0.15–0.40 Hz), and low frequency (LF, 0.04–0.15 Hz) components of HRV were monitored visually and in addition calculated in off-line mode (Berntson et al. 1997). PNG signal was used to calculate respiration rate.

Procedure of Auditory Oddball Test (Mismatch Negativity Test)

Stimulus tones were presented through Logitech-5 audio system. This attention task was programmed in E-Prime (Psychology Software Tools, PA). EEG was recorded by a 128 channel Electrical Geodesics Inc. (Eugene, OR) system with Net Station software (v. 4.2).Auditory evoked potentials were recorded from 128 scalp electrodes (10–10 system) and the average reference across all channels was used. Each subject in the auditory oddball test was presented with two sequences of stimuli; each sequence consisted of audio stimuli with an intensity of 70 dB nHL (i.e., 70 decibel over normal hearing level) and an inter-stimulus interval (ISI) of 800 ms. Two types of stimuli are presented through a loudspeaker placed in front of the subject: (1) *standard* stimuli were 1000 Hz sinusoidal tones of 100 ms duration and represented 80 % of stimuli in each sequence; (2) *deviant* stimuli were 1300 Hz sinusoidal tones of 100 ms duration and represented 20 % of stimuli in each sequence, randomly presented among the standard stimuli. The epoch acquisition time was 200 ms and includes 200 ms before the stimulus and 400 ms after. Signals were band-pass filtered at 0.2–30 Hz and sampled at 1000 Hz. During the recording sessions, the attention of the subjects was directed to a computer screen showing written instructions to sit still (without audio).Responses were averaged separately for each stimulus type in each subject and the 0 μV baseline was determined as the mean amplitude of the pre-stimulus period (200 ms pre stimulus). To quantify the MMN, the evoked response to the standard tone were subtracted from the corresponding deviant stimulus response and its amplitude (value relative to the baseline) and latency at peak were measured over the midline frontal, fronto-central, and central electrodes (Fz, FC1, and FC2, Cz), though the main site selected for MNN analysis was Fz. Similarly, mean amplitude (value relative to the baseline) along with amplitude and latency at peak were measured over the same electrodes. Moreover, the amplitude (value relative to the baseline) and latency at peak for the N1 and P3 components of the auditory evoked potential were obtained for the standard and deviant stimuli measured at Fz, Cz, and Pz midline sites. According to recent systematic review of 34 studies of MNN (Bartha-Doering et al. 2015 most studies used EEG for recording the MMN, and all EEG studies except one (97 %) measured MMN at frontal sites, 94 % also used central electrodes, 68 % recorded MMN from parietal, 44 % from temporal, and 24 % from occipital electrodes in addition to frontal sites. Our study limited MNN recording to midline frontal, central and parietal sites for comparability purposes, as majority of studies of MMN used these topographic EEG sites for MMN calculation.

Parent Questionnaires

Social and behavioral functioning for participants were evaluated utilizing caregiver report and clinician ratings of improvement. Participants were evaluated prior to receiving training and within one week of completing Berard AIT. Measures included: *Aberrant Behavior Checklist* (*ABC*). The ABC (Aman and Singh 1986, 1994) is a rating scale assessing five problem areas: (1) *Irritability*, *Agitation*; (2) *Lethargy*, *Social Withdrawal*; (3) *Stereotypic Behavior*; (4) *Hyperactivity*, *Noncompliance*; and (5) *Inappropriate Speech* based on caregiver report. Each area contains multiple items receiving a rating from 0 to 3. Instructions of the ABC manual advise not to calculate total scores across subscales, as the subscales are largely independent (Aman 2012). Normative data for parent ratings presented by age and gender combined, gender alone, and age alone can be found in Brown et al. (2002). The original factor structure of the Aberrant Behavior Checklist was cross-validated with numerous samples of persons with moderate to profound mental retardation (Bihm and Poindexter 1991; Brown et al. 2002). An extensive psychometric assessment of the ABC has indicated that the subscales have high internal consistency, adequate reliability, and established validity. The ABC has been translated into 39 languages and it has been used around the world (Aman 2012). The ABC has been shown to be effective in assessing behavior changes in autism (Aman 2004).

Another questionnaire was *Repetitive Behavior Scale—Revised* (*RBS-R*). The RBS (Bodfish et al. 1999) is a caregiver completed rating scale assessing repetitive and restricted behavior patterns. The RBS is a measure of different behaviors: stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted range (Bodfish et al. 2000). The items of the RBS-R have been conceptually grouped into six subscales including: (1) *Stereotyped Behavior* (movements with no obvious purpose that are

repeated in a similar manner); (2) *Self-injurious Behavior* (actions that cause or have the potential to cause redness, bruising, or other injury to the body); (3) *Compulsive Behavior* (behavior that is repeated and performed according to a rule or involves things being done ''just so''); (4) *Ritualistic Behavior* (performing activities of daily living in a similar manner); (5) *Sameness Behavior* (resistance to change, insisting that things stay the same); and (6) *Restricted Behavior* (limited range of focus, interest, or activity) (Lam and Aman 2007). The questionnaire was validated in an independent sample individuals with ASD and showed high internal consistency in outpatient settings (Lam and Aman 2007). The results of other validation studies (Mirenda et al. 2010; Lam et al. 2008) confirmed the utility of the RBS-R as a measure of repetitive behaviors in children with ASD.

In addition we used the *Comprehensive Performance Index* (*CPI*) questionnaire (Brockett 2012). The CPI questionnaire asks parents to rate the child's behaviors/performance for the past three days. For each item, parents have to decide whether the behavior is a problem and circle the appropriate number (i.e., 0 = no problem, 1 = mild problem, 2 = moderate problem, 3 = severe problem). This questionnaire was developed by a Berard AIT provider and evaluates items related to auditory processing, sensitivity, receptive and expressive language, problematic behaviors, socialization, emotional state, fine and gross motor activity, academic and organizational performance and other relevant domains. The questionnaire is not yet validated in independent samples and was used in our study as an exploratory outcome instrument.

Results

Subjects: Age and Demographics

Twenty children were enrolled in the study and 18 of them completed all 20 sessions of Berard AIT and all required pre- and post-intervention assessments and auditory oddball tests. Mean age was 11.06 ± (standard deviation) 2.26 years. There were 15 boys and 3 girls among study completers. The racial demographic was following: 12 Caucasians, 4 Asians, one African-American, and one of the participants was Hispanic. Six subjects were out of city and families arrived to Louisville specifically for participation in the Berard AIT course and other psychophysiological evaluations at the lab. The group of the TD children was slightly older but not statistically different from the ASD group (N = 16, 12.6 ± 3.14 years, 12 boys, 4 girls). Data of 2 TD children were not used for evoked potential analysis due to excessive artifacts. All parents were representatives of the middle class.

Autonomic Outcomes

Heart Rate (*HR*) did not show statistically significant linear regression over 20 sessions of AIT (F = 0.35, $p = 0.56$, n.s.). Nevertheless, *t* test showed an increase of the HR at the last session (95.52 ± 11.32 bpm) as compared to the first session of AIT (90.36 ± 10.78 bpm), with the mean change being 5.16 ± 8.35 bmp, t = 2.62, $df = 17$, $p = 0.018$, 95 % CI from 1.01 to 9.31 bmp. Frequency domain measures of Heart Rate Variability (HRV) did not show any statistically significant regression over AIT sessions nor any pre- versus post-AIT changes (i.e., LF, $p = 0.21$, n.s.; HF, $p = 0.44$, n.s.). Time-domain measure of (HRV (i.e., *Standard Deviation of HR*, *[STDEV-HR]*) showed statistically significant linear regression (R = 0.72, $R^2 = 0.52$, adjusted $R^2 = 0.49$, $F_{1,19} = 19.68$, $p < 0.001$, normality test passed at $p = 0.11$, observed power = 0.96 at alpha = 0.05, see Fig. 1). Changes of *STDEV of HR* from the first to the last session of AIT were significant (t = 2.53, $p = 0.027$). *Respiration Rate* demonstrated steady and significant linear increase over 20 sessions of AIT (R = 0.71, $R^2 = 0.51$, adjusted $R^2 = 0.48$, $F_{1,19} = 18.96$, $p < 0.001$, normality test passed at $p = 0.55$, observed power = 0.96 at alpha = 0.05, see Fig. 2). This strong effect was corroborated by statistically significant change of *Respiration Rate* from the first to the last session of the AIT (from 19.86 ± 4.36 to 21.54 ± 4.37 breaths/min, t = 4.62, $df = 17$, $p = 0.001$, 95 % CI from 0.91 to 2.43 breaths/per min). *Skin conductance level* (*SCL*) did not show any statistically significant liner regression over 20 sessions of AIT and changes from the first to the last session of AIT also were not statistically significant.

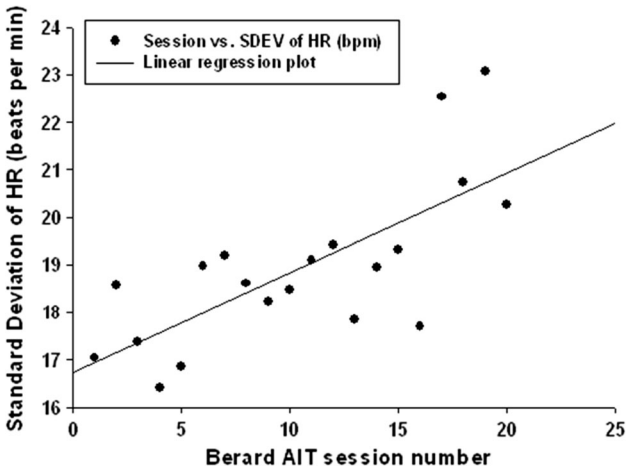

Fig. 1 Linear regression plot of Standard Deviation of Heart Rate (STDEV-HR) during 20 sessions of Berard AIT in 18 children with ASD. Linear increase of STDEV-HR was statistically significant (R = 0.72, $p < 0.001$)

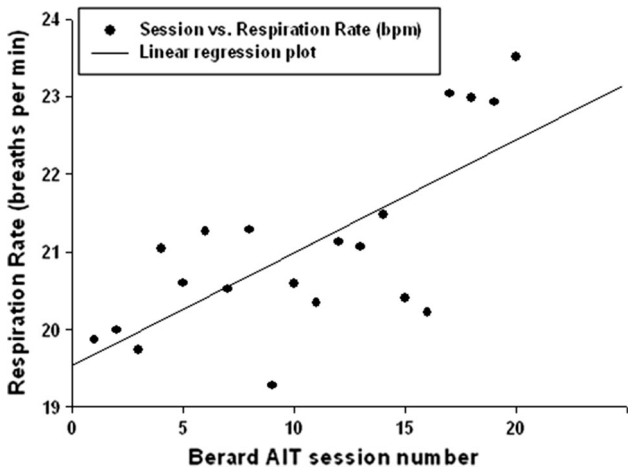

Fig. 2 Linear regression plot of mean Respiration Rate during 20 sessions of Berard AIT in 18 children with ASD. Linear increase of Respiration Rate was statistically significant ($R = 0.71$, $p < 0.001$)

Auditory Evoked Potentials

Evoked Potentials at Baseline: ASD versus Typically Developing Controls

N1 Comparison of N1 amplitude at the baseline auditory oddball test showed no group differences at the frontal and parietal sites. One-way ANOVA showed significant differences between the groups in the latency of the N1 to rare stimuli both at the midline frontal (Fz, 72.5 ± 33.4 ms in TD vs. 107.6 ± 46.3 ms in ASD, $F_{1,31} = 6.10$, $p = 0.018$) and midline parietal (Pz, 111.1 ± 35.8 ms in TD vs. 140.7 ± 46.5 ms in ASD, $F_{1,31} = 4.19$, $p = 0.048$) sites. Differences of N1 latency were significant also in response to frequent stimuli (Fz, 84.4 ± 42.9 ms in TD vs. 112.1 ± 47.5 ms in ASD, $F_{1,31} = 4.63$, $p = 0.038$; Pz, 112.3 ± 45.5 ms in TD vs. 139.9 ± 34.8 ms in ASD, $F_{1,31} = 4.58$, $p = 0.039$). Group difference between amplitude (but not latency) to frequent and rare stimuli evoked N1 component was statistically significant and was manifested as a larger difference in the ASD group (−1.01 ± 1.57 μV in TD vs. −2.22 ± 1.78 μV in ASD, $F_{1,31} = 4.58$, $p = 0.039$).

MMN Mean amplitude of the mismatch negativity at Fz site showed differences between TD and ASD groups being more negative in the autism group (−0.67 ± 2.05 μV in TD vs. −2.24 ± 1.90 μV in ASD, $F_{1,31} = 5.36$, $p = 0.029$). Amplitude of the MMN peak was also different in a similar manner ($F_{1,31} = 0.64$, $p = 0.041$), but difference in the latency of MMN peak was not significant ($F_{1,31} = 2.13$, $p = 0.15$, n.s.).

P3a and P3b There was a group difference in the frontal P3a to frequent stimuli, which was of higher amplitude in the ASD group ($F_{1,31} = 5.51$, $p = 0.026$) without any differences in the latency of P3a. At the parietal site (Pz) there were no amplitude differences, but the latency of P3b to rare sounds was significantly prolonged in the ASD group (335.9 ± 44.0 ms in TD vs. 387.3 ± 54.7 ms in ASD, $F_{1,31} = 8.21$, $p = 0.008$).

Post-AIT Evoked Potentials outcomes in ASD group

N1 Amplitude of the frontal N1 component to rare stimuli post-AIT decrease and became less negative (from −1.37 ± 1.55 μV pre- vs. −0.23 ± 1.18 μV post-AIT, $F_{1,35} = 4.83$, $p = 0.037$). In a similar way, post training difference between peak amplitude of N1 to rare and frequent stimuli became less negative (from −1.56 ± 1.55 μV pre- vs. −0.24 ± 1.57 μV post-AIT, $F_{1,35} = 5.13$, $p = 0.032$).

MMN Mean amplitude of MMN marginally decreased post-AIT ($F_{1,35} = 4.37$, $p = 0.046$) as well as amplitude of the MMN peak ($F_{1,35} = 4.48$, $p = 0.043$, Fig. 3). The latency of MMN peak did not show any significant changes.

P3a and P3b Amplitude of the frontal P3a to frequent stimuli decreased ($F_{1,35} = 4.98$, $p = 0.036$) without any latency changes. At the parietal site (Pz), the amplitude of P3b increased, but very barely reached statistically significant level (from 1.24 ± 3.29 μV to 3.93 ± 3.04 μV, $F_{1,35} = 4.29$, $p = 0.05$, Fig. 4).

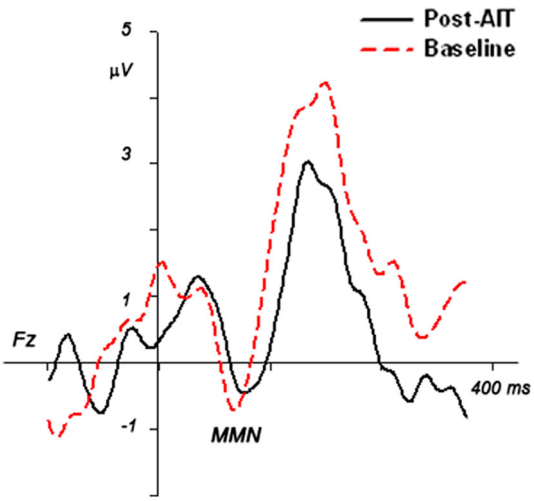

Fig. 3 Mismatch negativity (MMN) in a passive auditory oddball tasks pre- and post-AIT in 18 children with ASD. Amplitude of the midline frontal MMN tended to decrease post-AIT

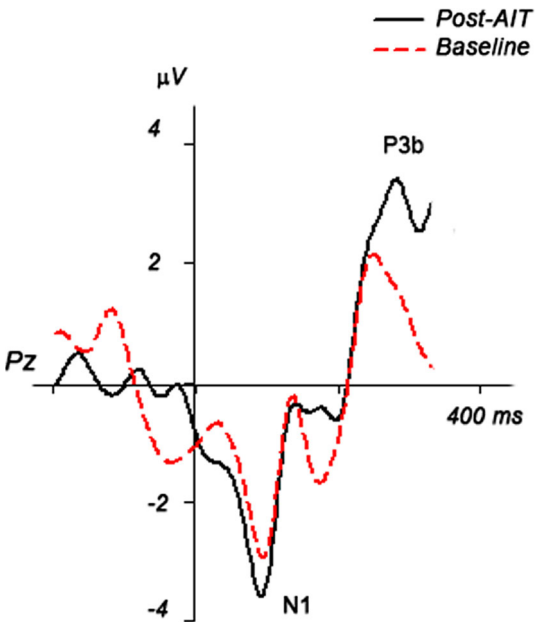

Fig. 4 Evoked potentials (parietal N1 and P3b marked) to rare stimuli in a passive auditory oddball tasks pre- and post-AIT in 18 children with ASD. Amplitude of the parietal P3b component to rare stimuli increased post-AIT

Comparison of Post-AIT Evoked Potentials Outcomes in ASD to Baseline of TD Group

N1 Amplitude of the frontal N1 component to both rare and frequent stimuli decreased but was not different from the values in the TD group (Fz, rare, $F_{1,31} = 0.04$, $p = 0.82$, n.s.; frequent, $F_{1,31} = 0.03$, $p = 0.85$, n.s.). However, the latency to rare stimuli post-AIT in the ASD group was still prolonged as compared to TD children at the midline frontal (Fz, $F_{1,31} = 5.59$, $p = 0.025$) but not at the parietal site (Pz, $F_{1,31} = 0.22$, $p = 0.63$, n.s.). Latencies of N1 at both sites to frequent stimuli did not show any group differences.

Mmn Mean amplitude of MMN at the frontal site post-AIT was not different from the values of TD group ($F_{1,31} = 0.91$, $p = 0.75$, ns.), though the latency of the MMN peak post-AIT became different from the TD group ($F_{1,31} = 5.22$, $p = 0.031$).

P3a and P3b The amplitude of the frontal P3a to frequent stimuli that decreased post-AIT in the ASD group was no longer different from the TD group ($F_{1,31} = 0.47$, $p = 0.49$, n.s.). The amplitude of the parietal P3b to rare stimuli that increased post-AIT showed a trend to be higher than in the TD group ($F_{1,31} = 2.49$, $p = 0.12$, n.s.), while the latency of P3b tended to remain still more prolonged as compared to the TD group ($F_{1,31} = 3.44$, $p = 0.74$, n.s.)

Behavioral Questionnaires Outcomes

Aberrant Behavior Checklist (ABC) and Repetitive Behavior Scale (RBS-R) Outcomes

As it was expected, the ABC and RBS behavioral checklists did show statistically significant improvements in several domains when analyzed using a paired sample Student's t-test. *Irritability subscale* showed significant score decrease (from 12.06 ± 8.84 (SD) down to 9.78 ± 7.23 post-AIT). Mean decrease was -2.28 ± 3.86, $t = 2.50$, $df = 17$, $p = 0.02$, 95 % confidence interval (CI) from -0.35 to -4.19. *Hyperactivity* subscale of the ABC showed a significant score reduction (from 19.44 ± 10.81 down to 14.22 ± 9.38, mean decrease being -5.22 ± 5.98, $t = 3.70$, $df = 17$, $p = 0.002$, 95 % CI from -2.24 to -8.19). Individual ABC subscale rating score changes are depicted in the Fig. 5.

We found a significant decrease in stereotype repetitive and restricted behavior patterns following 20 sessions of AIT as measured by the RBS-R (Bodfish et al. 1999). *Total RBS-R* score decreased from 26.94 ± 16.39 to 19.94 ± 13.50, with the mean decrease being -7.00 ± 5.65, $t = 4.95$, $df = 17$, $p < 0.001$, 95 % CI from -3.98 to -10.01. Changes in individual subscale rating score on RBS are shown in Fig. 6, where *Stereotypic Behavior* subscale score shows significant decrease (from 6.31 ± 5.46 to 4.81 ± 4.41, mean change -1.50 ± 1.67, $t = 3.58$, $df = 17$, $p = 0.003$, 95 % CI -0.61 to -2.39) and *Ritualistic/Sameness Behavior* subscale score ratings also showed a significant decrease (from 9.00 ± 5.31 down to 6.50 ± 5.36, mean change being—2.50 ± 1.82, $t = 5.47$, $p < 0.001$, 95 % CI from -1.51 to -3.47).

Comprehensive Performance Index (CPI) Outcomes

Half of 14 CPI domains showed statistically significant improvements, and most informative of them are illustrated in Fig. 7 (using pre-minus-post AIT). *Receptive Language* scores improved by 5.17 ± 5.69, $t = 3.74$, $df = 17$, $p = 0.002$, 95 % CI from 2.25 to 8.10. *Behaviors* scores also showed improvement by 8.31 ± 7.58 points, $t = 4.38$, $df = 17$, $p = 0.001$, 95 % CI from 4.27 to 12.35. *Emotional behavior* scores improved by 3.05 ± 4.46, $t = 2.83$, $df = 17$, $p = 0.012$, along with similar increase in *Socialization* scores ($t = 2.78$, $p = 0.013$). *Organization* scores showed only marginal significance (mean improvement by 2.29 ± 4.47, $t = 2.13$, $p = 0.048$). Other domain scores (e.g., *Auditory Sensitivity*, *Expressive Language*, *and Miscellaneous*) showed positive trends, though their changes did not reach statistically significance levels (p values being in the 0.057–0.094 range)

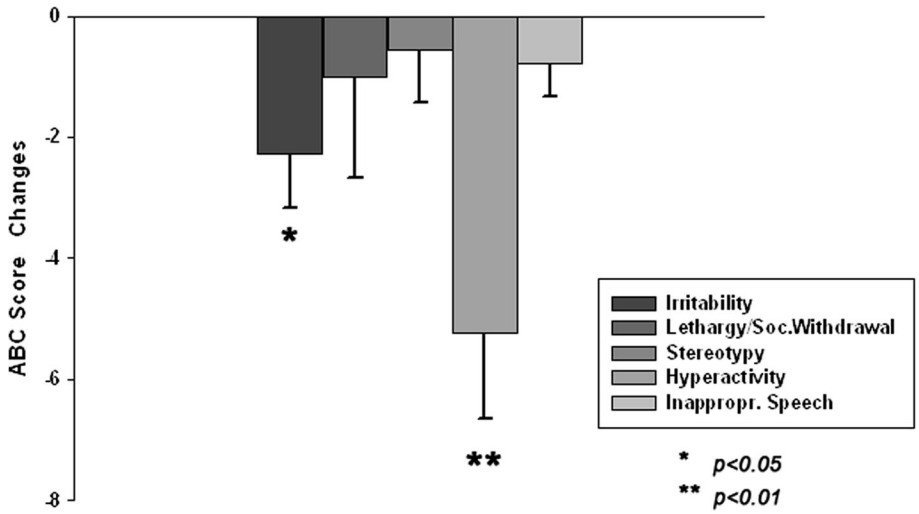

Fig. 5 Aberrant Behavior Checklist (ABC) score changes post-AIT (post-minus-pre) intervention in 18 children with ASD. *Irritability/Agitation* and *Hyperactivity* rating scores decreased significantly

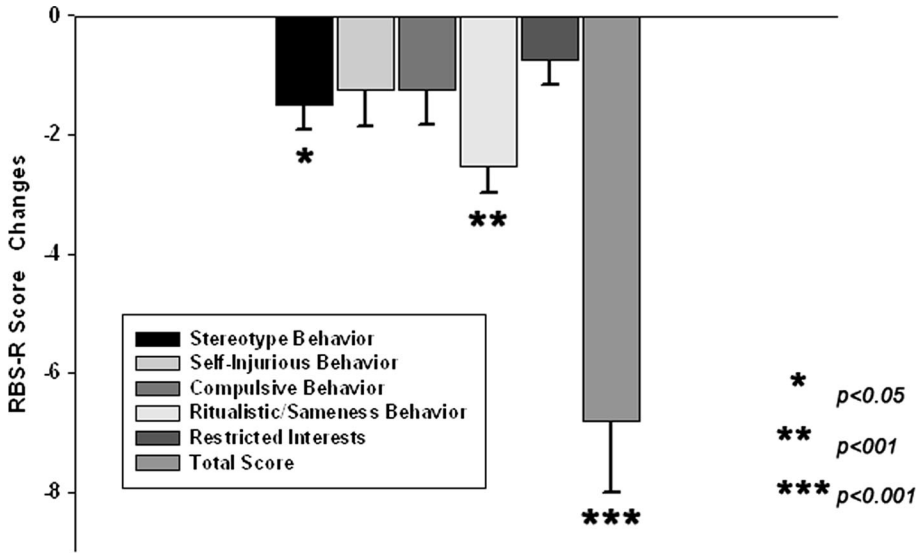

Fig. 6 Repetitive Behavior Scale (RBS-R) score changes post-AIT intervention in 18 children with ASD. *Stereotype Behavior*, *Ritualistic/Sameness Behavior*, and *Total Repetitive Behavior* rating scores decreased significantly

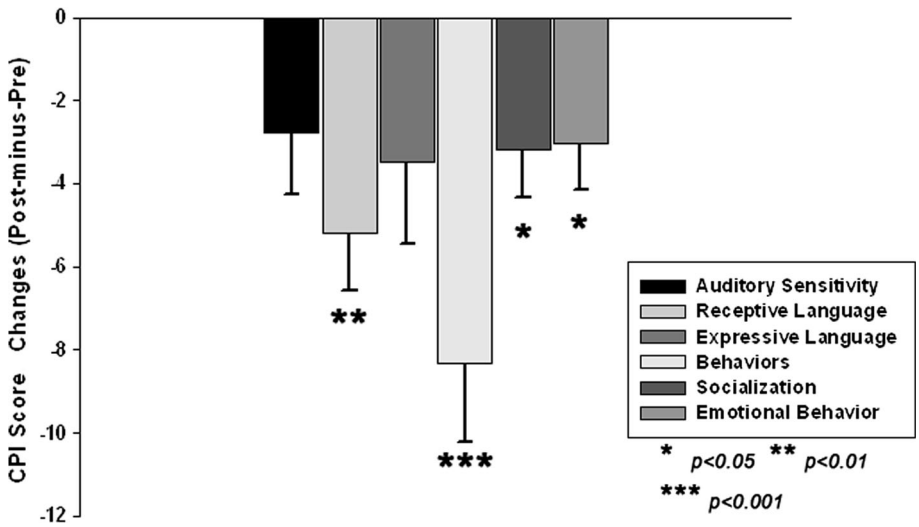

Fig. 7 Comprehensive Performance Index (CPI) score changes post-AIT in 18 children with ASD. *Receptive Language*, *General Behaviors*, *Socialization*, *and Emotional Behavior* rating scores decreased significantly

Discussion

Overview of Results

Among the most notable feasibility related outcomes should be listed the following: (1) the majority (i.e., 18 completers out of 20 enrolled) of children with ASD could tolerate AIT procedure and comply with quite demanding lab visit regimen; (2) children complied with psychophysiological monitoring requirements and allowed acquisition of useful electrophysiological data throughout the AIT course; (3) children with ASD diagnosis complied with auditory oddball task-based evoked potential testing with EEG recording that allowed collection of N1, MMN and P3 components data for evoked potential changes analysis; (4) behavioral questionnaires used in the study were sensitive instruments to detect post-AIT changes in various behavioral domains. Behavioral surveys and questionnaires showed significant symptom severity decrease on ABC, RBS, and CPI. Most other studies using these behavioral measures monitored change at 1, 3, and 6 months following Berard AIT. In these studies, the majority of change occurs at 1 month and additional change is typically measured at 3, and sometimes 6 months (Berard and Brockett 2011; Brockett et al. 2014; Edelson et al. 1999; Rimland and Edelson 1994, 1995). Therefore, additional change for children in this study may occur after the period of data collection. Unlike other known studies, this study documents that significant changes actually occur earlier than previously measured. Autonomic outcomes of the study reflected a gradual linear increase of time domain heart rate variability measures and respiration rate across AIT course, and in addition HR and respiration rate showed a significant increase post-AIT course. These results could be explained by the increased emotional reactivity to modulated music as the AIT course progressed. Comparison of evoked potential characteristics of children with ASD versus typically developing children revealed several interesting findings, even though some of the group differences were only marginally significant: (1) delayed latency of N1 component both rare and frequent stimuli in autism; (2) more negative mismatch negativity in the ASD group; (3) higher P3a amplitude to frequent stimuli, and at the same time delayed latency and higher amplitude of P3b to rare stimuli.

Post-AIT changes in evoked potentials could be summarized in the following way: (1) decreased magnitude of N1 peak to rare stimuli; (2) decreased negativity of N1 response differences between rare and frequent stimuli in N1 time window; (3) marginally lower negativity of the mismatch negativity post-AIT; (4) decreased frontal P3a potential to frequent stimuli, and shorter latency of the parietal P3b to the rare stimuli. These evoked potential changes following completion of Berard AIT course are in a positive direction, making them less distinct from those recorded in age-matched group of typical children, thus could be considered as changes towards normalization.

General Discussion

A substantial body of MMN research provides evidence for atypical processing of auditory change in individuals with ASD relative to typically developing controls. It should be noted that results of MMN studies in autism are not as consistent as they could be, especially considering that majority still show differences but not the same type of abnormality. Ferri et al. (2003) found that MMNs to a frequency deviant were significantly larger in a group of mentally retarded autistic boys than in a group of age but not IQ matched boys. In contrast, some studies found no amplitude differences in the MMN between autistic and control groups of children. For instance, Ceponiene et al. (2003) found that the MMNs elicited from high-functioning children with autism were similar in amplitude to those elicited from normal controls for frequency deviants in streams of synthesized vowels, complex and simple tones. Kemner et al. (1995) also found no evidence of an abnormality in timing, amplitude or topography of the MMN in children with autism in response to changes in vowels as compared to normally developing children. In a similar manner, Jansson-Verkasalo et al. (2003) found no amplitude differences in the MMN elicited from children with Asperger syndrome in comparison to typically developing controls. However, latency of MNN was prolonged over the right hemisphere for a consonant change and later over both hemispheres for a tonal change in the children with Asperger. Kujala et al. (2005) examined MMN elicited by pitch, duration and vowel changes in speech and non-speech stimuli and found that MMN amplitudes were similar for pitch and vowel deviants but were smaller for duration deviants in the children with autism and with Asperger syndrome than in typically developing children. Still, several more studies have found smaller MMNs in children with autism than in controls. Seri et al. (1999) found smaller and later MMN to tonal deviants in children with autism with tuberous sclerosis than in non-autistic children with tuberous sclerosis. Abdeltawwab and Baz (2015) also reported smaller MMN to tone bursts in school-age children with autism.

There are, however, viable explanations for these inconsistent findings, and they are at least partially due to heterogeneity of the subjects and paradigms employed

among studies (Samson et al. 2006). Further, most of these studies tested small groups of children and failed to control for IQ, even when children with IQs in the mentally retarded range participated. Severity of symptoms in autism are definitely contributing to atypical auditory processing and sensory integration (Brandwein et al. 2015).There are reports of atypical MMN in people with autism in response to emotional voices, (Fan and Cheng 2014) that suggested that individuals with autism may process emotionally laden voices in an atypical fashion at the very early stage of perception. This processing abnormality can be used as a functional diagnostics tool in ASD and for predicting social communication deficits in this population. A series of studies by Orekhova and Stroganova group (Orekhova and Stroganova 2014; Orekhova et al. 2009; Stroganova et al. 2013) investigated arousal and re-orienting of attention in children with autism using ERPs and found abnormalities of pre-attentive arousal and hemispheric differences that might contribute to atypical auditory responses in ASD.

There is a need to consider several factors related to significance of the topography where MMN was recorded and also specifics of particular auditory test used. As it was stated above, MMN appears as a negative deflection in the difference waveform, typically peaking between 120 and 250 ms post-stimulus onset. Maximal amplitudes are elicited over frontal–central regions (Näätänen and Alho 1997). Neuronal generators underlying this potential are postulated to originate predominantly from the bilateral supratemporal cortices, with possible contributions from the frontal lobes (Näätänen and Picton 1987; Näätänen et al. 2007). In general, MMN peak latencies become shorter and amplitudes larger as the magnitude of stimulus change increases (Näätänen and Picton 1987), reflecting the greater ease of auditory cortex to detect stimulus modifications. Cognitively, the MMN most likely reflects comparison of 'deviant' (rare) stimuli to standards (frequent) stored in working memory (Näätänen et al. 2005). The inter-stimulus interval (ISI) thus must be short enough to enable adequate representation and comparison of standard and deviant stimuli in working memory. If the inter-stimulus interval (ISI) is too long then the MMN will not be elicited (Näätänen et al. 2005). Our study used 800 ms ISI without any changes in ISI. Perhaps the main benefit of the MMN is that it is elicited in the absence of attention, making it a useful tool to assess sensory memory in difficult to test populations such as young children and individuals with developmental disorders (Näätänen and Picton 1987). Our test also did not deliver any specific attention-related instructions to participants, and the task was in a form of passive listening in the sound-proof experimental room.

Interpretation of the functional significance of mismatch negativity measure is important for better understanding of observed trends of MMN changes post-AIT. According to a review by Fishman (2014) two dominant explanations for the MMN have been proposed. According to the "neural adaptation" hypothesis, repeated presentation of the standards results in adapted (i.e., attenuated) responses of feature-selective neurons in the auditory cortex. Rare deviant sounds activate neurons that are less adapted than those stimulated by the frequent standard sounds, and thus elicit a larger 'obligatory' response, which yields the MMN following the subtraction procedure. In contrast, according to the "sensory memory" hypothesis, the MMN is a 'novel' (non-obligatory) ERP component that reflects a deviation between properties of an incoming sound and those of a neural 'memory trace' established by the preceding standard sounds. Though MMN is elicited by any discriminable change in auditory stimulation at the very early stages of perception and could be mostly considered as pre-attentive process, some studies proposed that MMN may have a place in higher-order cognitive processes such as those involving grammar and semantic meaning (Näätänen et al. 2007). Furthermore, MMN may even reflect the presence of automatic processes such as stimulus anticipation at the level of auditory cortex, especially when auditory inter-stimulus interval is kept constant. In addition, as it was outlined in studies of Näätänen group (2005, 2007) the MMN enables initiation of the brain processes related to the need of attention switch to deviant sound, and more conscious perception of sound parameter changes in an unattended stimulus stream.

Some authors recently considered that it is time to move MMN into the clinic as an important functional diagnostic measure (Schall 2015) as it represents a valuable index of central auditory processing (Näätänen et al. 2007). Our study provides ground also for utility of MMN as an outcome measure in AIT. Definitely more studies are needed to better understand mechanisms and meaning of the mismatch negativity (Fishman 2014). Nevertheless, it is clear that mismatch negativity can be effectively used to reveal specifics of auditory processing abnormalities and consequent atypical sensory perception behavior in children with ASD (Ludlow et al. 2014; Lepistö et al. 2006; Tecchio et al. 2003). For instance, in a study of Dunn et al. (2008) amplitude of MMN in children with autism was significantly smaller than in children with typical development in unattended conditions, however, children with autism exhibited a typical amplitude MMN when attending to the stimuli. The authors concluded that auditory discrimination of infrequent changes in streams of auditory stimuli appears to be accomplished through a different mechanism than in typical children, specifically through the investment of attention. Sensory processing is a crucial underpinning

of the development of social cognition, a function which is compromised in variable degree in ASD (Seri et al. 1999). In less severely impaired patients with an autism diagnosis, increased response to perception of change in physical characteristics of the sound (e.g., pitch) according to Seri et al. (1999) can be interpreted as an indicator of increased local processing (rather than global processing), probably representing a compensatory mechanism for the lack of so called "central coherence" (Brock et al. 2002).

Several discrepancies in our results with reported MMN data in the literature can be explained by the hypothesis of Samson et al. (2006) that the level of neural complexity explains the relative level of performance and brain activity in autistic individuals. The authors claim that available behavioral, ERP and imaging findings related to the perception of increasingly complex auditory material under various processing tasks in autism suggest that tasks involving simple material (pure tones) and/or low-level operations (detection, labeling, detection of pitch changes) show a superior level of performance and shorter ERP latencies in individuals with ASD. Our MMN task definitely belongs to this simple manipulation category. In contrast, as Samson et al. (2006) pointed out, tasks involving spectrally- and temporally-dynamic material and/or complex operations (evaluation) are poorly performed by children with autism, or generate more attenuated ERPs and difference waves such as MMN. Level of complexity required to perform auditory tasks may therefore explain the pattern of performance and activation of autistic individuals during auditory tasks and provide insight about existing discrepancies in comparison of MNN in ASD and typically developing children.

Several limitations of the current study should be mentioned. The study was not controlled as it did not use a placebo control group (i.e., group of children randomly assigned to listening to music without Earducator modulation) as it was initially planned, mostly due to difficulties recruiting children and families who would agree to participate in such a randomized controlled trial. We plan to have this type of design in our future studies of Berard AIT effects. We analyzed and reported only mean values of autonomic variables across the AIT course (e.g., HR, SDEV-HR, respiration rate, SCL, etc.) though it would be useful as well to conduct an analysis of minute-by-minute changes of HR, HRV and SCL to find if there were any meaningful changes in autonomic variables within individual sessions depending on the stage of the AIT intervention. We could not compare autonomic activity between ASD and TD groups as we did not record autonomic measures in typical children because they were enrolled only in the baseline auditory oddball test. Several more important modifications could be added to auditory oddball test, for instance, manipulation of deviant stimuli frequencies, changing ISI, etc., as we selected the most simple version of auditory oddball test to be able collect data even from relatively low functioning children.

We believe that this study provided important feasibility information for future research. Future studies using MMN and other auditory evoked potential data may provide important insight to the definition of endophenotypes of ASD, which may have the potential for early diagnosis and the creation of informed interventions for children with autism (Schall 2015). Research data on MMN provides important promise for clinical translation potential of this measure, which after standardization of recording procedure and collection of ASD-specific normative database can become a valuable investigation tool.

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Compliance with Ethical Standards

Conflict of interest The authors do not have any potential conflict of interest to disclose. All authors therefore declare that they do not have any conflict of interests.

Ethical Approval All procedures performed in this study that involved human subjects were in accordance with the ethical standards of the institutional research committee (IRB) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol of the study was approved by the University of Louisville IRB. Signed informed consent forms (from parents) and informed assent forms (from children) were obtained from all individual participants and parents of children included in the study. The results of the study propose that more controlled research is necessary to document behavioral and psychophysiological changes resulting from Berard AIT and to provide explanation of the neural mechanisms of how auditory integration training may affect behavior and psychophysiological responses of children with ASD.

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