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Controlled Evaluation of the Effects of Hyperbaric Oxygen Therapy on the Behavior of 16 Children with Autism Spectrum Disorders

Bryan Jepson · Doreen Granpeesheh · Jonathan Tarbox ·
Melissa L. Olive · Carol Stott · Scott Braud ·
J. Helen Yoo · Andrew Wakefield · Michael S. Allen

Abstract Hyperbaric oxygen therapy (HBOT) has been used to treat individuals with autism. However, few studies of its effectiveness have been completed. The current study examined the effects of 40 HBOT sessions at 24% oxygen at 1.3 ATA on 11 topographies of directly observed behavior. Five replications of multiple baselines were completed across a total of 16 participants with autism spectrum disorders. No consistent effects were observed across any group or within any individual participant, demonstrating that HBOT was not an effective treatment for the participants in this study. This study represents the first relatively large-scale controlled study evaluating the effects of HBOT at the level of the individual participant, on a wide array of behaviors.

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Andrew Wakefield is no longer affiliated with The Thoughtful House.

B. Jepson · C. Stott · A. Wakefield
Thoughtful House Center for Children, Austin, TX, USA

D. Granpeesheh · J. Tarbox (✉) · M. L. Olive · S. Braud ·
J. H. Yoo · M. S. Allen
Center for Autism and Related Disorders, Inc.,
19019 Ventura Blvd., Tarzana, CA 91356, USA
e-mail: j.tarbox@centerforautism.com

Present Address:
J. H. Yoo
New York State Institute for Basic Research, New York, NY,
USA

S. Braud
HOPE Reach, Holland, MI, USA

M. S. Allen
Connecticut Behavioral Heath, Middletown, CT, USA

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Introduction

Autism spectrum disorders (ASDs) are developmental disorders which are characterized by impairment in two or more of the following areas: communication, social interaction, and stereotypic or repetitive behaviors (American Psychiatric Association 2000). The current prevalence in the United States is estimated, on the basis of a 2007 reporting period, at 1 in 91 children (Kogan et al. 2009). The large scope of the problem demands an equivalent large response by the medical and scientific community to look for novel and effective ways to treat the disorder. Unfortunately, in practice, the desire to develop novel treatment approaches often exceeds the scientific community's pace at rigorously evaluating them. Thus, over 100 treatments for autism are in wide use (Green et al. 2006), despite the fact that the effectiveness of very few has been directly researched.

Previous Studies on Hyperbaric Oxygen Therapy

One such treatment that has been growing in popularity over recent years is hyperbaric oxygen therapy (HBOT). HBOT consists of the use of an increased concentration of ambient oxygen delivered under pressurized conditions, above the regular atmospheric pressure of 1 atmosphere absolute (ATA). HBOT has been used as a treatment modality since the 1930s when Behnke and Shaw used pressurized chambers to treat patients with decompression sickness (Jain 2004). Currently, HBOT is approved by the Undersea and Hyperbaric Medical Society (UHMS) and

the Food and Drug Administration for conditions ranging from carbon monoxide poisoning to compromised skin grafts (Gessell 2008).

Hyperbaric oxygen therapy has been investigated in the treatment of many neurological conditions including stroke (Anderson et al. 1991; Nighoghossian & Trouillas 1995; Rusyniak et al. 2003; Singhal 2007), traumatic brain injury (Bennett et al. 2004; McDonagh et al. 2004; Rockswold et al. 2007; Shi et al. 2006), cerebral palsy (Collet et al. 2001; Hardy et al. 2002; McDonagh et al. 2007), and multiple sclerosis (Bennett & Heard 2004; Kleijnen & Knipschild 1995).

Proposed Mechanism of Action

The proposed mechanisms of effect in neurological disorders includes the relief of hypoxia, improvement of microcirculation, relief of cerebral edema by a vasoconstrictive effect, preservation of partially damaged tissue, and improvement of cerebral metabolism. Little sound research on the use of HBOT to treat neurological conditions has been published thus far, with the exception of cerebral palsy. A review of the current state of the research in HBOT and cerebral palsy reports that although small improvements in motor function were noted in observational studies, there was no difference between the control group and the treatment group in either of the two controlled studies published to date (Collet et al. 2001; Hardy et al. 2002).

HBOT has emerged as an adjunctive treatment option in autism in response to preliminary evidence of several potential underlying pathophysiological mechanisms which might be amenable to hyperbaric treatment. Several studies using single photon emission computed tomography (SPECT) scans have shown a decrease in blood flow (hypoperfusion) to various brain regions in individuals with autism (Ryu et al. 1999; Starkstein et al. 2000; Wilcox et al. 2002). It has been hypothesized by some that this might leave certain brain cells at risk of dysfunction due to a chronic state of hypoxia (Rossignol 2007; Rossignol & Rossignol 2006). Preliminary evidence shows some benefit from HBOT on cerebral tissues (Helms et al. 2005).

Research has also documented chronic inflammation, both in the gut (Ashwood et al. 2003; Ashwood et al. 2004; Balzola et al. 2005; Furlano et al. 2001; Horvath et al. 1999; Torrente et al. 2002; Wakefield et al. 2000) and in the brain (Pardo et al. 2005; Vargas et al. 2005; Zimmerman et al. 2005) in individuals with autism. HBOT has been shown to be effective at treating inflammation in various tissues, including the gut (Al-Waili & Butler 2006; Buchman et al. 2001; Gorgulu et al. 2006; Gulec et al. 2004; Gurbuz et al. 2003a, b; Nikfarjam et al. 2007; Vlodavsky et al. 2006; Wilson et al. 2007; Wilson et al. 2006).

Autism HBOT Studies and Limitations

To date, few studies have been completed regarding the effectiveness of HBOT as a treatment for autism. Two discussion papers by Rossignol and colleagues presented hypotheses, based on a retrospective case series of 6 children (Rossignol 2007; Rossignol & Rossignol 2006). However, based on the lack of an experimental design, the improvements noted within the small group should not be attributed to HBOT. Replication of study results with additional participants within the context of valid experimental methodology would be necessary to draw causal conclusions.

The same research group followed up with a small open-label pilot study looking at safety and efficacy (Rossignol et al. 2007). They measured biomarkers of inflammation (C-reactive protein) and oxidative stress (e.g. oxidized glutathione), as well as parent reports of behavior in 18 children with autism over a treatment course of 40 sessions. Six of the children were treated with 1.5 ATA pressure and 100% oxygen, while 12 children were treated with 1.3 ATA pressure and 24% oxygen (using an air concentrator). They reported no significant worsening of oxidative stress, a non-significant trend of improvement in C-reactive protein values (in a small subgroup that started out high) and improvement in parent reports of some measures associated with autism (speech, motivation and cognitive awareness). However, the weaknesses of the open-label design and the lack of a control group make it difficult to reach definitive conclusions. Specifically, it is possible that the improvement in parent report measures was due to a placebo effect, or due to improvement over time due to other concurrent treatments taking place outside of the HBOT.

In the first controlled study of HBOT, Lerman et al. (2008) evaluated the effects of HBOT on direct measures of task engagement, spontaneous communication, and problem behavior. The study employed a multiple baseline across three children. HBOT was delivered at 88% oxygen and 1.3 ATA. Two participants received 40 sessions of HBOT and the third received 27. One participant demonstrated a potential increase in communication during HBOT treatment but the effect was not replicated across the other two participants. In addition, one participant demonstrated a potential decrease in challenging behavior during HBOT treatment and subsequent worsening of the behavior when HBOT was removed. However, this too was not replicated across participants. The decrease in behavior during HBOT could have been accounted for by the overall decrease in demands during days in which HBOT treatment was delivered.

The Lerman et al. (2008) study made a significant contribution by including direct measures of behavior. Overall, participants might have experienced positive changes but the changes were not observed consistently

across the 3 participants. Replication of the treatment effect across participants is required to demonstrate experimental control in a multiple baseline design. The lack of such replication in the Lerman et al. (2008) study makes it difficult to determine whether the potential effects observed were due to HBOT or some other concurrent treatment.

Rossignol et al. (2009) conducted a randomized, double-blind placebo-controlled trial on the effects of HBOT using 1.3 ATA and 24% oxygen. Participants received 40 sessions comprised of two 1-h HBOT sessions per day, 5 days per week over 4 consecutive weeks. Although forty sessions is a commonly studied dosing regimen, the weekly intensity of HBOT treatment hours (i.e., 10) was higher than in previous HBOT-autism studies. The outcome measures included a physician-reported response to question 2 on the Clinical Global Impression Scale (CGI: Guy 1976). Outcome measures also included several parent report measures: the Aberrant Behavior Checklist (ABC: Aman & Singh 1994); the Autism Treatment Evaluation Checklist (ATEC: Autism Research Institute 2007) and the CGI.

A statistically significant difference in outcomes between groups was observed on the Sensory/Cognitive subscale of the ATEC, but not on any other ATEC subscales. There were no statistically significant differences on any ABC subscale when comparing the HBOT group to the placebo group. The results indicated that both groups improved over the course of the study which suggests either a placebo effect and/or treatment effects from concurrent treatments other than HBOT. It should be noted that the ATEC has not been validated in the scientific community subjecting its use in a study such as this to be questionable. Additionally, the authors reported a significant difference between groups on both the physician CGI ($P < 0.0008$) and the parent CGI ($P < 0.0336$). It should be noted that no baseline measure was completed by the physicians prohibiting the authors from detecting a pre-post effect based on their ratings. Moreover, the physicians failed to complete the entire CGI and instead focused on one item.

The authors analyzed individual participant treatment data further and reported a statistically significant improvement in several subscales. While the authors attributed the differences to a treatment effect, the authors failed to note that the study design did not allow for such a comparison to be made. The authors interpreted the overall findings as positive and recommended HBOT for the treatment of autism.

In a subsequent study, Granpeesheh et al. (2010) conducted a randomized, double-blind, placebo controlled evaluation of HBOT, consisting of 80 1-h sessions at 24% oxygen and 1.3 ATA. Sessions were administered 6–10 times per week. There were 18 participants in the treatment group and 16 controls. The control group received 1-h

sessions in the HBOT chambers which were filled with ambient air at a pressure sufficient to keep the chamber inflated (not significantly above 1 ATA). Results indicated that both groups improved to a small degree over time but that there was no significant difference in improvement between the HBOT and placebo groups. Since all participants were also receiving behavioral intervention services during the course of the study and the number of hours per week of behavioral intervention was matched between groups, it is possible that the improvement seen in both groups was due to the behavioral intervention.

Although the Granpeesheh et al. (2010) study did not demonstrate a significant effect of treatment, it is possible that the group design used did not allow for careful examination of the results of treatment at the level of the individual participant. Regardless of what the mean response to a treatment may be across a group of individuals, the response of a particular patient over time is of primary concern to the practicing clinician, and this fact makes single-subject experimental design particularly well-suited to evaluate treatment effect. Given the small scale of the Lerman et al. (2008) study and the conflicting results of the Rossignol et al. (2009) and Granpeesheh et al. (2010) studies, it remains possible that some children with ASDs might respond favorably to HBOT and that this subgroup was obscured by the study designs of existing research.

Purpose of Current Study

One method for examining this possibility would be to evaluate the effectiveness of HBOT at the level of the individual participant, using a single-subject design, and replicating the evaluation across a relatively large sample of participants. Such a design would have the benefit of identifying any possible effects at the level of the individual participant and would likely include at least some responders if a large enough sample was included. The purpose of the current study was to conduct such an investigation. We evaluated the effects of HBOT on direct measures of 11 topographies of behavior, representing a wide sample of behaviors characteristic of autism, across five replications of multiple baselines across children, with a total of 16 participants.

Method

Participants

Following appropriate approval from an independent Institutional Review Board, participants were recruited by listing the study on the public trials registry, posting the

study on autism list serves, and informing existing clients at both clinical centers where the authors are employed. All interested participants were provided study information and initial screenings were conducted to ensure that inclusion criteria were met.

Inclusion criteria were as follows: (a) diagnosis of autistic disorder, pervasive developmental disorder not otherwise specified (PDD NOS), or Asperger's disorder; (b) between 2 and 10 years of age; (c) no change in medical treatment regimen or dietary regimen for 6 weeks prior to the study; and (d) caregiver agreement to refrain from changing any treatment regimens during the course of the study. Potential participants were excluded if they displayed any medical conditions which would contraindicate HBOT (i.e., current otitis media, current sinus infection, history of seizures). Two participants were excluded from enrollment in the study due to a history of seizure activity.

Twenty participants were initially enrolled for participation in the study. One child's parents terminated participation after 19 HBOT sessions after they reported an increase in stereotypy and a decrease in language. It should be noted that these changes were not evident in the patient's data. Two terminated during baseline because of difficulty with the travel commitment and one participant was excluded because the diagnosis could not be confirmed when the ADOS was administered. Therefore, a total of 16 children completed participation in the study. The mean age of participants was 5 years 9 months (range = 3 years 10 months–9 years 5 months). Table 1 depicts age, gender, and diagnosis for each participant.

Prior to the start of the study, participants were assessed on a number of measures. First, an independent diagnosis of an autism spectrum disorders was required. Then participants were administered the Autism Diagnostic Observation Schedule (Lord et al. 1989). A measure of IQ was obtained by administering the Wechsler Preschool and Primary Scale of Intelligence™– Third Edition (Wechsler 2002) for children between 2 and 6 or the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999) for children over 6 years. The Vineland Adaptive Behavior Scale-II (Sparrow et al. 2005) and the Aberrant Behavior Checklist (Aman & Singh 1994) were also administered. Results of these measures are reported in Table 1.

Materials

Several materials were used in this study. First, all direct observation play sessions were conducted in an empty room dedicated to this study. The room was approximately 4 × 4 m. Materials in the room included two small tables, a chair, a video camera on a tri-pod, a hand held digital timer, and 3–5 toys that were preferred by the participating child.

Second, all HBOT sessions were conducted in separate clinic room dedicated for HBOT therapy. The room was approximately 15 × 10 m. Materials in the room consisted of a desk and chair for the medical technician, three HBOT chambers, and storage shelves. HBOT therapy was delivered using "soft-shell" inflatable chambers (Vitaeris 320). This apparatus was selected due to its popularity and frequent use by families and physicians prescribing HBOT.

Finally, materials used for coding videotaped sessions included the !Observe data collection software, run on PalmZ3© personal data assistants.

Response Measurement and Inter-observer Agreement

The dependent variables in this study were direct measures of behavior, which were collected from video tapes of behavioral observation play sessions. Because it was not known which behaviors, if any, might be affected by HBOT, a wide variety of behaviors relevant to social functioning, verbal functioning, and problematic behaviors were measured. Frequency data were collected on: (a) vocal initiations defined as participant vocalizations that did not occur in response to therapist behavior; (b) physical initiations defined as child-initiated hugs, hand holding or grabbing, giving high-fives, hand-shakes, tapping on the shoulder or leg, showing objects, or gesturing; (c) vocal response defined as any vocal behavior which occurred in response to a therapist vocalization (e.g., saying "thank you" in response to a compliment); (d) physical response defined as any non-vocal behavior which occurred in response to a therapist behavior (e.g., showing a toy air plane in response to a therapist saying "Look, I have a cool car"); (e) self-injurious behavior or aggression defined as hitting, kicking, pinching, scratching, biting, and pulling hair directed toward self or others; (f) disruption, defined as kicking objects, throwing objects, breaking objects, tearing paper, tipping over chairs, and hitting walls; (g) tantrums defined as crying or screaming above a conversational level of volume; (h) vocal stereotypy defined as successively repeating words, reciting passages from movies or books in a non-functional manner, making repetitive noises; and (i) physical stereotypy defined as hand flapping, rocking, spinning, flicking, waving objects in a repetitive manner, or manipulating objects in a repetitive nonfunctional manner. A new instance of stereotypy was scored when stereotypy had not occurred for 10 s. Additionally, 10-second partial interval data were collected on: (a) toy contact defined as contact of hand with a toy; and (b) physical activity defined as two footsteps being taken within a 10 s interval.

Interobserver agreement (IOA) was assessed by having a second, independent observer collect data for at least 32% of all sessions for each participant. IOA was assessed by dividing the smaller number of behaviors recorded by the

Table 1 Age, gender, and diagnoses

Participant	Age[a]	Gender	Diagnosis	ADOS[b]	IQ	VABS[c]	ABC-C[d]
001	3–10	Male	Autistic disorder	18	N/A	62	26
003	6–0	Male	Autistic disorder	17	N/A	61	97
004	6–7	Male	Autistic disorder	19	112	93	60
005	6–5	Male	Autistic disorder	8	115	85	52
007	3–11	Male	Autistic disorder	18	N/A	67	20
008	5–6	Male	Autistic disorder	10	112	91	18
009	5–2	Male	PDD NOS	9	85	104	44
010	3–7	Male	PDD NOS	9	N/A	105	43
011	5–9	Female	Autistic disorder	19	63	70	43
012	5–0	Male	PDD NOS	17	59	69	74
013	6–6	Male	PDD NOS	5	132	95	79
014	9–5	Male	Autistic disorder	8	N/A	81	24
015	7–3	Male	Autistic disorder	18	N/A	54	26
018	4–3	Male	Autistic disorder	16	N/A	56	77
019	4–9	Male	Autistic disorder	10	N/A	68	60
020	8–6	Male	Asperger's disorder	7	85	83	67

[a] in years and months, [b] Autism diagnostic observation schedule, [c] Vineland adaptive behavior scales, [d] Aberrant behavior checklist-community

larger, in each consecutive 10 s interval, averaging the resulting decimals for the session, and converting the average to a percentage. In order to avoid inflating average agreement by both observers agreeing on non-occurrence of a behavior for an entire session, IOA was not assessed for a given behavior on a given session when the primary data indicated that the behavior did not occur during that session. Table 2 depicts the percentage of sessions with IOA for each participant, as well as the mean and range of IOA for each class of behavior.

Experimental Design and Analysis

A non-concurrent multiple baseline across participants design was used to evaluate the effects of HBOT on the behaviors of participants because anecdotal reports of the effectiveness of HBOT have described treatment effects that persist after HBOT treatment is terminated. A multiple baseline design is well-suited to studying treatments which produce lasting effects because it does not depend on a deterioration of the treatment effect after treatment is

Table 2 Interobserver agreement (IOA) data

Participant #	% sessions with IOA	% Agreement adaptive	%Agreement aberrant	%Agreement stereotypy
001	77	98 (96–100)	94 (85–99)	87 (51–98)
003	64	97 (93–100)	94 (77–99)	77 (58–90)
004	64	94 (87–99)	N/A[a]	94 (90–100)
005	61	96 (69–97)	N/A	94 (90–98)
007	60	95 (78–100)	93 (72–100)	74 (50–89)
008	48	89 (74–95)	N/A	100
009	38	85 (69–93)	98 (97–100)	85 (68–97)
010	40	94 (76–100)	98 (96–100)	93 (82–98)
011	41	99 (95–100)	95 (92–98)	75 (54–90)
012	38	99 (98–100)	N/A	90 (50–98)
013	39	90 (72–100)	96 (95–97)	97 (97–97)
014	33	96 (78–100)	98 (78–100)	89 (70–100)
015	32	99 (97–100)	98 (95–100)	80 (54–93)
018	65	97 (93–100)	97 (92–100)	90 (80–97)
019	36	97 (92–100)	N/A	90 (78–98)
020	41	90 (78–100)	97 (95–98)	100

[a] N/A indicates the behavior never occurred during sessions for which IOA was assessed

withdrawn (Kazdin 1982). In order to demonstrate that a treatment is effective in a multiple baseline across participants, it is necessary to demonstrate that the treatment produces an effect with one participant when it is administered to him/her and that the behavior in question for another participant does not improve until the same treatment is administered to the second participant (Kazdin 1982). Further evidence for the causal relation between treatment and improvement in behavior is demonstrated with further replication across additional participants in the same multiple baseline and across additional participants in additional multiple baselines.

Visual inspection is used to evaluate changes in the level, trend, and variability displayed in repeated measures of the dependent variable over time. Although statistical analyses can be accommodated in the multiple baseline design, visual inspection is generally preferred because only robust and stable treatment effects are readily visually apparent and weak or transient treatment effects are therefore "filtered out" (Kazdin 1982). In the current study, four non-concurrent multiple baselines were conducted across three participants and one non-concurrent multiple baseline was conducted across four participants.

Baseline

Baseline was comprised of behavioral observation play sessions which were conducted as the play/control condition of the standard experimental functional analysis described by Iwata et al. (1994). The play condition was used in order to set up a stable environmental condition under which the occurrence of free operant problem behavior and adaptive behavior could vary as a function of the effects of HBOT. A similar approach to utilizing functional analysis sessions for assessing drug effects has been described elsewhere in the literature (Crosland et al. 2003; Zarcone et al. 2004; Zarcone et al. 2008).

Behavioral observation play sessions were 10 min in duration and conducted by trained research assistants twice per week during the baseline phase, immediately prior to each HBOT session, and at all follow-up appointments. The trained research assistants were not informed of the purpose of the study. However, participants received HBOT therapy immediately after the play session. Thus, the research assistant may have surmised the purpose of the play sessions. The trained research assistants were not familiar with participants prior to the study. However, the baseline period of observation most likely allowed the research assistant and participant to feel comfortable with one another. The research assistant did not score data on personal sessions but rather on sessions conducted by other research assistants. The purpose of this was to prevent research assistants from obtaining an expected effect.

Finally, the use of interobserver agreement helps to ensure the fidelity of the data.

HBOT Procedures

The chamber was used to deliver an estimated 24% oxygen at 1.3 ATA (Rossignol et al. 2007). During HBOT treatment sessions, the participant and his/her parent/guardian sat or reclined in the chamber. Participants' parents were encouraged to bring toys or other items or activities which were preferred by the participant into the chamber. Parents were otherwise encouraged not to interact with their child in a potentially therapeutic way. During treatment sessions, the pressure in the chamber was slowly increased to the target pressure over the course of 10–15 min, followed by a period of 60 min at the target pressure, and finally by a period of 10–15 min in which the pressure was gradually decreased back to ambient pressure. A group mean of 4.78 sessions were conducted per week, with individual participant weekly mean sessions ranging from 2.46 to 7.0. Each participant received a total of 40 HBOT sessions over an average of 56 days ($r = 39$–68).

The first author was responsible for participant safety and medical oversight of the study. A trained HBOT technician was present for every treatment session. Additionally, parents provided a daily report of the child's response to the intervention. Any negative side effect was reported immediately to the first author. There were two incidents reported. First, a parent reported that her child's stereotypy increased and language decreased. This was not supported with observational data that were being collected. Another child experienced a small skin abscess behind his left external ear. The abscess required a needle aspiration and drainage and oral antibiotics. However, the incident was not deemed related to HBOT.

Follow-Up

Participants were scheduled for two follow-up direct observation play sessions 2 weeks after the last HBOT session and for two additional direct observation play sessions 3 months after the last HBOT session.

Results

Due to the large number of participants and the large number of topographies of behavior measured in the current study, space does not permit graphical display of each topography for each participant (i.e., 11 topographies × 16 participants = 176 data paths). In the interest of space, data for individual participants were summed three in classes: (1) adaptive behavior, (2) stereotypy, and (3) aberrant behavior.

The adaptive behavior class is an overall rate of the following behaviors: *vocal initiations*, *physical initiations*, *vocal response*, *and physical response*. The stereotypy class is a total rate of *vocal* and *physical stereotypy*. The aberrant behavior class is a total rate of *aggression, SIB, tantrums,* and *disruption*. The corresponding author may be contacted for copies of the complete data sets.

The results are depicted in Figs. 1, 2, 3, 4, 5, 6. Each panel of each multiple baseline graph depicts the rate of a particular class of behavior for a particular participant. Participant numbers are depicted near the right margin of the panel. A visual inspection of changes in level, trend, and variability in the data after the onset of HBOT reveal no consistent effect on any class of behavior across any of

Fig. 1 Rates of stereotypy, aberrant behaviors, and adaptive behaviors for Group 1 (Participants 011, 008, and 015)
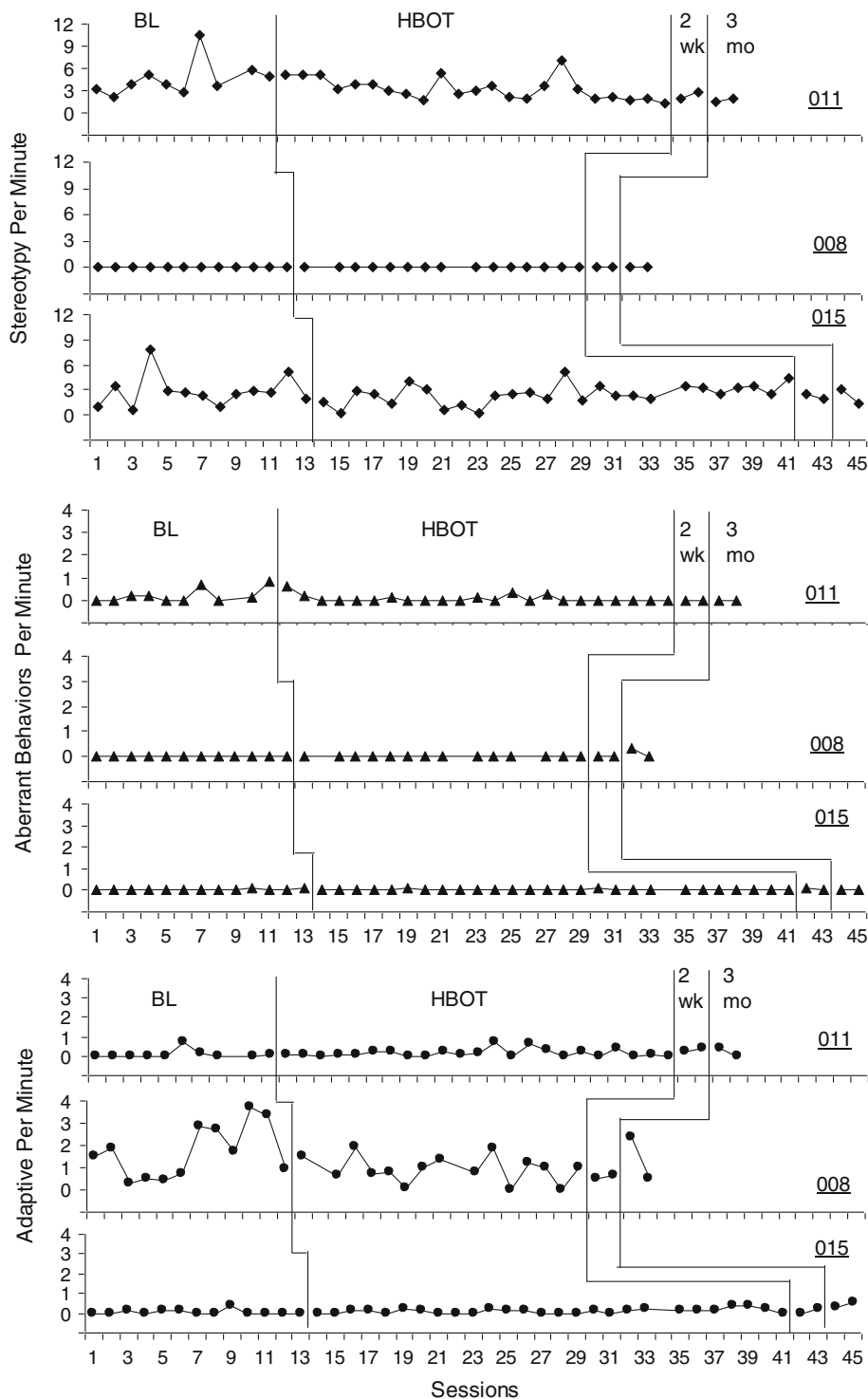
the multiple baselines. In addition, no clear effect was apparent for any individual participant. It is possible that adaptive behavior decreased slightly for participant 008 and that stereotypy increased slightly for 007, but neither of these changes constituted clear or immediate changes in level and neither effect was replicated across additional

participants so it is unlikely that these modest potential effects were due to HBOT.

In the interest of space, data on toy contact and physical activity are not presented in graphical format. All data were graphed and visually inspected. However, visual inspection revealed no effect for any participant across any direct

Fig. 2 Rates of stereotypy, aberrant behaviors, and adaptive behaviors for Group 2 (Participants 007, 010, 014)
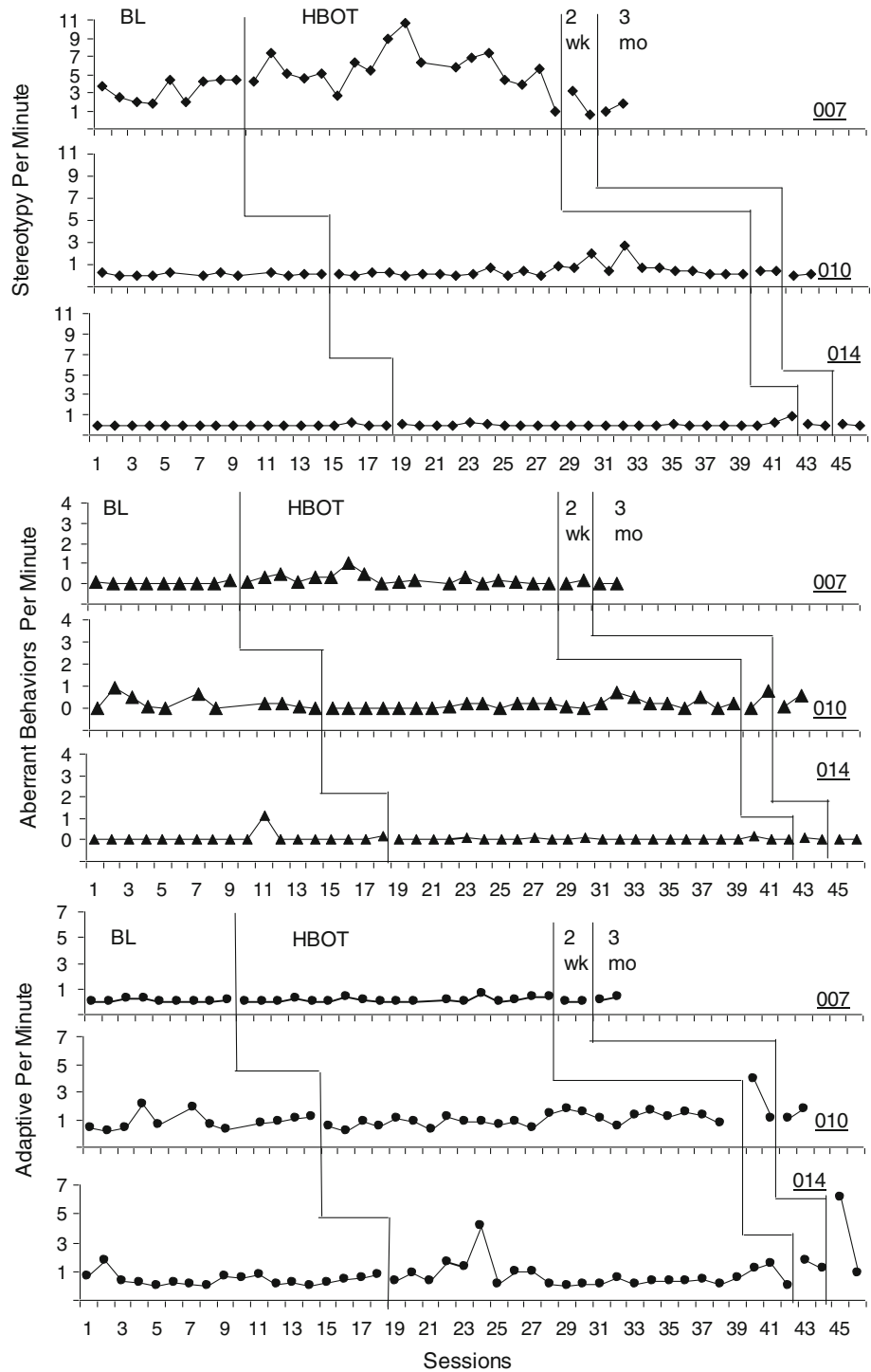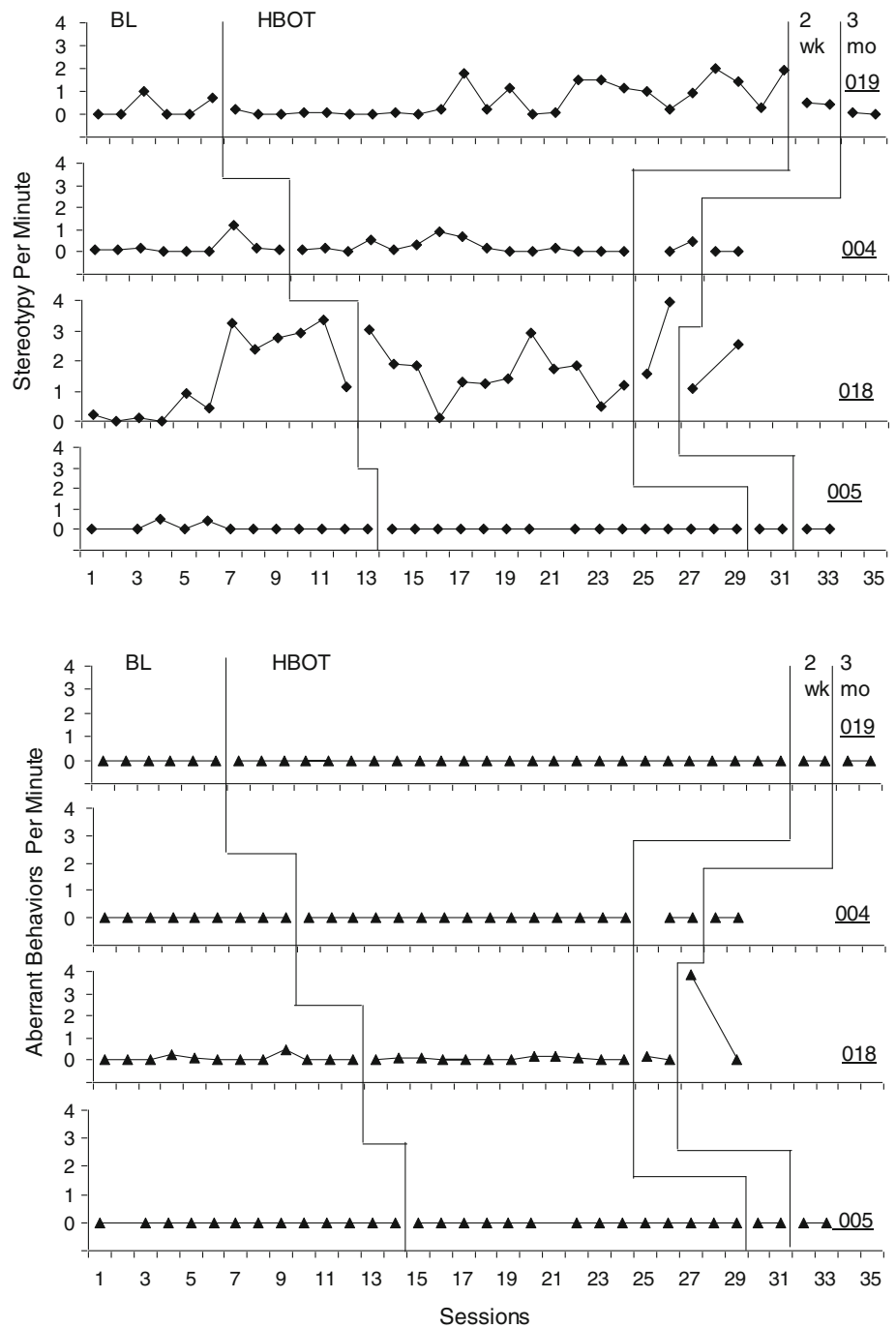
Fig. 3 Rates of stereotypy and aberrant behaviors for Group 3 (Participants 019, 004, 018, and 005)


observation measure (data available from authors, upon request).

Discussion

This study is the first controlled study to evaluate the effects of HBOT as a treatment for children with autism, at the level of the individual participant, via repeated direct measures of a large number of behaviors, across a relatively large number of participants. Multiple topographies of behavior were measured under carefully controlled conditions and no consistent effects (positive or negative) were observed. Based on these results, there is no compelling evidence to suggest that HBOT, delivered at 24% oxygen and 1.3 ATA, is an effective treatment modality for the core behavior symptoms of autism.

Fig. 4 Rates of adaptive behaviors for Group 3 (Participants 019, 004, 018, and 005)
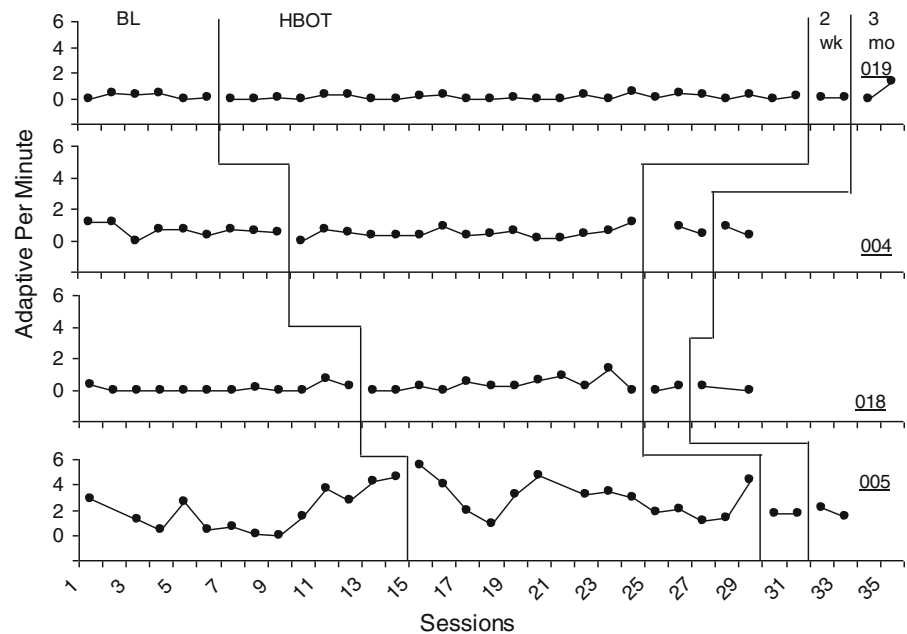
These findings diverge considerably from those of Rossignol et al. (2009). The current study controls for the potential "washing out" of the effect when group data are averaged (as must be done in a between-groups design) by carefully measuring potential changes in 11 topographies of behavior over time across 16 individuals. If there was a subgroup for which HBOT was effective, it seems likely that at least one such child would have participated in the current study. The lack of an effect for any participant in the current study makes the existence of such a subgroup seem implausible.

This study also extends Lerman's findings by examining a larger number of behaviors which constitute a broader sampling of symptoms of autism and by extending the evaluation to a larger number of participants. The result of this study did not replicate the positive findings demonstrated in one of the participants in the (Lerman et al. 2008) study. This finding increases the probability that the effect seen in the Lerman participant was an aberration, as suggested by the study's authors.

This study also extends findings from the Granpeesheh et al. (2010) study suggesting that HBOT delivered at 24% oxygen and 1.3 ATA may not be an effective therapy for the treatment of the behavioral symptoms of autism. As was done in the Granpeesheh et al. study, parents in this study were instructed to refrain from altering their child's therapy during the course of the study. This technique helps to more accurately account for any behavioral changes observed in study participants.

One potential limitation to the current study was that the observation technique used might have been insufficient to detect other benefits of HBOT that have been anecdotally reported by others (e.g., improvements in attention or memory). Future studies could attempt to detect such potential effects by including assessment conditions in which participants are required to actively engage in a learning task or memory activity. Two such possibilities include a repeated acquisition task or the demand condition from the standard functional analysis. Other measures that could potentially detect differences, though not behavioral in nature, would include SPECT scans or functional MRI. Finally, an assessment such as the PDD-Behavior Inventory (Cohen & Sudhalter 2005) could be completed by a non-biased or blind rater in order to detect differences before and after HBOT.

A second limitation in the current study was that measures of possible changes in biochemical variables were not collected (e.g., markers of inflammation or oxidative stress). Therefore, it is not possible to determine whether such variables were affected by the HBOT procedure. It is possible that HBOT delivered at a different dosing regimen, higher pressure, or for longer period of time might produce an effect. Rossignol et al. (2009) used almost twice the average number of treatment sessions per week compared to the current study and this may contribute to the differences in outcome between studies. Future studies should consider directly comparing various dosing regimens. Nevertheless, it should also be noted that the dosing regimen studied here is one that is used widely in the autism community along with associated anecdotal reports of improvement, increasing the probability that the current results can be generalized to a

Fig. 5 Rates of stereotypy, aberrant behaviors, and adaptive behaviors for Group 4 (Participants 020, 013, and 001)
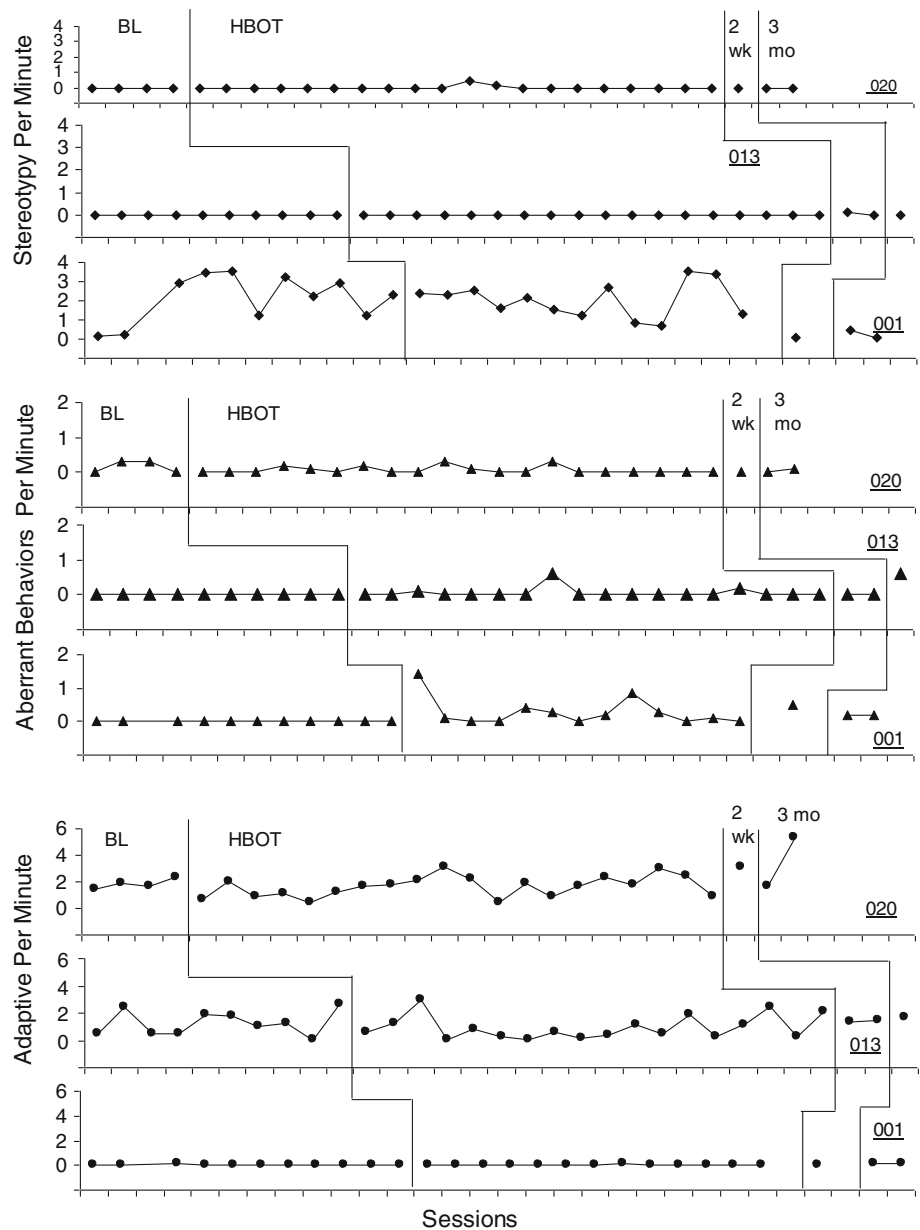

significant proportion of individuals practicing HBOT treatment in the community.

A third limitation relates to the characteristics of participants. Specifically, participants were not included or excluded based on their physical well-being. As such, it is possible that participants with more physical dysfunction may have responded, as a group, differently than the sample that was included in this study. Future studies should consider studying sub-groups of children with physical dysfunction to determine if HBOT therapy is effective for them.

News programs and community blogs report that many families of children with autism are using HBOT therapy.

The cost of such treatment may range up to $150 per hour. Families report using anywhere from 40 to 120 h of HBOT. These hours are in lieu of other therapies such as applied behavior analysis, speech therapy, and occupational therapy and do not include travel time to the medical center where the therapy is provided. Some families purchase the chambers in order to provide therapy in their home. A number of websites focus on renting ($1,395 per month) and selling ($8,495–27,995) chambers to families. Given the financial and time-investment required for HBOT and the conflicting study outcomes to date, we cannot recommend HBOT as a treatment for autism until such time as more conclusive favorable results are demonstrated.

Fig. 6 Rates of stereotypy, aberrant behaviors, and adaptive behaviors for Group 5 (Participants 003, 012, and 009)
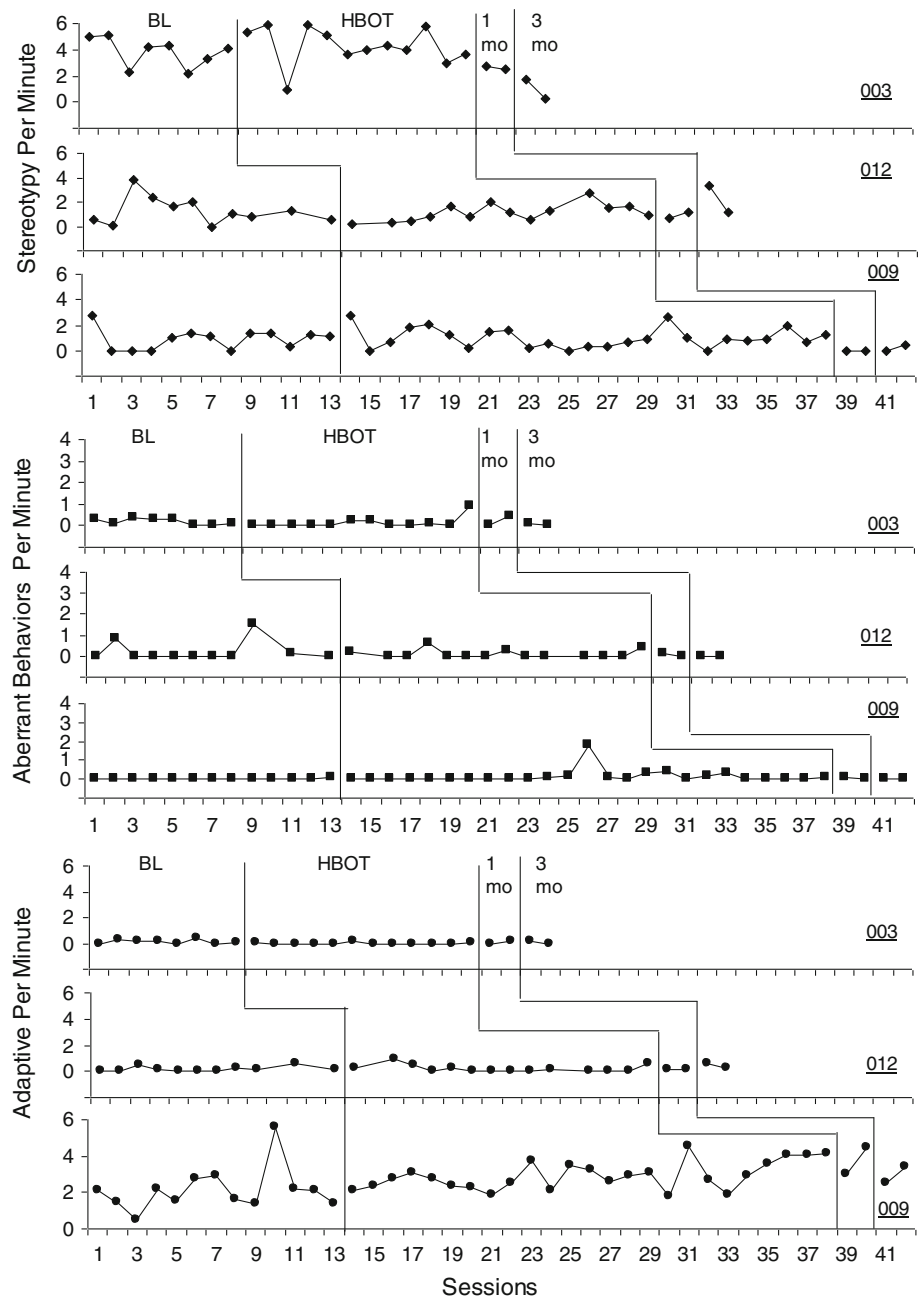
References

Al-Waili, N. S., & Butler, G. J. (2006). Effects of hyperbaric oxygen on inflammatory response to wound and trauma: Possible mechanism of action. *The Scientific World Journal, 6*, 425–441.

Aman, M. G., & Singh, N. N. (1994). *Aberrant behavior checklist–community: Supplementary manual*. East Aurora, NY: Slosson Educational Publications.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th edn, Text Revision). Washington, DC: American Psychiatric Association.

Anderson, D. C., Bottini, A. G., Jaqiella, W. M., Westphal, B., Ford, S., Rockswold, G. L., et al. (1991). A pilot study of hyperbaric oxygen in the treatment of human stroke. *Stroke, 22*, 1137–1142.

Ashwood, P., Anthony, A., Pellicer, A. A., Torrente, F., Walker-Smith, J. A., & Wakefield, A. J. (2003). Intestinal lymphocyte populations in children with regressive autism: Evidence for extensive mucosal immunopathology. *Journal of Clinical Immunology, 23*, 504–517.

Ashwood, P., Anthony, A., Torrente, F., & Wakefield, A. J. (2004). Spontaneous mucosal lymphocyte cytokine profiles in children

with autism and gastrointestinal symptoms: Mucosal immune activation and reduced counter regulatory interleukin-10. *Journal of Clinical Immunology, 24*, 664–673.

Autism Research Institute (2007). *Autism Treatment Evaluation Checklist*. Retrieved from http://autism.com/ari/atec/.

Balzola, F., Barbon, V., Repici, A., Rizzetto, M., Clauser, D., Gandione, M., et al. (2005). Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the wireless capsule enteroscopy: Another piece in the jigsaw of this gut-brain syndrome? *The American Journal of Gastroenterology, 100*(4), 979–981.

Bennett, M., & Heard, R. (2004). Hyperbaric oxygen therapy for multiple sclerosis. *Cochrane Database of Systematic Reviews, 1*, CD003057.

Bennett, M. H., Trytko, B., & Jonker, B. (2004). Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database Systemic Reviews, 4*, CD004609.

Buchman, A. L., Fife, C., Torres, C., Smith, L., & Aristizibal, J. (2001). Hyperbaric oxygen therapy for severe ulcerative colitis. *Journal of Clinical Gastroenterology, 33*, 337–339.

Cohen, I. L., & Sudhalter, V. (2005). *The PDD behavior inventory*. Lutz, FL: Psychological Assessment Resources, Inc.

Collet, J. P., Vanasse, M., Marois, P., Amar, M., Goldberg, J., Lambert, J., et al. (2001). Hyperbaric oxygen for children with cerebral palsy: A randomised multicentre trial. *HBO-CP Research Group. Lancet, 357*(9256), 582–586.

Crosland, K. A., Zarcone, J. R., Lindauer, S. E., Valdovinos, M. G., Zarcone, T. J., Hellings, J. A., et al. (2003). Use of functional analysis methodology in the evaluation of medication effects. *Journal of Autism and Developmental Disorders, 33*, 271–279.

Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A., et al. (2001). Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *The Journal of Pediatrics, 138*, 366–372.

Gessell, L. B. (2008). *Hyperbaric oxygen therapy indications*. Durham, NC: Undersea and Hyperbaric Medical Society.

Gorgulu, S., Yagci, G., Kaymakcioglu, N., Ozkara, M., Kurt, B., Ozcan, A., et al. (2006). Hyperbaric oxygen enhances the efficiency of 5-aminosalicylic acid in acetic acid-induced colitis in rats. *Digestive Diseases and Sciences, 51*, 480–487.

Granpeesheh, D., Tarbox, J., Dixon, D., Wilke, A. E., Allen, S., & Bradstreet, J. J. (2010). Randomized trial of hyperbaric oxygen therapy for children with autism. *Research in Autism Spectrum Disorders, 4*, 265–268.

Green, V. A., Pituch, K. A., Itchon, J., Choi, A., O'Reilly, M., & Sigafoos, J. (2006). Internet survey of treatments used by parents of children with autism. *Research in Developmental Disabilities, 27*, 70–84.

Gulec, B., Yasar, M., Yildiz, S., Oter, S., Akay, C., Deveci, S., et al. (2004). Effect of hyperbaric oxygen on experimental acute distal colitis. *Physiological Research, 53*, 493–499.

Gurbuz, A. K., Elbuken, E., Yazgan, Y., & Yildiz, S. (2003a). A different therapeutic approach in patients with severe ulcerative colitis: Hyperbaric oxygen treatment. *Southern Medical Journal, 96*(6), 632–633.

Gurbuz, A. K., Elbuken, E., Yazgan, Y., & Yildiz, S. (2003b). A different therapeutic approach in severe ulcerative hyperbaric oxygen treatment. *Romanian Journal of Gastroenterology, 12*(2), 170–171.

Guy, W. (1976). *Clinical global impression. ECDEU Assessment Manual for Psychopharmacology, revised*. Rockville, MD: National Institute of Mental Health.

Hardy, P., Collet, J., Goldberg, J., Ducruet, T., Vanasse, M., Lambert, J., et al. (2002). Neuropsychological effects of hyperbaric oxygen therapy in cerebral palsy. *Developmental Medicine and Child Neurology, 44*(7), 436–446.

Helms, A. K., Whelan, H. T., & Torbey, M. T. (2005). Hyperbaric oxygen therapy of cerebral ischemia. *Cerebrovascular Diseases, 20*(6), 417–426.

Horvath, K., Papadimitriou, J. C., Rabsztyn, A., Drachenberg, C., & Tildon, J. T. (1999). Gastrointestinal abnormalities in children with autistic disorder. *Journal of Pediatrics, 135*, 559–563.

Iwata, B. A., Dorsey, M. F., Slifer, K. J., Bauman, K. E., Richman, G. S. (1994). Toward a functional analysis of self-injury. *Journal of Applied Behavior Analysis, 27*, 197–209. (Reprinted from Analysis and Intervention in Developmental Disabilities, 2, 3–20, 1982).

Jain, K. (2004). *Textbook of hyperbaric medicine*. Toronto: Hogrefe & Huber Pub.

Kazdin, A. E. (1982). *Single-case research designs: Methods for clinical and applied settings*. New York, NY: Oxford University Press.

Kleijnen, J., & Knipschild, P. (1995). Hyperbaric oxygen for multiple sclerosis. Review of controlled trials. *Acta Neurologica Scandinavica, 91*(5), 330–334.

Kogan, M. D., et al. (2009). Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. *Pediatrics, 124*, 1395–1403.

Lerman, D. C., Sansbury, T., Hovanetz, A., Wolever, E., Garcia, A., O'Brien, E., et al. (2008). Using behavior analysis to examine the outcomes of unproven therapies: An evaluation of hyperbaric oxygen therapy for children with autism. *Behavior Analysis in Practice, 1*, 50–58.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., et al. (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders, 19*, 185–212.

McDonagh, M., Helfand, M., Carson, S., & Russman, B. S. (2004). Hyperbaric oxygen therapy for traumatic brain injury: A systematic review of the evidence. *Archives of Physical Medicine and Rehabilitation, 85*, 1198–1204.

McDonagh, M. S., Morgan, D., Carson, S., & Russman, B. S. (2007). Systematic review of hyperbaric oxygen therapy for cerebral palsy: The state of the evidence. *Developmental Medicine and Child Neurology, 49*(12), 942–947.

Nighoghossian, N., & Trouillas, P. (1995). Hyperbaric oxygen in the treatment of acute ischemic stroke. A double-blind pilot study. *Stroke, 26*(8), 1369–1372.

Nikfarjam, M., Cuthbertson, C. M., Malcontenti-Wilson, C., Muralidharen, V., Milar, I., & Christophi, C. (2007). Hyperbaric oxygen therapy reduces severity and improves survival in severe acute pancreatitis. *Journal of Gastrointestinal Surgery, 11*, 1008–1015.

Pardo, C. A., Vargas, D. L., & Zimmerman, A. W. (2005). Immunity, neuroglia and neuroinflammation in autism. *International Review of Psychiatry, 17*, 485–495.

Rockswold, S. B., Rockswold, G. L., & Defillo, A. (2007). Hyperbaric oxygen in traumatic brain injury. *Neurological Research, 29*, 162–172.

Rossignol, D. A. (2007). Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism. *Medical Hypotheses, 68*, 1208–1227.

Rossignol, D. A., & Rossignol, L. W. (2006). Hyperbaric oxygen therapy may improve symptoms in autistic children. *Medical Hypotheses, 67*, 216–228.

Rossignol, D. A., Rossignol, L. W., James, S. J., Melnyk, S., & Mumper, E. (2007). The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: An open-label pilot study. *BMC Pediatrics, 7*, 36.

Rossignol, D. A., Rossignol, L. W., Smith, S., Schneider, C., Logerquist, S., Usman, A., et al. (2009). Hyperbaric treatment

for children with autism: A multicenter, randomized, double-blind, controlled trial. *BMC Pediatrics, 9:* doi: 10.1186/1471-2431-9-21.

Rusyniak, D. E., Kirk, M. A., Kao, L. W., Brizendine, E. J., Welch, J. L., Cordell, W. H., et al. (2003). Hyperbaric oxygen therapy in acute ischemic stroke: Results of the hyperbaric oxygen in acute ischemic stroke trial pilot study. *Stroke, 34*(2), 571–574.

Ryu, Y. H., Lee, J. D., Yoon, P. H., Kim, D. I., Lee, H. B., & Shin, Y. J. (1999). Perfusion impairments in infantile autism on technetium-99 m ethyl cysteinate dimer brain single-photon emission tomography: Comparison with findings on magnetic resonance imaging. *European Journal of Nuclear Medicine, 26*(3), 253–259.

Shi, X. Y., Tang, Z. Q., Sun, D., & He, X. J. (2006). Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury. *Chinese Medical Journal (Engl), 119*, 1978–1982.

Singhal, A. B. (2007). A review of oxygen therapy in ischemic stroke. *Neurological Research, 29*(2), 173–183.

Sparrow, S., Cicchetti, D., & Balla, D. (2005). *Vineland adaptive behavior scales* (2nd ed.). Minneapolis, MN: Pearson Assessment.

Starkstein, S. E., Vazquez, S., Vrancic, D., Nanclares, V., Manes, F., Piven, J., et al. (2000). SPECT findings in mentally retarded autistic individuals. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12*(3), 370–375.

Torrente, F., Ashwood, P., Day, R., Machado, N., Furlando, R. I., Anthony, A., et al. (2002). Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Molecular Psychiatry*, 7(4) 375–382, 334.

Vargas, D. L., Nascimbene, C., Krishnan, C., Zimmerman, A. W., & Pardo, C. A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology, 57*, 67–81.

Vlodavsky, E., Palzur, E., & Soustiel, J. F. (2006). Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. *Neuropathology Applied Neurobiology, 32*, 40–50.

Wakefield, A. J., Anthony, A., Murch, S. H., Thomson, M., Montgomery, S. M., Davies, S., et al. (2000). Enterocolitis in children with developmental disorders. *The American Journal of Gastroenterology, 95*(9), 2285–2295.

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence (WASI)*. San Antonio, TX: Harcourt Assessment.

Wechsler, D. (2002). *Wechsler primary and preschool scale of intelligence^{TM}–Third edition (WPPSI^{TM}-III)*. San Antonio, TX: Harcourt Assessment.

Wilcox, J., Tsuang, M. T., Ledger, E., Algeo, J., & Schnurr, T. (2002). Brain perfusion in autism varies with age. *Neuropsychobiology, 46*(1), 13–16.

Wilson, H. D., Wilson, J. R., & Fuchs, P. N. (2006). Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. *Brain Research, 1098*, 126–128.

Wilson, H. D., Toepfer, V. E., Senapati, A. K., Wilson, J. R., & Fuchs, P. N. (2007). Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. *The Journal of Pain, 8*, 924–930.

Zarcone, J. R., Lindauer, S. E., Morse, P. S., Crosland, K. A., Valdovinos, M. G., McKerchar, T., et al. (2004). Effects of risperidone on destructive behavior of persons with developmental disabilities: III. Functional analysis. *American Journal on Mental Retardation, 109*, 310–321.

Zarcone, J. R., Napolitano, D., & Valdovinos, M. (2008). Measurement of problem behaviour during medication evaluations. *Journal of Intellectual Disability Research, 52*, 1015–1028.

Zimmerman, A. W., Jyonouchi, H., Comi, A. M., Connors, S. L., Milstien, S., Varsou, A., et al. (2005). Cerebrospinal fluid and serum markers of inflammation in autism. *Pediatric Neurology, 33*(3), 195–201.