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Positive behavioral and electrophysiological changes following neurofeedback training in children with autism

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Abstract

Two electrophysiological studies tested the hypothesis that operant conditioning of mu rhythms via neurofeedback training can renormalize mu suppression, an index of mirror neuron activity, and improve behavior in children diagnosed with autism spectrum disorders (ASD). In Study 1, eight high-functioning ASD participants were assigned to placebo or experimental groups before 10 weeks of training of the mu frequency band (8–13 Hz). Following training, experimental participants showed decreased mu power and coherence, increased sustained attention ability, and improved scores on subscales of the ATEC compared to the placebo group. Both groups showed improvement in imitation ability. In Study 2, 19 high-functioning ASD children underwent a similar procedure with verified diagnoses, a modified double-blind protocol, and training of the high mu band (10–13 Hz). The results showed decreases in amplitude but increases in phase coherence in mu rhythms and normalization of mu rhythm suppression in experimental participants compared to placebo. Furthermore, like Study 1, participants showed improvements in sustained attention and in ATEC scores but no improvements in imitation following training. This suggests that training of the mu rhythm can be effective in producing changes in EEG and behavior in high-functioning ASD children, but does not affect imitation behavior *per se*.

Keywords: Mu rhythm; Mirror neurons; Imitation; TOVA; ATEC

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1. Study 1

The DSM-IV diagnostic criteria for autism spectrum disorders (ASD) includes deficits in social and communicative skills such as imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors (American Psychiatric Association, 2000). Additionally, variation in individual symptoms is wide, both in terms of levels of functioning and discrete diagnosis, including Autism (low-, medium, high-functioning), Asperger syndrome, or pervasive developmental disorder-not otherwise specified (Allen, 1988; Matson, 2007; Volkmar et al., 1994). While ASD has been the focus of much research, its complex nature has complicated the search for an underlying common cause. To date, no single explanation can account for the broad and varied profile of the attending deficits (Muller, 2007). However, there has been a recent convergence of evidence suggesting that a dysfunction in imitation and specifically in the frontal mirror neuron system (MNS) of the human brain may be a unifying factor in many of the heterogeneous symptoms of autism (Dapretto et al., 2006; Oberman et al., 2005; Williams et al., 2006; Williams, Whiten, Suddendorf, & Perrett, 2001).

Mirror neurons were first reported by Rizzolatti and colleagues (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992) in area F5 of macaque premotor cortex. This area is thought to be the homolog of ventral sensorimotor cortex, lying just posterior to Broca's area (Brodmann's area 44) in humans (Buccino et al., 2001; Buccino, Binkofski, & Riggio, 2004; Petrides, Cadoret, & Mackey, 2005). Mirror neurons have motor properties in that they fire in response to self-performed actions. In addition, they have visual properties in that they also fire to the observation of another's performance of a meaningful action (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Furthermore, it appears that these cells respond to implied actions or the intention of the movement, even in the absence of direct visual perception of the action itself (Iacoboni et al., 2005; Kohler et al., 2002; Umilta et al., 2001). TMS and fMRI studies support the existence of mirror neurons in humans. Fadiga et al. (1999) found enhancement of motor-evoked potentials in response to TMS while viewing another's actions, presumably the result of mirror neuron activity in prefrontal cortex. Other studies have found that repetitive TMS of inferior frontal cortex interferes with action imitation (Heiser, Iacoboni, Maeda, Marcus, & Mazziotta, 2003) and action understanding (Pobric & de, 2006). Similarly, Iacoboni et al. (Iacoboni et al., 1999) found increased blood oxygen level-dependent (BOLD) signal activity in BA 44 in response to self-performed and observed actions, while Molnar-Szakacs and colleagues (Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2005) found increased activation in the pars opercularis of inferior frontal gyrus for observed and imitated finger movements.

Attempts to study mirror neuron activity noninvasively have led several investigators to suggest that such activity is reflected in the mu frequency band of the human EEG (8–25 Hz oscillations measured over sensorimotor cortex) (Altschuler, Vankov, Wang, Ramachandran, & Pineda, 1997; Cochin, Barthelemy, Roux, & Martineau, 1999; Hari, Salmelin, Makela, Salenius, & Helle, 1997; Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy, Johnson, & McNair, 2004; Pineda, Allison, & Vankov, 2000). Classical alpha and mu rhythms exhibit overlapping frequencies but differ in terms of neural sources generating the rhythms (Niedermeyer, 1997). In general, mu rhythms reflect sensorimotor processing in frontoparietal networks, while classical alpha reflects primarily visual processing in occipital networks (Pineda, 2005). It is known that sensorimotor neurons fire synchronously while at rest, producing high-amplitude oscillations, and that input from premotor areas, including mirror neurons, produces asynchronous firing in the sensorimotor circuits during self-movement and the observation of movement, leading to reduced mu amplitude (mu suppression) (Gastaut & Bert, 1954;

Pfurtscheller & Aranibar, 1979; Pineda, 2005; Pineda et al., 2000). This mu suppression to the observation of movement in the absence of self-performed action is taken to reflect downstream modulation of sensorimotor circuits by the premotor MNS (Altschuler et al., 1997; Oberman et al., 2005; Pineda, 2005).

Studies performed over the past several decades suggest that children with ASD suffer from impairments that closely parallel the putative functioning of MNS, primarily in terms of imitation and imitation learning (Buxbaum, Kyle, & Menon, 2005; Leslie, Johnson-Frey, & Grafton, 2004; Rogers, Hepburn, Stackhouse, & Wehner, 2003; Williams, Whiten, & Singh, 2004). Though recognized over 50 years ago, the cause of this imitation impairment in ASD has yet to be identified, but several hypotheses about its origin have been proposed. One suggestion is that this is a core deficit that could impede early affective, social and communicative development (Ozonoff, Pennington, & Rogers, 1991). Specifically, it is suggested that imitation deficits result from an inability to ''form and coordinate social representations of self and others via amodal or cross-modal representation processes''—the type of function ascribed to mirror neurons (Rogers et al., 2003). Anatomical evidence adds further support to the link between MNS and ASD. Villalobos, Mizuno, Dahl, Kemmotsu, and Muller (2005) found reduced functional connectivity between inferior frontal cortex and V1, and Just, Cherkassky, Keller, and Minshew (2004) found reduced functional connectivity between inferior frontal cortex and other areas during a language task. Neurophysiological evidence over the past several years is also consistent with an MNS dysfunction in individuals with ASD (Dapretto et al., 2006; Nishitani, Avikainen, & Hari, 2004; Oberman et al., 2005; Takeuchi, Harada, Matsuzaki, Nishitani, & Mori, 2004; Theoret et al., 2005; Villalobos et al., 2005). Specifically, children with autism show mu suppression for self-performed but not observed actions (Oberman et al., 2005), and show no inferior frontal gyrus activation during imitation of facial expressions compared to typically developing children (Dapretto et al., 2006).

Whether the cortical dynamics of the MNS can be changed to improve function in ASD has led to questions of how such dynamics can be affected under controlled conditions. Neurofeedback training (NFT) offers the opportunity to operantly condition these dynamics and examine the consequences of such training on cognition and behavior (Lubar, 1997). NFT has been successfully utilized for over 25 years in both the clinic and in research. However, support for the efficacy of NFT is limited and based primarily on a few case studies, rather than randomized, controlled, blinded studies (Lilienfeld, 2005). Thus, the goal of the present studies was to test the efficacy of this methodology on ASD symptoms, primarily reflected in behavior and electrophysiology. One hypothesis of the mechanisms involved in NFT posits that learning to self-regulate endogenous brain rhythms allows an individual to access and control regulatory systems that increase/decrease synchronous activity in neuronal cell populations. Specifically relevant to this issue are two published investigations involving NFT with autistic children. Jarusiewicz (2003) administered NFT to 12 autistic children and reported an average of 26% improvement on autistic symptoms as rated by the Autism Treatment Evaluation Checklist (ATEC), compared to 3% improvement in a matched placebo group. While these results appear significant, the study lacked a consistent protocol for modulating the EEG, that is, different protocols were administered to different participants. Additionally, the control group lacked a true placebo condition and participants were aware of the test condition. Sichel (1995) in a single case study using NFT, reported improvement in all diagnostic dimensions for autism.

Because of the relative lack of well-controlled research using NFT with ASD, the present studies sought to examine whether training focused on the mu rhythm would affect mirror neuron-related aspects of the EEG and consequently affect behavior in children. It specifically

tested the hypothesis that a change in mirror neuron dynamics would positively affect children's imitation ability and generalize to attentional and other behaviors, as well as to normalize mu suppression to the observation of actions. In both studies, NFT of the mu rhythm was administered for several weeks to a group of high-functioning autistic children and compared to a group of high-functioning autistic children in a placebo condition.

2. Methods

2.1. Participants

Eight high-functioning males (age 7–17; $M = 9.3 \pm 2.8$ years) were included in the study. All participants were recruited via Valerie's List, a San Diego Internet autism support group. Parents were asked to provide evidence of outside diagnosis of high functioning ASD, which included an IQ > 80. Only those assessed by a clinician and meeting the criteria were included. Participants were randomly assigned to placebo ($n = 3$) or experimental ($n = 5$) conditions and neither participants nor parents were informed of group membership until after final testing was completed. Participants and parents gave informed assent and consent, respectively. The University of California, San Diego's Institutional Review Board approved the study. One subject in the experimental group dropped out midway through the training.

2.2. Cognitive assessments

All participants underwent a series of EEG, cognitive, and behavioral assessments before and after 15 h of NFT over a 10-week period. The assessments included a quantitative EEG (QEEG) and the development of a mu suppression index (MSI). The MSI, developed by Oberman et al. (2005), was used to assess changes in mu power in response to the observation of movement. For this, participants viewed silent action videos (120 s each) on a computer monitor while performing an attention task (i.e. counting the number of pauses in the action). A baseline ''Ball'' condition consisted of two light gray balls (32.9 cd/m^2) on a black background (1.0 cd/m^2) that moved vertically towards each other touching in the middle of the screen and then moving apart to their initial starting position. This motion was visually equivalent to the trajectory taken by the tips of the fingers and thumb in the hand video. The ball stimulus subtended 2° of visual angle when touching in the middle of the screen and 5° at its maximal point of separation. Experimental videos included both simple and complex non-goal and goal-directed movements, such as a simple action of a hand opening and closing (Hand), a targeted hand action such as a hand pulling a crayon from a crayon box using a precision grip (Crayon), and social interaction movement of three people playing catch with a ball (Social) (see Fig. 1A–D). Videos were presented at a viewing distance of approximately 48 cm and the hand subtended 5° of visual angle when open and 2° when closed. The hand, crayon, and crayon box were medium gray (8.6 cd/m^2) on a black background (3.5 cd/m^2). The social video was in color.

Participants were also administered the visual form of the test of variables of attention (TOVA), a computerized visual continuous performance test for the diagnosis and treatment of children and adults with attentional disorders (Greenberg & Waldman, 1993). It is a continuous performance task that has been normed in the general population to assess sustained attention. The Apraxia Imitation Scale, developed and normed in the general population by De Renzi (De, Motti, & Nichelli, 1980) was used to assess imitation ability. This test includes subsections for imitation of arm/hand, finger, and general movements of varying complexity. Finally, parents

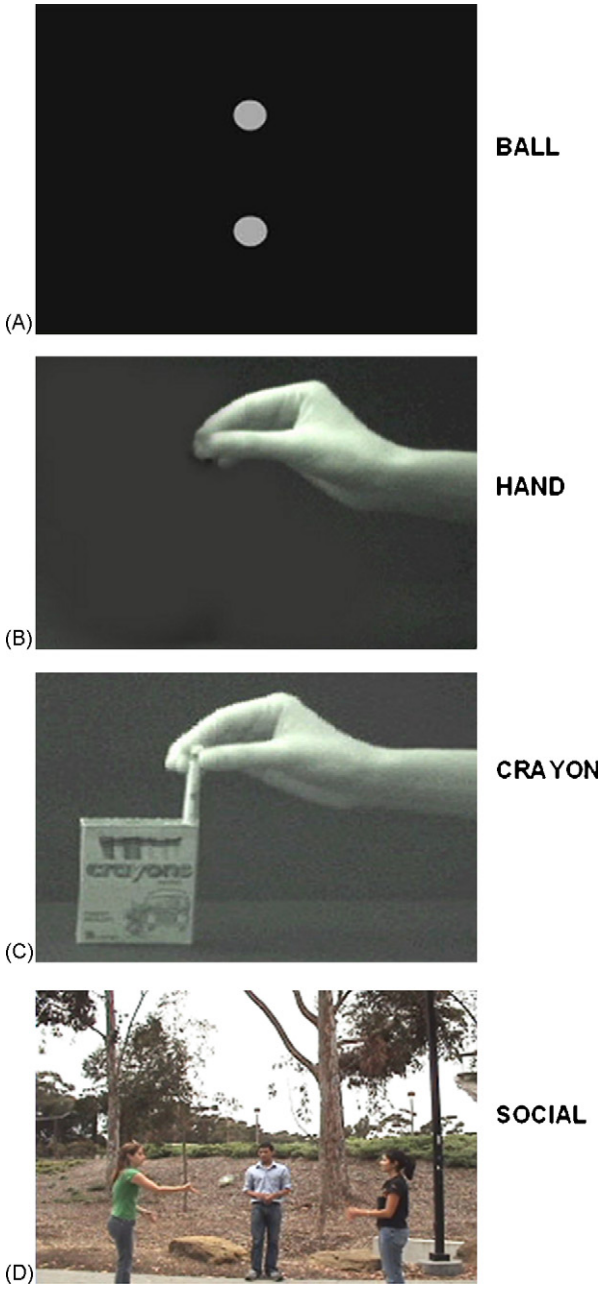

Fig. 1. Videos used for developing the mu suppression index. A baseline ball condition consisted of two light gray balls on a black background moving vertically towards each other, touching in the middle of the screen, and then moving apart to their initial starting position. The stimulus subtended 2° of visual angle when touching in the middle of the screen and 5° at its maximal point of separation. Other experimental conditions included non-goal and goal-directed movements, such as a hand opening and closing at the same rate as the moving balls (Hand), a hand pulling a crayon from a crayon box using a precision grip (Crayon), and three people playing catch with a ball (Social).

completed the Autism Treatment Evaluation Checklist (ATEC), an assessment questionnaire designed to assist parents, physicians and researchers in evaluating treatments for autism. It includes four subscale scores (speech/language communication, sociability, sensory/cognitive awareness, and health/physical behavior) and a total score, which are weighted according to the response and the corresponding subscale. The higher the subscale and total scores, the more impaired the subject.

2.3. EEG recording

QEEG involved the recording of resting EEG using a Brainmaster amplifier system and Mini-Q software. Twelve paired sites were recorded, two at a time, at a sampling rate of 256 Hz, referenced to mastoids (linked computationally) and grounded at Fpz. During assessment of the MSI, EEG was recorded with a bandpass of 8–13 Hz at a sampling rate of 256 Hz from site C4 over the right hemisphere referenced to the right earlobe and grounded at the left earlobe. BioExplorer software and a Brainmaster amplifier system were used during NFT. The same electrode configuration was used for all participants. EEG was recorded from site C4 using a sampling rate of 256 Hz, referenced to the right earlobe, grounded at the left earlobe, and bandpass filtered for 8–13 Hz. A second channel was recorded from an electrode placed over the right trapezius muscle of the shoulder, referenced to the left trapezius, and bandpass filtered for 30–60 Hz. This frequency range was found to be sensitive to movement artifact in a pilot study.

2.4. Neurofeedback training

Participants received a total of 15 h of training in 30 min sessions three times a week for approximately 10 weeks. Experimental participants received feedback based on their own mu rhythm recorded from the right hemisphere C4 site and from EMG activity from the trapezius muscles. Placebo participants received feedback based on EMG activity and an artificially generated mu-like signal filtered at 8–13 Hz. EMG feedback was included in the design for two reasons. First, it ensured that children could not advance in the game by producing movement-induced power increases in the entire EEG spectrum. Second, it allowed us to distinguish improvement effects as a function of EEG modulation, modulation of autonomic nervous system activity, or placebo effects. More importantly, inclusion of a closed, non-EEG feedback loop in the placebo condition created a subjective experience of control more similar to the experimental condition.

All participants viewed a computer screen displaying two bars on the left and right side of a video game window (see Fig. 2 for examples of four such displays). The left bar corresponded to the 8–13 Hz activity from the mu band of the EEG (for experimental group) or from the artificially generated signal (for placebo group). The right bar corresponded to EMG activity measured at the shoulder electrodes. Participants were instructed to make the left bar bigger (to be above a threshold marked by a black line on the screen) while making the right bar smaller (to be below a threshold marked by a black line). In order to help children stay focused during the training sessions, the experimenter encouraged and challenged children to pay attention to the game and meet the goals. A variety of video games were used for training, the most frequently being a racecar, robots, and space exploration, all developed using Macromedia Flash.

Feedback was based on satisfying two conditions: first, 8–13 Hz power from the C4 electrode site exceeding the threshold, and second, 30–60 Hz power from the EMG electrodes remaining

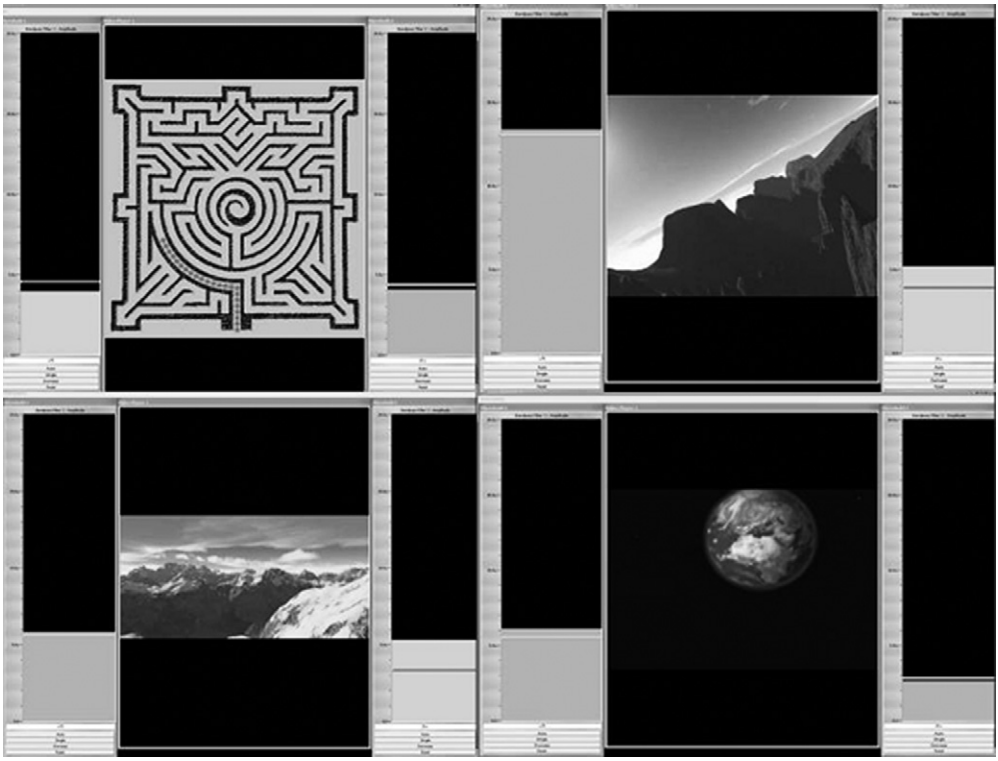

Fig. 2. Four screen shots of video games used during training. All videos included semi-realistic objects, such as a vehicle or animals, moving towards some goal or carrying out some action. Level of mu power controlled the movement of the object (clockwise from top-left—no reward: both below threshold; no reward: right bar above threshold; reward: left bar above threshold/right bar below threshold; no reward: both above threshold).

below threshold. When both criteria were met, the video game progressed (e.g. car moved forward) and a pleasant tone sounded. When neither criterion was met, visual and auditory feedback paused. Thresholds for EEG and EMG channels were set as a function of the preceding one-second of activity and adjusted automatically so as to provide a reward 75% of the time, to make training challenging but not frustrating.

2.5. Data analysis

2.5.1. QEEG

Covariance of power at two sites (amplitude coherence), covariance in time (phase coherence), symmetry, and attention indices (theta/alpha,[1] theta/low beta, theta/beta, alpha/beta ratios) were measured as part of QEEG analysis and analyzed using repeated measures ANOVAs with training (pre, post), frequency (delta, theta, alpha, SMR, low beta, beta, high beta, gamma) and sites (Fz–Cz, F3–F4, C3–C4, P3–P4, T3–T4, O1–O2) as within factors and group

[1] Although the term alpha is used, it refers specifically to classical alpha when discussing activity over posterior sites (e.g. occipital: O1, O2) and the mu rhythm when discussing activity over anterior brain sites (e.g. central: C3, C4).

(experimental, placebo) as a between factor. A covariance analysis measures the strength of the relationship in the amplitude of a signal measured at successive time delays. If the signal is periodic and the interval between points being measured is equal to the cycle time of the signal then the correlation between amplitude at those successive points will be high.

2.5.2. Mu suppression index

During the assessment of mu suppression, suppression indices for delta (0.5–4 Hz), theta (4–8 Hz), mu (8–13 Hz), SMR (13–15 Hz), beta (15–25 Hz), and gamma (35–45 Hz) frequencies were calculated as the ratio of the power during the experimental conditions (viewing of Hand, Crayon, and Social videos) relative to the power during the baseline video condition (Ball). A previous study (Oberman et al., 2005) has indicated that viewing of non-biological ball movement does not produce suppression (particularly of mu rhythms) and is therefore a good control for movement since the balls move at approximately the same rate as movement in the other videos. Ratios were used to control for variability in absolute power as a result of individual differences such as scalp thickness and electrode placement and impedance. Since ratio data are inherently non-normal as a result of lower bounding, a log transform was used for data analysis. A log ratio of less than zero indicates suppression whereas a value of zero indicates no suppression and values greater than zero indicate enhancement. A within subject, three-way repeated measures ANOVA was used to analyze suppression indices. Factors included training (pre, post), frequency (6), and movement (Hand, Crayon, Social). Step down ANOVAs and post hoc comparisons were performed on data with significant effects. The Greenhouse-Geisser correction for degrees of freedom was used in determining significance.

2.5.3. TOVA

The various dimensions of the TOVA scores before and after training were analyzed using paired-sample *t*-tests (two-tailed). These included the attention deficit hyperactivity disorder (ADHD) scores, errors of omission, errors of commission, time response, variability reaction time, and d'. Bonferroni corrections for multiple comparisons were applied.

2.5.4. ATEC

This test includes four categories of symptoms: speech/language communication (SLC), sociability (SOC), sensory/cognitive awareness (SCA), and health/physical behavior (HPB). Each category contains multiple symptoms that are each rated on a scale of 1–5. Each subject's score on each of the dimensions of the ATEC was calculated as a percentage of the highest possible score for that dimension. The four dimensions were then analyzed using repeated measures ANOVAs with training (pre, post) and category (SLC, SOC, SCA, HPB) as within factors and group (experimental, placebo) as a between factor.

2.5.5. Apraxia imitation scale

Accuracy scores on the Apraxia imitation scale were subjected to a repeated measures ANOVA using factors of training (pre, post), movement (general, finger, hand/limb), and time (initial, middle and final) as within factors and group as a between factor.

2.5.6. Mu power during training

Because artifact such as general movement, yawns, and speech create power increases across all frequency bands, and some children were more active during training than others, relative mu power during training was calculated as a ratio of power in the 8–13 Hz band relative to power in

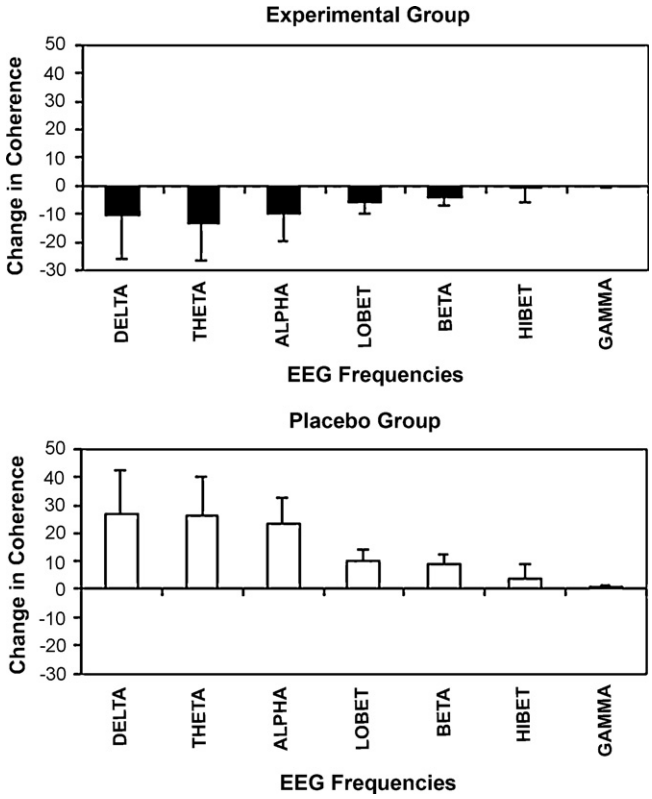

Fig. 3. Change in EEG coherence (post training minus pre training levels) at C3 and C4 sites for delta, theta, alpha, low beta, beta, high beta, and gamma for both placebo and experimental groups. Note the decrease in coherence for all frequencies in the experimental group compared to the increases in coherence for all frequencies in the placebo group.

the broadband spectrum (1–60 Hz). Changes in relative mu power during the 30 sessions of training were analyzed with a repeated measures ANOVA using sessions (30) as the within factor and group (experimental, placebo) as a between factor.

3. Results

3.1. QEEG

3.1.1. Coherence/phase/asymmetry

Lower frequency bands (delta, theta, and alpha) showed greater coherence than higher frequency bands (low beta, beta, high beta, gamma). For the lower frequency bands, frontal sites (F3/F4) had the highest coherence, followed by central sites (C3/C4) and then temporal sites (T3/T4). Although the difference between experimental and placebo groups only approached significance ($p < 0.1$), there was a significant frequency × group interaction in amplitude coherence, $F(6,24) = 3.27$, $p < 0.02$. As shown in Fig. 3, which depicts changes in amplitude coherence between pre- and post-training, those in the experimental group showed primarily *decreases* in coherence at C3/C4 for most frequency bands. In contrast, the placebo group

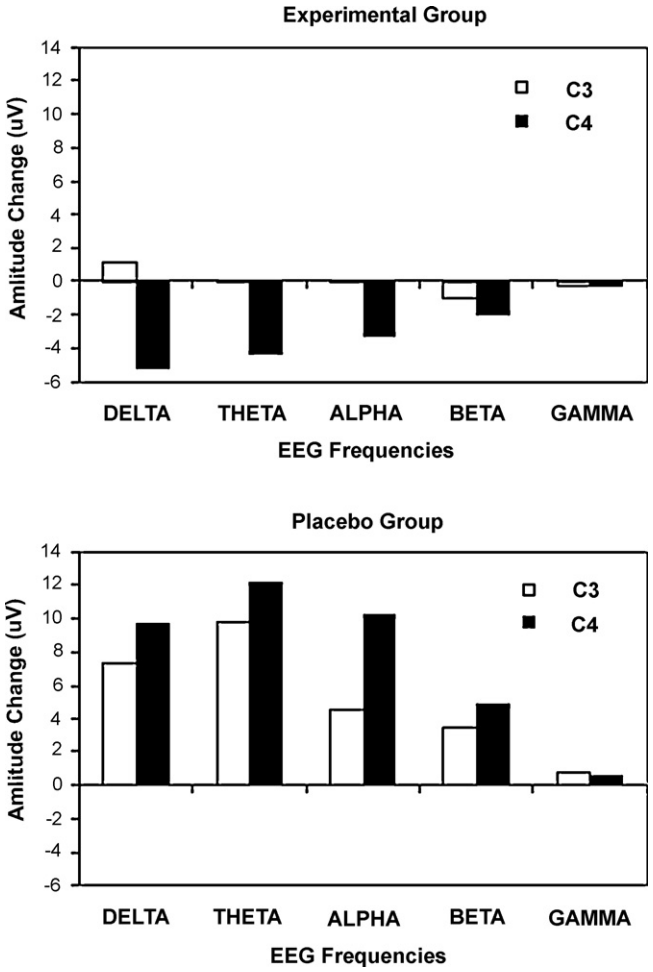

Fig. 4. Change in EEG amplitude (post-training minus pre-training levels) at C3 and C4 sites for delta, theta, alpha, beta, and gamma for both placebo and experimental groups. Note the general decreases for the experimental group compared to the large increases for the placebo group for all frequencies.

showed *increases* in coherence. Phase coherence did not exhibit any significant differences at C3/C4, although it was especially high (ranged between 35 and 45%) at temporal sites (T3/T4) for all the frequency bands, whereas it ranged between 10 and 30% for all other pairs of electrodes. There were no significant effects on asymmetry.

3.1.2. Mu amplitude

As shown in Fig. 4, experimental participants showed decreases at nearly all sites and in nearly all frequency ranges, while placebo participants showed amplitude increases. Specifically, there was a main effect of group ($F(1,4) = 9.42$, $p < 0.05$) such that placebo participants showed an increase in mu amplitude at C3/C4 (6.6 uV), while experimental participants showed a decrease (-1.7 uV).

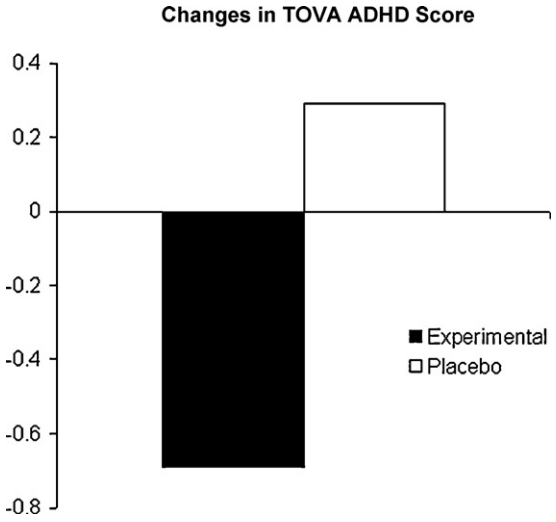

Fig. 5. Change in TOVA ADHD score (post-training minus pre-training levels) in experimental and placebo groups. The ADHD score reflects the sum of the response time in the first half, the d' in the second half, and the total variability reaction time (RT) scores. The experimental group showed a nearly 70% improvement compared to the placebo group.

3.2. Mu suppression index

Prior to training, participants showed the expected lack of mu suppression to the Hand and Social videos. They did show some pre-training suppression to the Crayon video but this level of suppression is relatively small compared to typically developing children (Oberman et al., 2005). Analysis of MSI showed a training × frequency × movement interaction, ($F > 1$). Step down ANOVAs showed that during pre-training there was only a marginally significant frequency × movement interaction, $F(10,40) = 3.7$, $p = 0.07$. In contrast, in the post-training condition, there was a main effect of frequency, $F(5,20) = 5.0$, $p < 0.05$. Although pairwise comparisons between the different frequency bands did not elicit statistically significant results, they did indicate that the largest changes occurred in the delta and mu frequency bands.

3.3. TOVA

Only two dimensions of the TOVA were significantly affected by training: the overall ADHD score and errors of commission. The ADHD score reflects the sum of the response time in the first half, the d' in the second half, and the total variability reaction time (RT). As shown in Fig. 5, there was no change in the placebo group but a 70% decrease in the experimental group. A paired-sample t-test (two-tailed) showed this difference to be significant ($p < 0.02$). Errors of commission before training (−0.035) were fewer compared to after training (0.77), $p < 0.01$ suggesting that response rates actually increased with training.

3.4. ATEC

Table 1 shows the differences between pre- and post-training in the ATEC's four categories. A significant category × group interaction was observed, $F(3,12) = 4.76$, $p < 0.05$, with the

Table 1
Percent changes in subscale and total ATEC from before and after training for placebo and experimental participants

Subject	Speech/language/ communication	Sociability	Sensory/cognitive awareness	Health/physical behavior	Total
5001 (placebo)	0.07	−0.1	0.0	−0.04	−0.03
5003 (placebo)	0.0	−0.05	−0.08	0.04	−0.01
5004 (experimental)	0.04	0.05	0.06	−0.01	0.02
5006 (experimental)	−0.11	−0.18	−0.14	−0.12	−0.13
5008 (placebo)	0.11	0.05	0.0	0.04	0.04
5010 (experimental)	−0.14	−0.08	0.0	−0.13	−0.09
5011 (experimental)	0.07	0.08	0.08	0.04	0.06

experimental group showing a clear increase in the sensory/cognitive awareness (SCA) dimension compared to a decrease shown by those in the placebo group.

3.5. Apraxia imitation scale

There was a main effect of movement ($F(2,10) = 16$, $p < 0.01$) such that both groups of participants were more accurate making general movements (95%) compared to hand/limb (75%) or finger (61%) movements. There was also a main effect of time ($F(2,10) = 5.4, p < 0.03$) indicating an overall improvement in accuracy from beginning (74%) to end (84%) of training. However, there was no significant difference between groups. Fig. 6 shows imitation test scores for all participants at initial, middle, and final testing.

3.6. Mu power during training

Analysis of mu power changes during training showed distinct differences in the mu (8–13 Hz) band, as well as in the individual narrow bands (8–10 Hz and 10–13 Hz). A significant sessions × group interaction occurred, $F(29,116) = 1.67$, $p < 0.05$. As shown in Fig. 7 for the broadband mu, experimental participants showed steady decreases in power as the training progressed across the 30 sessions. This is in contrast to placebo participants who showed little change. These differences were larger for the high mu band.

4. Discussion

Results from Study 1 show that the experimental group, which received NFT, successfully learned to control mu rhythms, as evidenced by a decrease in the ratio of mu band to broadband spectrum across the training sessions, especially for the high mu band. In contrast, the placebo group had no significant change in this ratio over the same number of sessions. The experimental group's decrease in mu power may seem counterintuitive, given that participants were being rewarded for increases in power during training. Several factors could contribute to such a decrease, including an increase in broadband spectrum activity, a decrease in the mu band activity, or a combination of the two. Analysis of absolute mu power revealed a decrease over sessions, as did an analysis of overall broadband spectrum activity. This is consistent with one study in which training a reduction in the theta/alpha power ratio produced a decrease across all measured bands (Fernandez et al., 1995). However, session logs showed that experimental participants were producing increasingly frequent high-amplitude mu bursts. This frequency

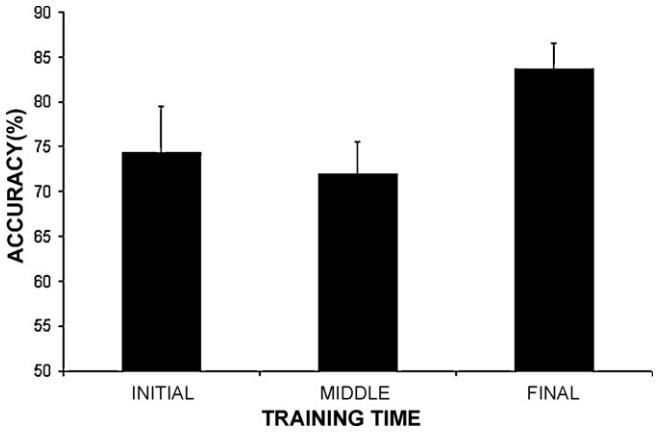

Fig. 6. Pre-training (initial), mid-training (middle), and post-training (final) imitation scores from the Apraxia imitation scale. There was overall improvement in accuracy from beginning (74%) to end (84%). There also was no significant difference between placebo and experimental groups.

band naturally occurs in discrete high-amplitude ''packets'' and sustaining high amplitude in the mu rhythm does not appear to be possible (Niedermeyer, Goldszmidt, & Ryan, 2004).

Following training, both experimental and placebo participants showed changes in resting EEG. Placebo participants showed *increased* coherence at sites C3/C4 across all measured frequency bands, while experimental participants had *decreased* coherence at these same sites across all bands. Additionally, placebo participants showed an increase while experimental participants showed a decrease in resting mu amplitude. At the beginning of training, all participants showed little change in mu power in response to biological motion, object-oriented grasping, and social interaction compared to baseline. This is consistent with the findings by Oberman (Oberman et al., 2005), in which ASD children were found to exhibit mu suppression during self-action but not during the observation of similar actions. Following training, both groups showed mu enhancement to these stimuli. Because high-amplitude oscillations of the mu rhythm occur during rest (and ostensibly, when mirror neurons are inactive), one interpretation of this result is that after training mirror neurons became less responsive to these events. However, this is probably not the case for two reasons. First, the MSI is a functional measure that includes a comparison to baseline activity using a log transform. If participants' mirror neurons were becoming less active as a result of training, their neural response to these stimuli would have been closer to the baseline response and the MSI would have shifted closer to zero. Second, there is at least one other known situation in which mu enhancement reflects a functional response rather than a resting state. Smokers show mu enhancement during the observation of another person grasping a cigarette compared to the same action involving a crayon, suggesting that actions involving motivationally significant stimuli produce synchronous activity (Pineda & Oberman, 2006). In the placebo group, mu enhancement is in line with their increased resting mu amplitude and coherence, while in the experimental group this runs counter to their decrease in resting mu amplitude and coherence.

EMG feedback training may have contributed to the placebo group's mu rhythm changes in the absence of mu feedback. In both groups, NFT was partially dependent on a low amount of EMG activity registered over the left and right trapezius. Therefore, both groups were essentially

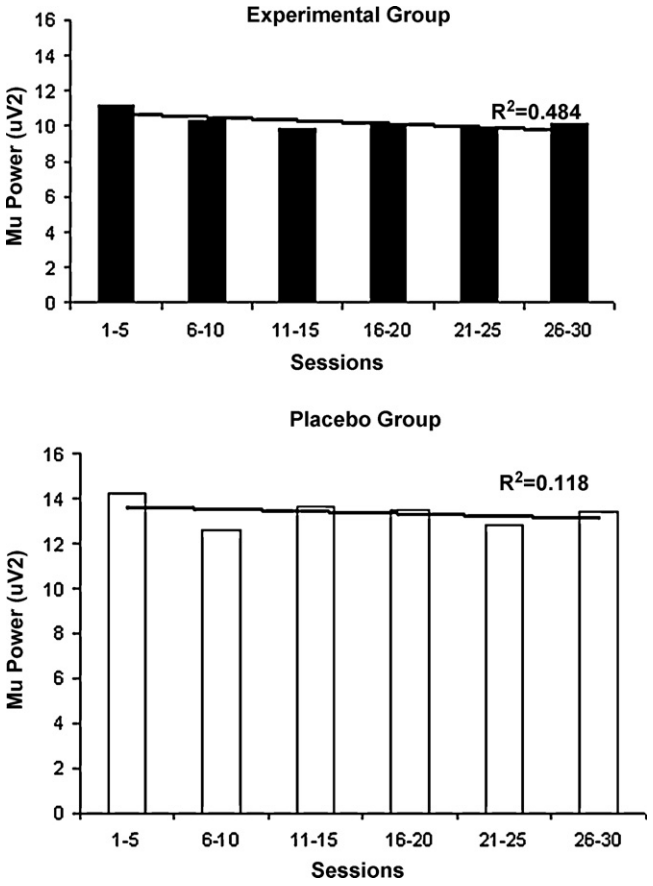

Fig. 7. Change in relative mu power (uV^2) during training sessions. Relative power was calculated because movement, yawns, and speech create power increases across all frequency bands, and some children were more active during training than others. Relative mu power was calculated as a ratio of power in the 8–13 Hz band relative to power in the broadband spectrum (1–60 Hz). Averages for the preceding five sessions are shown. Note that the experimental group shows a decrease from beginning to end, compared to no change in the placebo group.

being trained to physically relax and sit still. Because mu rhythm is related to motor activity, this training may have had some effect on the EEG. Since the bar corresponding to muscle activity was the only means the placebo participants had to control the game, while the experimental participants required control of both EMG and EEG, it may have been easier for the placebo group to learn the task and experience effects from it.

Both groups exhibited behavioral changes following training. The experimental group had a 70% improvement in the TOVA's attention deficit hyperactivity disorder (ADHD) score, reflecting increased sustained attention ability. This is consistent with Egner, Strawson, and Gruzelier (2002), in which improvement in continuous performance tests occurred after NFT in frequency bands that overlapped mu oscillations. Both groups also improved in imitation ability. In terms of the ATEC parental evaluation, the experimental group showed a clear increase in the sensory/cognitive awareness (SCA) dimension compared to a decrease shown by those in the placebo group.

5. Study 2

Pilot data from Study 1 showed that children with ASD can learn to control mu rhythms via NFT and that this leads to changes in functional and resting EEG as well as on behavior. However, several improvements to the research design could strengthen these findings. First, verification of the children's diagnoses might create more heterogeneity in the results. At the same time, a larger number of participants might increase statistical power and bring some inconclusive results to statistical significance. In addition, although participants and parents were unaware of their child's group assignment, the experimenters working with the children were aware and this may have created some biases. Another specific concern was the use of variable thresholds for the feedback, which may have interfered with learning. Finally, the effects of training on low versus high mu bands suggested that the high mu band (10–13 Hz) would be a better frequency for training.

To address these issues, we carried out a second, double-blind study using verified diagnoses with 19 subjects. In this study, we set thresholds as a function of a QEEG analysis and gradually increased them as a function of performance. Training focused on the high mu band. The second study, like the first, was designed to test the efficacy of NFT methodology on ASD individuals. Specifically, it tested the hypothesis that a NFT-induced change in mirror neuron functioning affects children's imitation ability and generalizes to and remediates other autistic symptoms. Study 2 built upon the earlier findings primarily with the use of a double-blind protocol to examine whether training using a narrow EEG band affects mirror neuron-related aspects of the EEG and behavior. NFT was administered to a group of high-functioning ASD children. This was compared to a group of high-functioning autistic children in a placebo condition.

6. Methods

6.1. Participants

Nineteen individuals diagnosed with ASD (16 males; 3 females; age 7–17; $M = 9.8 \pm 2.8$ years) were included in the study. Participants were randomly assigned to placebo ($n = 10$; all males; $M = 10.1 \pm 3.2$ years) or experimental ($n = 9$; 3 females; $M = 9.4 \pm 2.4$ years) conditions. All participants were considered high-functioning, defined as having age appropriate verbal comprehension abilities and an Intelligence Quotient (IQ) greater than 80 as assessed by a standardized IQ test. Participants and parents gave their informed consent and assent, and the University of California, San Diego's Institutional Review Board approved the study.

6.2. Verification of diagnosis

The Autism Diagnostic Interview—Revised (ADI-R) (Lord, Rutter, & Le, 1994), the Autism Diagnostic Observation Schedule—Generic (ADOS-G, (Lord et al., 2000) and Wechsler Abbreviated Scale of Intelligence (WASI) were administered to every participant prior to the beginning of training. Based on the results of these assessments in conjunction with clinical judgment, three children in the Experimental group met criteria for autistic disorder (AD), five met criteria for autism spectrum disorder (ASD), and one for Asperger Syndrome. In the placebo group, six children met criteria for AD and four for ASD. As illustrated in Table 2, there were no

Table 2
ADI, ADOS, and WASI comparison between experimental and placebo groups

	Experimental	Placebo
Number	9	10
WASI-verbal	94.3	89.7
WASI-performance	101.8	99.8
WASI-full scale	97.8	94.2
ADOS-communication	3.2	4.6
ADOS-social interaction	7.8	9.1
ADOS-communication/social interaction	11.0	13.7
ADOS-imagination/creativity	0.7	0.9
ADOS-stereotyped behavior and repetitive interests	1.2	2.6
ADI-reciprocal social interaction	19.0	20.1
ADI-communication	15.3	17.9
ADI-restricted, repetitive and stereotyped patterns of behavior	6.7	5.6
ADI-abnormality of development evidentator before 36 months	4.4	3.9

significant differences between the two groups. One-way ANOVAs comparing IQ in experimental and placebo groups showed no statistically significant differences in terms of verbal, performance, or full IQ between the groups ($F < 1$). Similarly, there were no group differences in terms of ADI or ADOS subscales.

6.3. Cognitive assessments

As in Study 1, all participants underwent a series of EEG, cognitive, and behavioral assessments before and after 15 h of neurofeedback training, including a QEEG assessment, determination of the MSI, TOVA, imitation test, and ATEC. Participants viewed the same four silent action videos used in Study 1 on a computer monitor while performing an attention task (counting the number of pauses in the action). Additionally, two new stimuli categories were included. The first of these was a video depicting biological motion. The point-light biological video was adapted from those used by other investigators (Saygin, Wilson, Hagler, Bates, & Sereno, 2004). It was created by videotaping an actor performing a specific movement (rope jumping) and then encoding the joint positions in the digitized videos (Ahlstrom, Blake, & Ahlstrom, 1997). It was composed of twelve small dots corresponding to the joints of the point-light actor. The motion sequence was presented at a rate of 20 frames/s, with 5/100 s between frames, using RealPlayer. The image was 3 in. $\times$ 3 in. in size and centered on the screen with a black background. Participants viewed the stimuli from about 36 in. away. Therefore, the dots subtended approximately 4.5° of visual angle against a uniform black background. All of the animations were continuous and actions were looped. That is, there were no abrupt changes in the location of the dots in the transition from the final frame to the first frame of the action. This allowed the natural flow of movement. The animations were adjusted so that the images appeared to be moving in place, which limited eye movements and maintained a central fixation. The second category of new stimuli was facial expressions. These were static, grayscaled photos from a standard set of facial affect photos (MacArthur Foundation Research Network EEBD NimStim stimulus set). The face was of an unfamiliar white female expressing one of two emotions, happiness or disgust. Stimuli were delivered using Presentation software at a visual angle of 8° degrees.

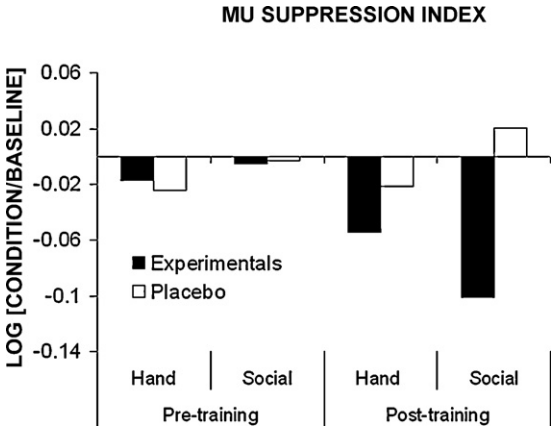

Fig. 8. . Mu suppression indices (MSI) for experimentals and placebo groups before and after training in response to a simple (Hand) and complex (Social) movement. MSI was computed by taking the log of the ratio between experimental conditions relative to baseline condition. Note the increased mu suppression post-training.

6.4. EEG recording

EEG and EMG recordings were similar to Study 1 for QEEG and NFT, with the exception that training focused on high mu band (10–13 Hz) only.

6.5. Neurofeedback training

NFT was similar to Study 1 with some exceptions. Participants received similar amounts of training a week for approximately 10 weeks, or a total of 15 h. Experimental participants received feedback based on EMG activity as well as their own mu rhythm recorded from the right hemisphere C4 site. Placebo participants received feedback based on EMG activity and an artificially generated signal filtered at 10–13 Hz. All participants viewed a computer screen displaying a threshold bar both on the left and right sides of a video game window. The left threshold bar corresponded to 10–13 Hz activity from the mu band of the EEG (for experimental group) or from the artificially generated signal (for placebo group), and the right threshold bar corresponded to EMG activity measured from the trapezius muscles. Thresholds were fixed as a function of the initial QEEG analysis and changed only when participants showed increased learning. That is, each week, thresholds for each experimental participant were raised only if performance during the previous week warranted it. As in Study 1, participants were instructed to increase the left bar above threshold while making the right bar fall below threshold. In order to help children stay focused during the session, experimenters encouraged and challenged children to pay attention to the game and meet those goals.

Feedback was based on satisfying the two conditions of increased power above threshold in the 10–13 Hz power from the C4 electrode site and reduced power falling below threshold in the 30–60 Hz EMG range. When both criteria were met, the video game progressed and a pleasant tone sounded. When either criterion was not met, visual and auditory feedback paused.

6.6. Data analysis

Analyses of QEEG, MSI, TOVA, ATEC, and imitation test were similar to those performed in Study 1.

7. Results

7.1. QEEG

7.1.1. Coherence/phase/asymmetry

There was a main effect of site on amplitude coherence, $F(5,75) = 5.79$, $p < 0.01$ indicating that significantly reduced coherence occurred at temporal sites (T3–T4) across all frequencies compared to other sites. Pairwise comparisons showed that central site coherence (C3–C4) was significantly reduced compared to frontal (F3–F4) sites ($p = 0.002$). Phase coherence also showed a main effect of site, $F(5,75) = 28.3$, $p < 0.001$. Pairwise comparisons showed that both temporal (T3–T4) and central (C3–C4) sites were significantly more in phase compared to other sites. There was a marginal frequency $\times$ training interaction for amplitude coherence, $F(7,105) = 2.55$, $p = 0.089$ that indicated a reduction trend in coherence of approximately 20–30% for the beta band (low beta, beta, and high beta).

7.2. Mu suppression index

Analyses of mu suppression showed statistically significant differences between the experimental and placebo participants. There was a movement $\times$ group interaction, $F(5,85) = 2.97$, $p < 0.05$, which indicated that the experimental group displayed greater mu suppression to most of the observation conditions compared to those in the placebo group following training. A step-down, one-way ANOVA of the post-training sessions showed a marginally significant group effect, $F(1,17) = 4.06$, $p = 0.06$. Seventy-five percent of experimental participants showed significant suppression in many of the observation conditions, including the Hand, Crayon, Social, and Happy face videos. There was an average of 32% and 26% increased suppression in the Hand and Crayon conditions, respectively and approximately a 32.5% increased suppression between initial and post training in the Social condition. Mu suppression to the Biological motion and Disgusted face conditions were more variable. In contrast, not a single subject in the placebo group showed suppression in these same conditions following training (see Fig. 8).

7.3. TOVA

The data indicate that the experimental participants' overall ADHD scores improved compared to the placebo group (see Fig. 9). The experimental group showed a reduction in z-scores while the placebo group showed an increase. As shown in Fig. 10, a similar positive trend was observed in total omission errors, with the experimental group decreasing their standard deviation from the norm by 21%, while the placebo group increased their standard deviation from the norm by 57%. In contrast, both the placebo and experimental groups improved their rate of total commission errors, total RT variability, and signal detection. However, both groups had slower response times during their post-testing TOVA compared to their pre-testing TOVA.

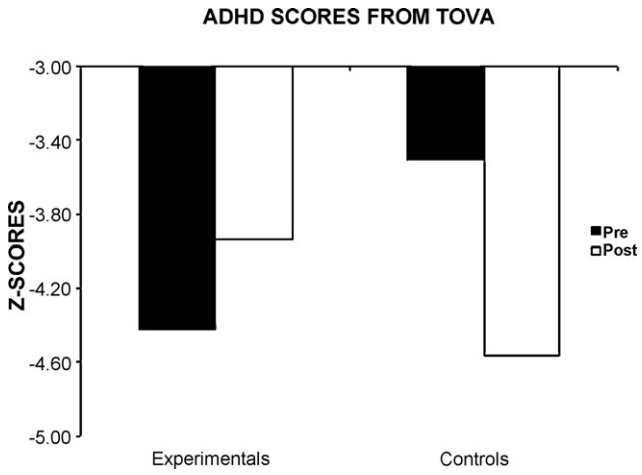

Fig. 9. Change in TOVA ADHD scores in experimental and placebo groups. The ADHD score reflects the sum of the response time in the first half, the d' in the second half, and the total variability reaction time (RT) scores. The experimental group showed a decrease in z-scores compared to the placebo group which showed an increase.

7.4. ATEC

There was a statistically significant category × group interaction, $F(4,68) = 4.82$, $p < 0.05$. As seen in Fig. 11, there was general positive change in all but the sensory/cognitive awareness dimension in the experimental participants compared to those in the placebo group. There were no correlations between ATEC scores and mu suppression indices.

7.5. Apraxia imitation scale

Analysis of the results from the apraxia imitation scale indicated a main effect of movement, $F(2,32) = 42.42$, $p < 0.001$, with accuracy being best for general movement (88.4%) and worst for finger movements (53.8%), with hand/limb accuracy in between (72%). However, there was no effect of training on overall imitation ($F < 1$). The majority of participants in both groups showed signs of improvement between the initial pre-training and final post-training sessions (see Fig. 12). In overall scores, four participants from the experimental group and two from the placebo group improved, while one showed very little change. Two participants from the experimental group and two from the placebo group showed a decrease in overall score. All but one placebo subject showed improvement in these specific movements.

8. Discussion

Study 2 used a larger population sample than the first study and implemented a more appropriate learning algorithm and control conditions. Results from Study 2 showed substantially stronger effects on QEEG parameters, MSI, TOVA, and ATEC scores but a similar absence of an effect on imitation behavior. The EEG signal contains both amplitude and phase information. Amplitude measures are considered indirect indices of neural synchrony, whereas phase measures are a more direct measure of synchrony. Furthermore, studies have

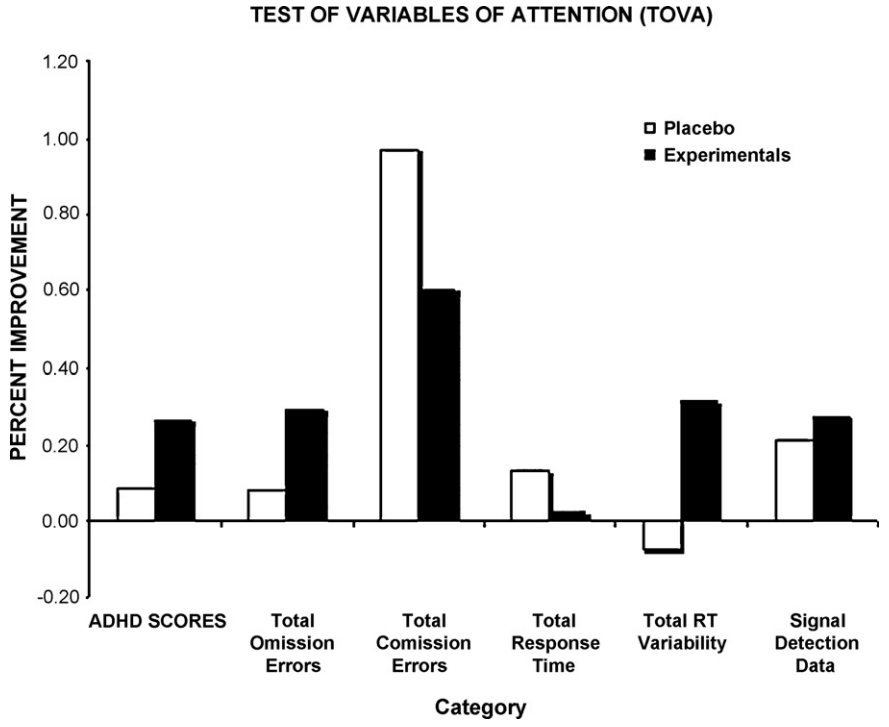

Fig. 10. Percent improvement in TOVA scores for the Experimentals and Placebo groups. Experimentals showed improvements in all but Total Commission Errors and Total Response Time.

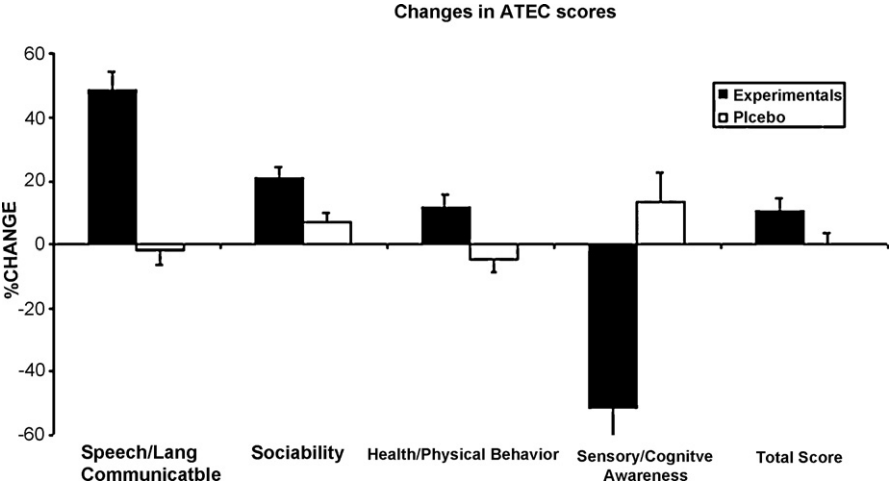

Fig. 11. Changes in ATEC scores for Experimentals and Placebo groups. Experimentals experienced positive changes in all but the Sensory/Cognitive Awareness dimension.

shown that changes in phase can occur without changes in amplitude (Lachaux, Rodriguez, Martinerie, & Varela, 1999; Rodriguez et al., 1999). Indeed, increases in neural synchrony have been hypothesized to reflect mechanisms for dynamic integration of distributed neural networks in the brain, while decreases in synchrony may reflect an unbinding of neural assemblies as a prelude to the next step in mental processing (For a review see Lachaux et al., 1999; Le Van et al., 2001). In the present study, ASD children showed decreased amplitude coherence and increased phase coherence at central (C3, C4) and temporal (T3, T4) sites before NFT. Following training there was a reduction in beta coherence of approximately 20–30% and some reduction in asymmetry for all frequencies. The effects of training on MSI were seen more clearly in Study 2 in which responses to all but the biological motion and disgusted face showed substantial mu suppression following training. Mirror neuron activity is assumed to desynchronize the firing of sensorimotor neurons during the observation of actions (Pfurtscheller & Neuper, 1997; Salmelin & Hari, 1994). Mu desynchrony is typically taken to reflect increased information processing of observed action by prefrontal mirror neurons, while synchronous, high-amplitude oscillations of the mu rhythm are taken to represent a resting or disconnected state (Gastaut, 1952). Therefore, these MSI results reflect a shift towards greater information processing, and an engagement of the MNS, in the experimental group compared to the placebo group.

Similar to Study 1, ADHD scores on the TOVA substantially improved, as did omission errors for experimental groups. Positive changes characterized both the experimental and placebo groups for commission errors, total RT variability, and signal detection. There were also significant improvements on most of the ATEC dimensions for the experimental group, with the exception of sensory/cognitive awareness (SCA). Why the SCA was the only subscale to improve in Study 1 but not in Study 2 is unclear and requires further investigation. The only assessed behavior which improved but did not show any differences between experimental and control groups was imitation. The fact that both groups exhibited changes in behavior implies that factors other than the mu NFT had an impact on imitation behavior. Because the training sessions required that the children attend to the computer game for 30 min at a time, one possibility could be that an improvement in sustained attention was partially responsible for the behavioral

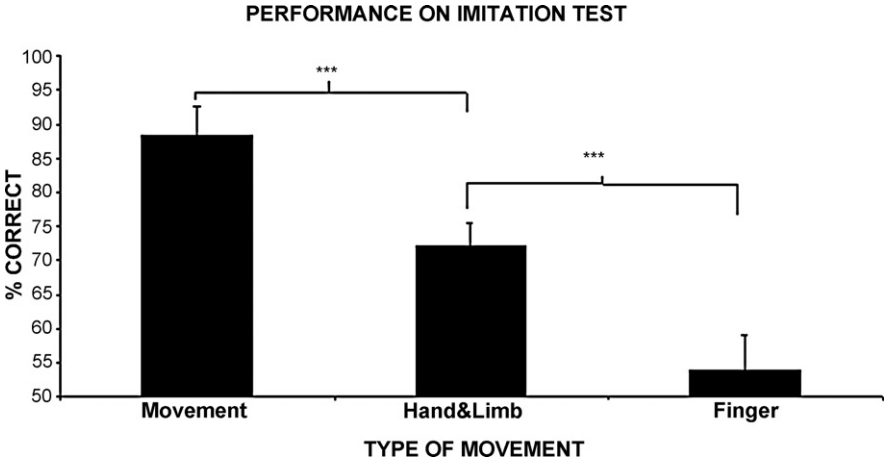

Fig. 12. Histogram showing the performance of participants on the imitation test. Both Experimentals and Placebo groups showed better performance for general Movement compared to Finger movements and intermediate performance for Hand and Limb movements. However, no effect of training occurred for imitation.

changes that were common to both groups. However, this is unlikely, because placebo participants had no change in sustained attention ability as measured by the ADHD score of the TOVA. The only other aspect of training shared by both groups was the training of the EMG component. It is, therefore, possible that control/awareness over the somatic motor system may have resulted in the improvement in both groups.

A more remote explanation of our imitation results is that children with autism may develop alternative strategies that partially compensate for their dysfunctional mirror neuron system. The high-functioning ASD participants in (Dapretto et al., 2006) study were able to imitate facial expressions of emotion as well as healthy controls, but showed no activation in inferior frontal gyrus. The authors suggested that the development of a compensatory network may have been responsible for their behavioral imitation performance. While we specifically recorded mu activity presumably linked to mirror neurons, and our assessments were designed to activate the mirror neuron system, it is impossible to know whether participants were using the same system that was being trained in NFT while they were performing the behavioral assessments. Therefore, we may be partially assessing the efficacy of this putative compensatory network in addition to assessing the efficacy of the mirror neuron network itself.

9. General discussion

Neurofeedback training, which involves operant conditioning of self-regulatory processes involved in the production of endogenous brain rhythms, can lead to functional changes in neural networks. This has been shown with typically developing individuals who learn to control their EEG rhythms using this methodology (Pineda et al., 2000; Pineda, Silverman, Vankov, & Hestenes, 2003; Sterman & Egner, 2006; Sterman & Macdonald, 1978; Vernon et al., 2003). Our studies suggest that neurofeedback training has behavioral and electrophysiological consequences for children with ASD. Mu suppression, which is typically absent in these children (Oberman et al., 2005) recovers following 10 weeks of mu rhythm NFT training compared to those receiving placebo training. At the same time, positive changes in attention, impulsivity, and other assessments of behavior assessed by parents also change. One obvious question that is unanswered by these studies is how long such effects last. These and other questions regarding anatomical changes during extended training are currently being assessed.

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