Flexyx Neurotherapy System in the Treatment of Traumatic Brain Injury:An Initial Evaluation

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Abstract

Objective: To conduct a preliminary experimental evaluation of the potential efficacy of Flexyx Neurotherapy System (FNS), an innovative EEG-based therapy used clinically in the treatment of traumatic brain injury (TBI).

Participants: Twelve people aged 21 to 53 who had experienced mild to moderately severe closed head injury at least 12 months previously, and who reported substantial cognitive difficulties following injury, which interfered with their functioning.

Design: Participants were randomly assigned to an immediate treatment group or a wait-list control group and received 25 sessions of FNS treatment. They were assessed at pre-treatment, post-treatment and follow-up using standardized neuropsychological and mood measures.

Results: Comparison of the two groups on outcome measures indicated improvement following treatment for participants' reports of depression, fatigue and other problematic symptoms as well as for some measures of cognitive functioning. The majority of participants experienced meaningful improvement in occupational and social functioning.

Conclusion: Based on these results, FNS appears to be a promising new therapy for TBI and merits more extensive evaluation.

Key Words: brain injuries, biofeedback, neurotherapy, alternative medicine

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Introduction

Traumatic brain injuries (TBI) affect as many as 500,000 Americans each year, producing sensory, cognitive, physical, affective and behavioral symptoms. In many cases problems are chronic and interfere with physical, occupational, and social functioning. Rehabilitation programs provide a variety of services, but once the acute stage has passed, it is often assumed that restoration of brain function is not possible, so therapies focus on compensatory strategies to address symptoms and functional problems.[1] Despite gains made during rehabilitation, many people with traumatic brain injury continue to experience symptoms that produce chronic impairments in occupational and interpersonal functioning. This study investigated an innovative therapy, Flexyx Neurotherapy System, which attempts to treat chronic sequalae of TBI in order to ameliorate symptoms and improve functional outcomes and quality of life in people with TBI.

Flexyx Neurotherapy

Flexyx Neurotherapy System (FNS) is a form of biofeedback that was developed by the fourth author. The rationale for its use was derived from a number of fields of study. First, it is known that cognitive problems, such as those observed in Attention Deficit Disorder and following TBI, are often associated with a particular electroencephalogram (EEG) pattern in which there is too much activity in lower frequencies of the EEG (i.e. 4-8 Hz) and/or reduced activity in higher frequencies (i.e. 12-18 Hz).[2-3] Second, it has been found that reversal of this EEG pattern using conventional EEG biofeedback is sometimes associated with improvement in cognitive symptoms and problematic behaviors.[4-6] Third, studies have revealed that rhythmic auditory and photic stimulation can alter EEG patterns in predictable ways.[7-8] Based on these observations, FNS was designed to combine conventional EEG biofeedback and photic stimulation in an effort to alter EEG patterns associated with cognitive dysfunction and ultimately to improve functioning.

The FNS equipment used in this study provides feedback in the form of subthreshhold photic stimulation. Clients wear glasses that have light emitting diodes (LEDs) embedded in the lenses. EEG activity is measured using standard equipment and a single electrode, which is moved to different places on the head during treatment. The EEG records the amount (amplitude) of electrical activity across a range of frequencies (1-30 Hz). During FNS, a client's momentary dominant, or peak, EEG frequency is measured and used to reset the frequency at which the LEDs pulse, which in turn influences the EEG. The intensity of the feedback is set at subthreshhold levels, and cannot be seen by the person wearing the glasses. Low levels of stimulation are used because many people who have experienced a head injury or other trauma to the central nervous system cannot tolerate exposure even to dim flashing light.

Although FNS was developed based on principles that also underlie conventional EEG biofeedback, the two treatments are somewhat different, particularly with regard to role of active learning and the portions of the EEG targeted for change. During conventional EEG biofeedback, clients learn to suppress EEG activity in certain frequency bands and/or to increase the amplitude in other bands. Auditory or visual cues provide clients with feedback that they have achieved the desired EEG pattern. Generally, the goal is to increase activity in the range of 12-18 Hz, and reduce activity in the range of 4-8 Hz. In contrast, during FNS treatment, clients do not attempt conscious control of EEG activity. The feedback system produces changes in EEG patterns without clients' effort. People with chronic symptoms following TBI often have greater EEG amplitudes in the lower frequency (1 – 8 Hz) range. The goal of FNS is to achieve a balance of activity across the EEG spectrum, not to exert any specific effect on higher frequency activity.

The beneficial effects of conventional EEG biofeedback have been supported by empirical research. There is modest evidence that conventional biofeedback produces improvements in disorders of the central nervous system, including attention deficit disorder (ADD).[4,6,9-11] Preliminary work has been done using conventional EEG biofeedback with people who have experienced a brain injury.[12] An early study using alpha training with 250 people with brain injury indicated improvement in many cases.[13] Results of a case study of a woman who was treated with 31 sessions of neurofeedback four years following a mild brain injury indicated improvement on neuropsychological measures and a checklist of symptoms typically reported following TBI.[14] Changes in quantitative EEG (QEEG) variables were also observed.

One drawback with conventional EEG biofeedback as it is currently practiced is that a large number of sessions may be required to produce the desired effects. Studies of ADD use upwards of 40 treatment sessions that are each 45 minutes in length.[9-10] One study has been attempted using EEG biofeedback for headache and cognitive dysfunction following traumatic brain injury.[15] While the technique was apparently helpful for some people, only 3 of 13 participants enrolled in the study completed all 30 treatment sessions, the others discontinuing treatment after fewer than 15 sessions. In contrast, clinical reports indicate that FNS produces changes in EEG activity and associated improvement in symptoms in many fewer sessions than conventional EEG biofeedback, but these claims require documentation in controlled studies.

While the present study represents preliminary work on a specific treatment system using EEG recording in relation to photic feedback, this paradigm is not unique. Other investigators have used fixed frequency photic stimulation, consisting of visible light flashes, as an adjunct to conventional EEG biofeedback in the treatment of 32 children with attention deficit disorder.[16] Following 15 sessions of treatment during which stimulation was gradually withdrawn, participants in the treatment group demonstrated decreased impulsivity and improved attention, while the wait-list control group showed no change. Another group of researchers has developed a system of EEG-driven photic stimulation, which is different from the Flexyx Neurotherapy System that is evaluated in this study in terms of (1) system hardware, (2) feedback intensity, and (3) relationship between EEG activity and feedback. This EEG-driven photic stimulation has been used in the treatment of depressive disorders, but no information is available regarding efficacy beyond a single case report.[17]

FNS has been used clinically to treat disturbances of the central nervous system, including TBI, autism, and ADD. Initial indications of the efficacy of FNS have come from clinical records, but until recently there was no experimental research. In one clinical case series, a sample of 20 outpatients with mild to moderately severe closed head injury were treated with FNS.[18] These patients had a range of symptoms and were, on average, 3 years post-trauma. They were given an average of sixteen 20-minute treatment sessions, with the number of treatments determined by the number and severity of remaining symptoms. Nineteen of 20 patients reported better sleep, less depression, irritability, and explosiveness, better concentration, more energy, and better ability to understand written and verbal information. For patients with head injury, Ochs reported that improvement in affect was generally seen after an average of six sessions of FNS.[19] More subtle neuropsychological skill recovery (including attention, concentration, ability to judge social cues, and academic performance) was observed after an average of 16 sessions.[18]

Clinical observations regarding the effectiveness of treatment require validation in experimental research. This study was designed as a preliminary evaluation of the efficacy of Flexyx Neurotherapy System for people who have experienced a traumatic brain injury. It differs from Ochs' clinical case series[18] by comparing people who receive immediate treatment to those in a wait-list control group, using standardized treatment procedures and outcome measures, and applying statistical tests to evaluate efficacy. Based on previous research on EEG biofeedback and

photic stimulation and on clinical observations of the use of FNS for people with brain injuries, it was hypothesized that (1) participants in the immediate treatment group would demonstrate greater improvement on measures of cognitive and emotional functioning compared to those in the wait-list control group, and (2) these improvements would be maintained over time.

Method

This study received IRB approval before recruitment of participants began. Potential participants were recruited from clients who sought treatment at the office of the third author and by informing area neurologists and rehabilitation specialists about the project. Prior to beginning study procedures, all participants signed an informed consent document. A structured interview and symptom checklist were administered in order to determine whether potential participants qualified for this study. People were excluded from the study if they had a penetrating head injury, pre-injury substance abuse or dependence, pre-injury diagnosis of psychotic illness, or pre- or post-injury seizure. Women who were pregnant or trying to become pregnant were also excluded.

Participants

Participants were 2 men and 10 women, aged 21 to 53 who had experienced mild to moderately severe closed head injury at least 12 months previously, as determined by referring professionals and medical history. Corroborating documentation from medical records was obtained for 9 participants. One additional participant was referred for treatment by a neurologist. Time since injury ranged from 36 months to 21 years. Eleven participants were injured in motor vehicle accidents and one fell from a second story balcony. Duration of loss of consciousness ranged from less than one minute to 27 days. Five participants reported post-traumatic amnesia. The injuries of most participants were classified as mild, although there were three people with moderately severe injuries. During the structured interview and on the symptom checklist, all participants reported substantial cognitive difficulties following injury, which interfered with their functioning.

Measures

Measures were selected to assess a range of symptoms frequently experienced following TBI including depression, fatigue, emotional distress and cognitive dysfunction. Specifically, neuropsychological measures evaluated memory, attention, information processing, verbal fluency, and integrated functions.

Individualized Symptom Rating Scale. Participants were asked to list the 5 primary symptoms for which they were seeking treatment and to rate the severity of each symptom over the past week using an 11 point Likert scale. An average score was obtained, with a range from 0-10.

Beck Depression Inventory (BDI). The BDI is a 21-item self-report scale used to assess symptoms of depression. The total score has a range from 0-63. The scale has good reliability and validity as assessed in a number of studies.[20]

Multidimensional Fatigue Inventory (MFI). The MFI is a 20-item self-report measure designed to measure fatigue and covers 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The severity of each item is rated on a 5-point scale, and scores on each subscale range from 4-20. The scale has adequate internal consistency, and construct validity has been confirmed using several different samples.[21]

Symptom Checklist-90-Revised (SCL-90-R). The SCL-90-R is a 90-item self-report inventory on which respondents rate symptom severity using 5-point scales. Nine primary dimensions are covered, including somatization, interpersonal sensitivity, and anxiety. The primary measure used in this study was the Positive Symptom Distress Index (PSDI), which reflects the intensity of symptoms that are endorsed. Internal consistency was quite good, Cronbach's alpha > .75 for all scales in two studies, and validity has been supported in a number of studies.[22]

Auditory Verbal Learning Test (AVLT). Rey's AVLT assesses memory using two lists of 15 nouns. Participants were read the first list 5 times and recall was tested after each trial. Recall was then tested once for a second, distractor list. Then, immediate and 30-minute recall were assessed for the first list. Scores range from 0-15 words for each trial. In order to minimize practice effects, alternate forms using different word lists were employed for each assessment. Equivalency to the Rey AVLT has been demonstrated for the alternate forms.[23] People with head injuries tend to have poorer than normative scores on all trials.[24]

Paced Auditory Serial Addition Test (PASAT). The PASAT assesses information processing and sustained attention using a serial addition task. Participants listened to an audiotape that presented a list of single digit numbers and were instructed to add the numbers in pairs, the first and second, second and third, etc. and to give their answers aloud.[25] There are four trials, with scores ranging from 0-49, in which the digits are presented at successively faster rates of speed. Many people with head injuries perform below control-group averages on this test.[24]

Rey-Osterrieth Complex Figure. This complex-figure task evaluates perceptual organization and visual memory in people with head injuries.[24] Participants were given up to 5 minutes to copy the figure and then were asked to reproduce the figure after a 20-minute delay. Recall scores were used to assess visual memory in this study, and explicit scoring criteria were used to increase reliability.[26] Points are given for accurate recall of specific elements of the figure, and the total score has a range from 0-36. Each drawing was scored by two raters who were unaware of participants' group assignment and date of assessment, and the average score was entered in data analyses. Inter-rater reliability was .96.

Trail Making Test. Part B of this test, which is included in the Halstead-Reitan battery, requires subjects to connect randomly placed numbers and letters in alternating order using pencil lines.[24] The task involves sustained attention, motor speed, and visuomotor tracking. The evaluator corrects errors as they occur and time to completion is used as the score. Part A was administered first in order to standardize administration, but scores were not analyzed.

Controlled Oral Word Association. Verbal fluency was assessed using this measure, which is commonly known as the F-A-S. Participants are asked to name as many words as they can with each of these initial letters; they are

allowed 60 seconds for each letter. Using proper names or giving the same word with a different ending are not allowed. The score is the sum of all admissible words. This test has proven a sensitive gauge of brain injury.[24]

Digit Span Backwards. During this task, increasingly long lists of numbers are read aloud, and participants must repeat each list in the reverse order. One point is given for each correct list. Raw scores range from 0-14. This subscale of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used because it is sensitive to the effects of brain injury.[24] The Digit Span Forward task was administered first in order to standardize administration, but scores were not analyzed.

Digit Symbol. During this symbol substitution task, participants draw symbols in rows next to single digit numbers based on a key that pairs a unique symbol to each number. The task involves sustained attention, response speed, and visuomotor coordination. One point is given for each correct symbol, and raw scores range from 0-93. This subscale of the WAIS-R is also sensitive to the effects of brain injury.[24]

Procedure

Following individual pretreatment assessments, participants were randomly assigned to one of two conditions: (1) immediate treatment or (2) wait-list control group, which received treatment following a 6-8 week waiting period. The experimental design is depicted in Figure 1.

Insert Figure 1 about here

For purposes of statistical analysis, the experimental design is divided into two parts. Part 1 is a classic between-groups design with repeated assessment (before-after) including a treatment group and a no-treatment control group. Part 2 is a within-groups longitudinal design, since both groups have received the treatment by Time 3. Two sets of complementary statistical analyses were conducted in order to examine the overall pattern of findings. Between-group analyses took advantage of the rigorous research design using a randomized control condition, but with a small sample size, statistical power was limited. Repeated measures (within-group) analyses examined changes over time with the groups combined. This provided more statistical power by allowing participants to serve as their own controls thereby reducing error variance. However, these analyses do not make use of a comparison group or control for practice effects. Since the within-groups analyses were conducted within the context of the Part 1 between-groups design, they can be interpreted as supporting or confirming results obtained there. At each assessment, participants were administered the same battery of self-report measures and neuropsychological tests.

Treatment

Treatments were administered using the J&J Enterprises I-400 EEG biofeedback system (Poulsbo, WA). The I-400 was connected to a Synetic Systems light generator PC board driving LED embedded glasses (Seattle, WA), which were also linked to a 486 DX2-66 PC running proprietary software developed by the fourth author (Flexyx, Walnut Creek, CA).

Participants received 25 sessions of treatment administered over a 5-8 week period. Treatment sessions were conducted by the third author at her outpatient office. During FNS treatment, participants sat comfortably with their eyes closed, wearing the LED embedded glasses, and engaged in no specific activity. Each patient's dominant EEG frequency, between 1 and 30 Hz, was extracted every 0.5 seconds and used to reset the frequency of the LEDs, which pulsed simultaneously in front of the left and right eyes. Feedback was administered in periods of 18 seconds duration. The strobe frequency was offset from the dominant EEG frequency in the range of +5 Hz to +20 Hz. The magnitude of the offset changed every 18 seconds, and the maximum strobe frequency was set at 30 Hz. All stimulation was minimized in brightness to lowest available level, and participants were unable to detect the LED output even when their eyes were open.

The first session was an introductory session during which a single electrode was placed at the FPZ site (the middle of the forehead between the eyes). EEG recording began with 1 minute of no stimulation, followed by up to 4 minutes of stimulation, and a final minute without stimulation. The subsequent few sessions were mapping sessions during which 18 seconds of stimulation were administered with monopolar EEG recording at each of 21 sites. This yields approximately 6 minutes of stimulation. If a movement artifact was detected, the time at that site was repeated in order to obtain accurate data. Average amplitude and variability of the EEG were recorded in both delta and alpha frequency bands at each site and used to create a sort sequence from lowest amplitude and variability to highest.

During remaining sessions, FNS treatment was administered following the delta activity sort sequence. Each site was treated in the following way. The reference electrode was applied to the left earlobe, the skin was prepared, and impedance was reduced to 3K Ohm. Then, the active lead was applied to sites successively, as specified in the delta activity sort sequence, and feedback was administered at each site. Although we attempted to standardize the amount of stimulation provided during treatment sessions, the exact duration of feedback during each session was based on participants' reactions. Some participants were quite sensitive to the feedback, and the duration was reduced in these cases. Participants' reactions changed over the course of treatment, and duration of feedback was modified accordingly. Therefore, the duration of stimulation received during an individual session ranged from 5 seconds to 20 minutes. Four participants received feedback for an average of less than 5 minutes per session. For other participants, feedback averaged between 10 and 15 minutes per session.

Results

Between-Groups Analyses

Analyses of covariance (ANCOVAs) were conducted to compare groups after only the immediate treatment group had received FNS treatment (see Time 2 in Figure 1), while controlling for baseline differences. Group means and standard deviations are found in Table 1. Because this was the first controlled evaluation of FNS, we did not want possible effects of treatment to go unnoticed. Therefore, alpha was set at .05 and was not adjusted for multiple tests. For the self-report measures, four ANCOVAs were conducted initially. The treatment group was significantly improved compared to the control group on the individualized rating scale ($F=12.38$, $p<.01$), and the Beck Depression Inventory ($F=10.01$, $p<.02$). Between-group differences were not significant for the total score on the Multidimensional Fatigue Inventory ($p<.09$), or the Positive Symptom Distress Index of the SCL-90 ($p<.19$). However, the MFI was designed with 5 independent subscales, which we analyzed separately to determine if there were between-group differences only for some of them. The treatment group was significantly improved compared

to the control group on the General Fatigue (F=8.04, p<.02), and Mental Fatigue (F=9.10, p<.02) subscales. No significant differences were noted for Physical Fatigue (p<.13), Reduced Activity (p<.64), or Reduced Motivation (p<.20).

Insert Table 1 about here

Similar ANCOVAs were conducted for the neuropsychological measures. The treatment group was significantly improved compared to the control group on Digit Span Backwards (F=5.37, p<.05), the interference trial (F=5.54, p<.05), and the delayed recall trial (F=7.47, p<.03) of the AVLT, and the most difficult trial of the PASAT (F=8.08, p<.02). In addition, the results approached significance for Digit Symbol (F=3.64, p<.09) and the first immediate recall trial of the AVLT (F=4.52, p<.07).

Within-Group Analyses

Repeated measures analyses of variance were used to examine changes over time. Data were used from three assessments: pre-treatment (just prior to treatment), post-treatment (just following treatment), and follow-up (the next subsequent assessment). The two groups (immediate treatment and delayed treatment control) were combined for these analyses, because all participants had received treatment before the third assessment. Means and standard deviations are found in Table 2.

Insert Table 2 about here

ANOVAs showed significant improvement over time for each self-report measure except the reduced activity and reduced motivation subscales of the Fatigue Inventory, which were less problematic for participants. Even prior to treatment, they remained motivated to participate in activities, despite their fatigue. Among the fatigue subscales, participants reported the greatest improvement in their mental fatigue. Most neuropsychological measures showed significant improvement over time.

If the repeated measures ANOVA was statistically significant for a measure (p<.05), then the within-subjects contrasts were examined to determine when changes occurred. Of particular interest were the hypotheses that improvement would occur following treatment and be maintained at follow-up assessment. Significant improvement was observed following treatment for almost all self-report measures, including the Fatigue Inventory total score and the Positive Symptom Distress Index, for which the differences between the immediate treatment and delayed treatment groups failed to reach significance. Results for the Fatigue Inventory subscales confirmed the results of the between-groups analyses. For the neuropsychological measures, there was significant change from pre-treatment to post-treatment for Digit Span Backwards (p<.01), Digit Symbol (p<.05), and the first (p<.05), third (p<.01), and fourth (p<.001) trials of the PASAT. Overall, these findings support and extend the results of the

between-groups analyses. Treatment gains were maintained from post-treatment to follow-up, and in some cases further improvement was observed. Participants reported even less emotional distress at follow-up on the Positive Distress Symptom Index ($p<.05$). Performance improved on a number of neuropsychological measures, and many scores were significantly better at follow-up than pre-treatment (see means in Table 2). Thus, participants did not experience a reversal of symptoms following the end of treatment, and continued improvement was observed for some measures.

Clinical Observations

Table 3 presents a summary of outcomes and selected participant characteristics. Four of the participants had been through extensive rehabilitation programs, three of them as inpatients. Prior to treatment, all 12 participants reported difficulty with their ability to work or complete academic courses. Following treatment, 7 of them were able to work professionally or engage in full academic work. Two other participants reported improvement in some areas following FNS treatment. Three people did not respond to the treatment. Three participants had very low amplitude resting EEGs, including two of the three who did not report much improvement. Clinical experience suggests that people with severely low amplitude EEG require a different treatment protocol than was used in this study.

With treatment, 2 of 8 participants who had been taking medications were able to reduce the dosage for these prescriptions and 3 were able to eliminate them entirely. Three had no change and 4 were not taking medication. For 15 years, one person had required large doses of pain medications as well as weekly walk-in clinic or emergency room visits to manage post-traumatic migraine headaches. After 9 treatments, the headaches were gone, pain medications were greatly reduced and mild headaches, which were responsive to over-the-counter medication, subsequently recurred less than once a month. One person with post-traumatic fibromyalgia substantially reduced medication by the end of treatment. After eighteen months, she still required only low doses of medication and was working full-time.

Insert Table 3 about here

Safety

FNS is generally safe, however, the most common side effect experienced during treatment was a temporary intensification of symptoms that had previously been problematic. Many of the participants experienced again symptoms that had occurred at the time of the TBI. Symptoms included pressure in the head or headache (3 people), dizziness (4 people), nausea (1 person), tingling sensation (1 person) or physical pain associated with broken bones or other injuries occurring at the time of the accident (2 people). Such reactions usually occurred within the first 6 or 7 sessions and typically resolved within a few days. Adverse reactions may also be caused by over-treatment. At each session, participants were asked about their reactions to treatment in order to determine the length of the next treatment session. Fatigue (3 people) and restlessness (1 person) were the most common indications of over-

treatment and session length was reduced accordingly. Following treatment, one person reported unexplained hair loss.

Discussion

The overall pattern of results from this preliminary investigation strongly suggests that Flexyx Neurotherapy System (FNS) may be an efficacious treatment for people who have experienced a traumatic brain injury. Compared to a wait-list control group, FNS treatment produced significant improvement in depression and a range of other symptoms reported by participants as most problematic. Treatment also produced significant improvement on some measures of cognitive functioning, specifically those involving working memory, immediate memory of new material, and retention of information. Results for other measures also indicated improvement, but failed to reach statistical significance. Longitudinal analyses of all participants receiving treatment supported and extended these findings. With the added statistical power afforded by repeated-measures analyses, significant improvement was observed for additional self-report and cognitive measures. Follow-up assessments showed clearly that improvements were maintained following the end of treatment. Although there were not any substantial delayed effects of treatment, some small continued improvements were noted.

The lack of significant findings for some measures suggests several possibilities. First, if the effect size is smaller for these measures, this sample may have been too small to detect the effect of treatment. This possibility is supported by the observation that a greater number of measures achieved statistically significant results when analyses with more statistical power (e.g. repeated-measures analyses) were used. Second, some of the neuropsycholgical tests used may not have been sensitive enough to detect changes experienced by study participants. Specifically, measures often fail to capture the complexity of a real-world environment that places multiple simultaneous demands on cognitive processing. Third, FNS treatment may be more effective for treating some symptoms than others. Fourth, practice effects on some neuropsychological measures may have been strong enough to obscure improvement produced by treatment. Fifth, variability in location and severity of damage to the brain may have obscured improvement as measured by average group scores, because changes were experienced by only some of the participants.

Efforts were made to reduce practice effects that result from multiple exposure to the same content. Alternate word lists were used for the AVLT. Sequences in digit span backwards and digit symbol cannot be memorized. However, practice effects still occur from increased familiarity with the process of each test. People develop better strategies for handling these tasks, particularly the participants in this study who generally had a high level of functioning prior to their injuries. Therefore, improvement in scores on neuropsychological measures may be due to repeated exposure to tests rather than effects of treatment. This is a difficult issue that impacts any research in which multiple assessments are required. In this study, the results of the within-groups analyses must be considered in the context of the between-groups design, which controls for practice effects by including a wait-list control group.

Because this study was among the first experimental examinations of the effects of FNS, we did not want to overlook any potential benefits of treatment. Therefore, given the small sample size, alpha level was not adjusted for multiple statistical comparisons. Nonetheless, the number of findings that reached statistical significance was greater that would be expected by chance.

The research design used in this study does not eliminate the possibility that participants improved simply because they believed that action was being taken to help them, rather than as a result of the specific treatment administered. This phenomenon of positive response to an intervention regardless of its content has been termed the Hawthorne effect, and was first described in studies with non-injured people performing repetitive low-skill tasks. The Hawthorne effect is almost certainly a minor explanatory factor in this study, however, because simple attention is unlikely to have a substantial long term effect on individuals who have experienced brain injuries and who have reached a stable performance plateau after receiving prior medical treatment and rehabilitation. Many of these participants experienced improvement with FNS after other interventions had failed to benefit them. Nonetheless, a placebo control group or a control group involving irrelevant attention will eventually be needed to completely eliminate attention as an explanatory cause of improvement, and should be included in future research on FNS.

It is important to note that clinical observations made by participants and therapist during the course of the study indicated that meaningful change occurred in many areas. Several participants were able to return to work or academic study following treatment. Generally, reports indicated improvements in quality of life, some of which were profound. However, there were three people (25%) for whom improvement was minimal. Clinical efforts are already underway to identify those people who may require a different FNS treatment protocol, or for whom FNS may not be appropriate.

Taken as a whole, the findings of this study are strong enough to identify FNS as a promising new treatment for traumatic brain injury, which merits further evaluation. The mechanism of action is unclear, but other research suggests that normalizing EEG activity is associated with benefits in cognitive and behavioral functioning.[3,12] Subsequent studies should use a larger sample and a more comprehensive assessment battery that includes quantitative EEG as an objective measure of change in addition to cognitive and functional measures. A more homogeneous group of people with regard to severity of injury, time since injury, and presenting problems would also be beneficial. Recently developed improvements in FNS technology will also enable the use of a double-blind procedure with a placebo control group, which will increase the quality of subsequent research. Such research will provide a clearer picture of the benefits of FNS in the treatment of traumatic brain injury and help determine which symptoms are most responsive to FNS and what circumstances optimize treatment outcome.

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Table 1

Means and Standard Deviations for Time 1 and Time 2 Assessments by Group

	Immediate Treatment Group		Delayed Treatment Control Group		
	Time 1	Time 2	Time 1	Time 2	
Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F
Symptom average	8.47 (1.31)	3.80 (2.38)	8.49 (0.91)	7.62 (0.96)	12.38**
Beck Depression	22.50 (9.89)	7.00 (5.25)	16.67 (9.81)	16.17 (12.19)	10.01*
Fatigue Inventory Total	74.83 (20.43)	48.50 (20.89)	61.50 (18.85)	61.33 (20.58)	3.68†
General Fatigue	17.17 (4.02)	9.83 (4.83)	14.83 (4.17)	14.00 (4.56)	8.04*
Physical Fatigue	16.00 (6.23)	10.00 (3.52)	10.50 (4.51)	10.83 (5.34)	2.88
Reduced Activity	14.33 (5.57)	11.33 (5.35)	10.67 (4.68)	10.83 (4.96)	0.24
Reduced Motivation	10.17 (4.75)	7.00 (2.83)	10.00 (3.90)	10.00 (4.86)	1.99
Mental Fatigue	17.17 (3.31)	10.33 (6.31)	15.50 (3.83)	15.67 (3.50)	9.10*
PSDI	2.42 (0.58)	1.65 (0.24)	1.96 (0.29)	1.82 (0.40)	2.04
AVLT trial 1	6.83 (2.64)	8.17 (1.94)	5.17 (1.72)	5.33 (1.63)	4.52†
AVLT trial 2	10.17 (3.19)	10.50 (2.26)	8.33 (1.75)	8.17 (2.32)	1.54
AVLT trial 3	11.50 (1.38)	12.00 (2.10)	10.67 (1.21)	10.33 (2.07)	1.40
AVLT trial 4	11.50 (2.74)	13.17 (0.98)	12.00 (1.41)	11.33 (2.16)	3.04
AVLT trial 5	12.17 (2.40)	13.50 (1.22)	11.67 (1.21)	11.67 (1.97)	3.26
AVLT list B	5.83 (2.23)	7.17 (1.72)	4.83 (2.48)	5.33 (0.52)	5.54*

AVLT immediate recall	11.00 (1.79)	11.00 (1.67)	8.50 (1.87)	10.00 (2.45)	1.29
AVLT delayed recall	10.33 (2.94)	12.00 (1.79)	9.00 (1.26)	9.00 (1.67)	7.47*

Measure	Immediate Treatment Group		**Delayed Treatment Control Group**		
	Time 1	Time 2	Time 1	**Time 2**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F
PASAT trial 1	25.00 (6.54)	36.17 (11.09)	27.17 (5.56)	33.50 (8.69)	0.45
PASAT trial 2	26.67 (6.09)	32.83 (8.04)	23.50 (6.44)	29.00 (6.03)	0.94
PASSAT trial 3	21.83 (6.49)	28.67 (6.12)	17.67 (6.71)	25.17 (10.30)	0.01
PASAT trial 4	15.83 (4.40)	24.50 (7.64)	17.33 (3.56)	18.17 (8.86)	8.08*
Trails B (in seconds)	78.17 (15.69)	70.83 (32.71)	79.00 (16.73)	71.00 (31.83)	0.01
Rey figure recall	13.79 (3.53)	17.75 (4.13)	16.50 (4.80)	18.75 (5.20)	1.45
F-A-S total	37.67 (15.19)	44.33 (13.09)	29.83 (8.77)	32.83 (8.08)	2.95
Digit Span Backward	6.00 (0.89)	8.17 (2.14)	5.83 (1.72)	5.67 (1.37)	5.37*
Digit Symbol	50.00 (6.96)	61.67 (13.02)	54.67 (14.04)	53.50 (12.28)	3.64†

Note: PSDI = Positive Symptom Distress Index from the Symptom Checklist 90 – Revised; AVLT = Auditory Verbal Learning Test; PASAT = Paced Auditory Serial Addition Test

†$p<.10$; * $p<.05$; ** $p<.01$

Table 2

Means and Standard Deviations with Groups Combined

Measure	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	3-Month Follow-Up Mean (SD)	F
Symptom Average	[a]8.04 (1.18)	[b]3.65 (2.04)	[b]3.67 (1.86)	34.42***
Beck Depression	[a]19.33 (11.09)	[b]7.92 (6.91)	[b]7.83 (6.74)	18.29***
Fatigue Inventory Total	[a]68.08 (20.78)	[b]50.08 (19.01)	[b]47.33 (20.03)	8.43**
General Fatigue	[a]15.58 (4.42)	[b]11.17 (4.76)	[b]10.45 (5.05)	6.50**
Physical Fatigue	[a]13.42 (6.16)	[a]9.83 (3.33)	[a]9.27 (4.89)	4.02*
Reduced Activity	12.58 (5.35)	10.08 (4.80)	8.00 (4.20)	3.48†
Reduced Motivation	10.08 (4.58)	8.00 (3.64)	7.73 (4.43)	2.72
Mental Fatigue	[a]16.42 (3.34)	[b]11.00 (4.94)	[b]10.73 (4.36)	14.68***
PSDI	[a]2.12 (0.57)	[b]1.53 (0.38)	[c]1.37 (0.35)	18.83***
AVLT trial 1	[a]6.08 (2.23)	[b]7.08 (1.93)	7.33 (2.06)	3.19†
AVLT trial 2	9.17 (2.86)	10.25 (2.05)	10.50 (3.00)	1.66
AVLT trial 3	[a]10.92 (1.78)	[ab]11.83 (1.90)	[b]12.58 (2.19)	4.32*
AVLT trial 4	[a]11.42 (2.35)	[ab]12.50 (1.31)	[b]13.42 (1.88)	3.93*
AVLT trial 5	11.92 (2.11)	12.33 (2.50)	13.17 (1.85)	1.68
AVLT list B	5.58 (1.56)	6.50 (2.20)	6.83 (1.70)	2.97†
AVLT immediate recall	10.50 (2.11)	10.17 (1.90)	12.25 (2.80)	3.26†
AVLT delayed recall	9.67 (2.39)	11.08 (2.54)	12.00 (2.86)	3.42†
PASAT trial 1	[a]29.25 (8.57)	[b]36.42 (8.99)	[b]40.42 (6.01)	13.97***

PASAT trial 2	[a]27.83 (5.91)	[a]31.67 (9.13)	[b]37.08 (8.76)	12.06***
	Pre-treatment	Post-treatment	3-Month Follow-Up	
Measure	Mean (SD)	Mean (SD)	Mean (SD)	**F**
PASAT trial 3	[a]23.50 (8.39)	[b]29.00 (8.02)	[c]32.75 (9.07)	18.48***
PASAT trial 4	[a]17.00 (6.78)	[b]23.75 (8.36)	[b]27.00 (8.95)	13.75***
Trails B (in seconds)	[a]74.58 (24.22)	[ab]67.17 (26.68)	[b]59.92 (20.67)	3.77*
Rey figure recall	[a]16.27 (4.97)	[ab]17.50 (6.39)	[b]19.02 (6.92)	3.43*
F-A-S total	[a]35.25 (11.87)	[ab]38.83 (11.68)	[b]40.50 (11.37)	3.45*
Digit Span Backward	[a]5.83 (1.11)	[b]7.33 (2.19)	[b]7.75 (2.34)	5.80**
Digit Symbol	[a]51.75 (9.69)	[b]59.00 (11.29)	[b]61.16 (11.62)	6.93**

Note: PSDI = Positive Symptom Distress Index from the Symptom Checklist 90 – Revised; AVLT = Auditory Verbal Learning Test; PASAT = Paced Auditory Serial Addition Test

[†]p<.10; *p<.05; **p<.01; ***p<.001

[a] Means with different subscripts differ significantly from each other (p<.05).

Table 3

Participant Characteristics and Outcome

ID	Time Since Injury (yrs.)	Severity of Injury	Very Low Amplitude EEG	Change in Medication	Functional Outcome
1	9.5	Mild	**No**	Eliminated	From working part-time with great effort to working full-time. Adult child with M.D. reported return to pre-injury functioning.
2	7.5	Moderate	No	Eliminated	Able to complete post-graduate courses with less effort.
3	5.5	Moderate	Yes	Not Taking	Little change. Did report improvement in spatial orientation, and was therefore able to travel by subway and car without getting lost.
4	3.0	Mild	Yes	Not Taking	From working in low-skill job to seeking position in pre-injury field of employment.
5	15.0	Mild	No	Decreased	**From no employment to working full-time.**
6	9.0	Mild	No	Not Taking	From no employment to working full-time with good reviews of job performance. Better social relationships due to decreased irritability.
7	21.0	Moderate	No	Eliminated	Able to complete tasks of daily living and to participate in other activities due to reductions in pain and fatigue.
8	7.0	Mild	No	Decreased	Taking required courses in preparation for return to work in professional field.
9	3.5	Mild	No	No Change	Little change.
10	3.0	Mild	Yes	No Change	Temporary improvement that did not persist.
11	5.5	Mild	No	No Change	Reduced anxiety / panic attacks. Little cognitive change.
12	3.0	Mild	No	Not Taking	From taking few college courses and getting low grades to making the Dean's list (3.5 grade point average with full course load). Better social relationships due to decreased irritability.

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Abstract

Objective: To conduct a preliminary experimental evaluation of the potential efficacy of Flexyx Neurotherapy System (FNS), an innovative EEG-based therapy used clinically in the treatment of traumatic brain injury (TBI).

Participants: Twelve people aged 21 to 53 who had experienced mild to moderately severe closed head injury at least 12 months previously, and who reported substantial cognitive difficulties following injury, which interfered with their functioning.

Design: Participants were randomly assigned to an immediate treatment group or a wait-list control group and received 25 sessions of FNS treatment. They were assessed at pre-treatment, post-treatment and follow-up using standardized neuropsychological and mood measures.

Results: Comparison of the two groups on outcome measures indicated improvement following treatment for participants' reports of depression, fatigue and other problematic symptoms as well as for some measures of cognitive functioning. The majority of participants experienced meaningful improvement in occupational and social functioning.

Conclusion: Based on these results, FNS appears to be a promising new therapy for TBI and merits more extensive evaluation.

Key Words: brain injuries, biofeedback, neurotherapy, alternative medicine

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Introduction

Traumatic brain injuries (TBI) affect as many as 500,000 Americans each year, producing sensory, cognitive, physical, affective and behavioral symptoms. In many cases problems are chronic and interfere with physical, occupational, and social functioning. Rehabilitation programs provide a variety of services, but once the acute stage has passed, it is often assumed that restoration of brain function is not possible, so therapies focus on compensatory strategies to address symptoms and functional problems.[1] Despite gains made during rehabilitation, many people with traumatic brain injury continue to experience symptoms that produce chronic impairments in occupational and interpersonal functioning. This study investigated an innovative therapy, Flexyx Neurotherapy System, which attempts to treat chronic sequalae of TBI in order to ameliorate symptoms and improve functional outcomes and quality of life in people with TBI.

Flexyx Neurotherapy

Flexyx Neurotherapy System (FNS) is a form of biofeedback that was developed by the fourth author. The rationale for its use was derived from a number of fields of study. First, it is known that cognitive problems, such as those observed in Attention Deficit Disorder and following TBI, are often associated with a particular electroencephalogram (EEG) pattern in which there is too much activity in lower frequencies of the EEG (i.e. 4-8 Hz) and/or reduced activity in higher frequencies (i.e. 12-18 Hz).[2-3] Second, it has been found that reversal of this EEG pattern using conventional EEG biofeedback is sometimes associated with improvement in cognitive symptoms and problematic behaviors.[4-6] Third, studies have revealed that rhythmic auditory and photic stimulation can alter EEG patterns in predictable ways.[7-8] Based on these observations, FNS was designed to combine conventional EEG biofeedback and photic stimulation in an effort to alter EEG patterns associated with cognitive dysfunction and ultimately to improve functioning.

The FNS equipment used in this study provides feedback in the form of subthreshhold photic stimulation. Clients wear glasses that have light emitting diodes (LEDs) embedded in the lenses. EEG activity is measured using standard equipment and a single electrode, which is moved to different places on the head during treatment. The EEG records the amount (amplitude) of electrical activity across a range of frequencies (1-30 Hz). During FNS, a client's momentary dominant, or peak, EEG frequency is measured and used to reset the frequency at which the LEDs pulse, which in turn influences the EEG. The intensity of the feedback is set at subthreshhold levels, and cannot be seen by the person wearing the glasses. Low levels of stimulation are used because many people who have experienced a head injury or other trauma to the central nervous system cannot tolerate exposure even to dim flashing light.

Although FNS was developed based on principles that also underlie conventional EEG biofeedback, the two treatments are somewhat different, particularly with regard to role of active learning and the portions of the EEG targeted for change. During conventional EEG biofeedback, clients learn to suppress EEG activity in certain frequency bands and/or to increase the amplitude in other bands. Auditory or visual cues provide clients with feedback that they have achieved the desired EEG pattern. Generally, the goal is to increase activity in the range of 12-18 Hz, and reduce activity in the range of 4-8 Hz. In contrast, during FNS treatment, clients do not attempt conscious control of EEG activity. The feedback system produces changes in EEG patterns without clients' effort. People with chronic symptoms following TBI often have greater EEG amplitudes in the lower frequency (1 – 8 Hz) range. The goal of FNS is to achieve a balance of activity across the EEG spectrum, not to exert any specific effect on higher frequency activity.

The beneficial effects of conventional EEG biofeedback have been supported by empirical research. There is modest evidence that conventional biofeedback produces improvements in disorders of the central nervous system, including attention deficit disorder (ADD).[4,6,9-11] Preliminary work has been done using conventional EEG biofeedback with people who have experienced a brain injury.[12] An early study using alpha training with 250 people with brain injury indicated improvement in many cases.[13] Results of a case study of a woman who was

treated with 31 sessions of neurofeedback four years following a mild brain injury indicated improvement on neuropsychological measures and a checklist of symptoms typically reported following TBI.[14] Changes in quantitative EEG (QEEG) variables were also observed.

One drawback with conventional EEG biofeedback as it is currently practiced is that a large number of sessions may be required to produce the desired effects. Studies of ADD use upwards of 40 treatment sessions that are each 45 minutes in length.[9-10] One study has been attempted using EEG biofeedback for headache and cognitive dysfunction following traumatic brain injury.[15] While the technique was apparently helpful for some people, only 3 of 13 participants enrolled in the study completed all 30 treatment sessions, the others discontinuing treatment after fewer than 15 sessions. In contrast, clinical reports indicate that FNS produces changes in EEG activity and associated improvement in symptoms in many fewer sessions than conventional EEG biofeedback, but these claims require documentation in controlled studies.

While the present study represents preliminary work on a specific treatment system using EEG recording in relation to photic feedback, this paradigm is not unique. Other investigators have used fixed frequency photic stimulation, consisting of visible light flashes, as an adjunct to conventional EEG biofeedback in the treatment of 32 children with attention deficit disorder.[16] Following 15 sessions of treatment during which stimulation was gradually withdrawn, participants in the treatment group demonstrated decreased impulsivity and improved attention, while the wait-list control group showed no change. Another group of researchers has developed a system of EEG-driven photic stimulation, which is different from the Flexyx Neurotherapy System that is evaluated in this study in terms of (1) system hardware, (2) feedback intensity, and (3) relationship between EEG activity and feedback. This EEG-driven photic stimulation has been used in the treatment of depressive disorders, but no information is available regarding efficacy beyond a single case report.[17]

FNS has been used clinically to treat disturbances of the central nervous system, including TBI, autism, and ADD. Initial indications of the efficacy of FNS have come from clinical records, but until recently there was no experimental research. In one clinical case series, a sample of 20 outpatients with mild to moderately severe closed head injury were treated with FNS.[18] These patients had a range of symptoms and were, on average, 3 years post-trauma. They were given an average of sixteen 20-minute treatment sessions, with the number of treatments determined by the number and severity of remaining symptoms. Nineteen of 20 patients reported better sleep, less depression, irritability, and explosiveness, better concentration, more energy, and better ability to understand written and verbal information. For patients with head injury, Ochs reported that improvement in affect was generally seen after an average of six sessions of FNS.[19] More subtle neuropsychological skill recovery (including attention, concentration, ability to judge social cues, and academic performance) was observed after an average of 16 sessions.[18]

Clinical observations regarding the effectiveness of treatment require validation in experimental research. This study was designed as a preliminary evaluation of the efficacy of Flexyx Neurotherapy System for people who have experienced a traumatic brain injury. It differs from Ochs' clinical case series[18] by comparing people who receive immediate treatment to those in a wait-list control group, using standardized treatment procedures and outcome measures, and applying statistical tests to evaluate efficacy. Based on previous research on EEG biofeedback and photic stimulation and on clinical observations of the use of FNS for people with brain injuries, it was hypothesized that (1) participants in the immediate treatment group would demonstrate greater improvement on measures of cognitive and emotional functioning compared to those in the wait-list control group, and (2) these improvements would be maintained over time.

Method

This study received IRB approval before recruitment of participants began. Potential participants were recruited from clients who sought treatment at the office of the third author and by informing area neurologists and rehabilitation specialists about the project. Prior to beginning study procedures, all participants signed an informed consent document. A structured interview and symptom checklist were administered in order to determine whether potential participants qualified for this study. People were excluded from the study if they had a penetrating head injury, pre-injury substance abuse or dependence, pre-injury diagnosis of psychotic illness, or pre- or post-injury seizure. Women who were pregnant or trying to become pregnant were also excluded.

Participants

Participants were 2 men and 10 women, aged 21 to 53 who had experienced mild to moderately severe closed head injury at least 12 months previously, as determined by referring professionals and medical history. Corroborating documentation from medical records was obtained for 9 participants. One additional participant was referred for treatment by a neurologist. Time since injury ranged from 36 months to 21 years. Eleven participants were injured in motor vehicle accidents and one fell from a second story balcony. Duration of loss of consciousness ranged from less than one minute to 27 days. Five participants reported post-traumatic amnesia. The injuries of most participants were classified as mild, although there were three people with moderately severe injuries. During the structured interview and on the symptom checklist, all participants reported substantial cognitive difficulties following injury, which interfered with their functioning.

Measures

Measures were selected to assess a range of symptoms frequently experienced following TBI including depression, fatigue, emotional distress and cognitive dysfunction. Specifically, neuropsychological measures evaluated memory, attention, information processing, verbal fluency, and integrated functions.

Individualized Symptom Rating Scale. Participants were asked to list the 5 primary symptoms for which they were seeking treatment and to rate the severity of each symptom over the past week using an 11 point Likert scale. An average score was obtained, with a range from 0-10.

Beck Depression Inventory (BDI). The BDI is a 21-item self-report scale used to assess symptoms of depression. The total score has a range from 0-63. The scale has good reliability and validity as assessed in a number of studies.[20]

Multidimensional Fatigue Inventory (MFI). The MFI is a 20-item self-report measure designed to measure fatigue and covers 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The severity of each item is rated on a 5-point scale, and scores on each subscale range from 4-20. The scale has adequate internal consistency, and construct validity has been confirmed using several different samples.[21]

Symptom Checklist-90-Revised (SCL-90-R). The SCL-90-R is a 90-item self-report inventory on which respondents rate symptom severity using 5-point scales. Nine primary dimensions are covered, including somatization, interpersonal sensitivity, and anxiety. The primary measure used in this study was the Positive Symptom Distress Index (PSDI), which reflects the intensity of symptoms that are endorsed. Internal consistency was quite good, Cronbach's alpha > .75 for all scales in two studies, and validity has been supported in a number of studies.[22]

Auditory Verbal Learning Test (AVLT). Rey's AVLT assesses memory using two lists of 15 nouns. Participants were read the first list 5 times and recall was tested after each trial. Recall was then tested once for a second,

distractor list. Then, immediate and 30-minute recall were assessed for the first list. Scores range from 0-15 words for each trial. In order to minimize practice effects, alternate forms using different word lists were employed for each assessment. Equivalency to the Rey AVLT has been demonstrated for the alternate forms.[23] People with head injuries tend to have poorer than normative scores on all trials.[24]

Paced Auditory Serial Addition Test (PASAT). The PASAT assesses information processing and sustained attention using a serial addition task. Participants listened to an audiotape that presented a list of single digit numbers and were instructed to add the numbers in pairs, the first and second, second and third, etc. and to give their answers aloud.[25] There are four trials, with scores ranging from 0-49, in which the digits are presented at successively faster rates of speed. Many people with head injuries perform below control-group averages on this test.[24]

Rey-Osterrieth Complex Figure. This complex-figure task evaluates perceptual organization and visual memory in people with head injuries.[24] Participants were given up to 5 minutes to copy the figure and then were asked to reproduce the figure after a 20-minute delay. Recall scores were used to assess visual memory in this study, and explicit scoring criteria were used to increase reliability.[26] Points are given for accurate recall of specific elements of the figure, and the total score has a range from 0-36. Each drawing was scored by two raters who were unaware of participants' group assignment and date of assessment, and the average score was entered in data analyses. Inter-rater reliability was .96.

Trail Making Test. Part B of this test, which is included in the Halstead-Reitan battery, requires subjects to connect randomly placed numbers and letters in alternating order using pencil lines.[24] The task involves sustained attention, motor speed, and visuomotor tracking. The evaluator corrects errors as they occur and time to completion is used as the score. Part A was administered first in order to standardize administration, but scores were not analyzed.

Controlled Oral Word Association. Verbal fluency was assessed using this measure, which is commonly known as the F-A-S. Participants are asked to name as many words as they can with each of these initial letters; they are allowed 60 seconds for each letter. Using proper names or giving the same word with a different ending are not allowed. The score is the sum of all admissible words. This test has proven a sensitive gauge of brain injury.[24]

Digit Span Backwards. During this task, increasingly long lists of numbers are read aloud, and participants must repeat each list in the reverse order. One point is given for each correct list. Raw scores range from 0-14. This subscale of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used because it is sensitive to the effects of brain injury.[24] The Digit Span Forward task was administered first in order to standardize administration, but scores were not analyzed.

Digit Symbol. During this symbol substitution task, participants draw symbols in rows next to single digit numbers based on a key that pairs a unique symbol to each number. The task involves sustained attention, response speed, and visuomotor coordination. One point is given for each correct symbol, and raw scores range from 0-93. This subscale of the WAIS-R is also sensitive to the effects of brain injury.[24]

Procedure

Following individual pretreatment assessments, participants were randomly assigned to one of two conditions: (1) immediate treatment or (2) wait-list control group, which received treatment following a 6-8 week waiting period. The experimental design is depicted in Figure 1.

Insert Figure 1 about here

For purposes of statistical analysis, the experimental design is divided into two parts. Part 1 is a classic between-groups design with repeated assessment (before-after) including a treatment group and a no-treatment control group. Part 2 is a within-groups longitudinal design, since both groups have received the treatment by Time 3. Two sets of complementary statistical analyses were conducted in order to examine the overall pattern of findings. Between-group analyses took advantage of the rigorous research design using a randomized control condition, but with a small sample size, statistical power was limited. Repeated measures (within-group) analyses examined changes over time with the groups combined. This provided more statistical power by allowing participants to serve as their own controls thereby reducing error variance. However, these analyses do not make use of a comparison group or control for practice effects. Since the within-groups analyses were conducted within the context of the Part 1 between-groups design, they can be interpreted as supporting or confirming results obtained there. At each assessment, participants were administered the same battery of self-report measures and neuropsychological tests.

Treatment

Treatments were administered using the J&J Enterprises I-400 EEG biofeedback system (Poulsbo, WA). The I-400 was connected to a Synetic Systems light generator PC board driving LED embedded glasses (Seattle, WA), which were also linked to a 486 DX2-66 PC running proprietary software developed by the fourth author (Flexyx, Walnut Creek, CA).

Participants received 25 sessions of treatment administered over a 5-8 week period. Treatment sessions were conducted by the third author at her outpatient office. During FNS treatment, participants sat comfortably with their eyes closed, wearing the LED embedded glasses, and engaged in no specific activity. Each patient's dominant EEG frequency, between 1 and 30 Hz, was extracted every 0.5 seconds and used to reset the frequency of the LEDs, which pulsed simultaneously in front of the left and right eyes. Feedback was administered in periods of 18 seconds duration. The strobe frequency was offset from the dominant EEG frequency in the range of +5 Hz to +20 Hz. The magnitude of the offset changed every 18 seconds, and the maximum strobe frequency was set at 30 Hz. All stimulation was minimized in brightness to lowest available level, and participants were unable to detect the LED output even when their eyes were open.

The first session was an introductory session during which a single electrode was placed at the FPZ site (the middle of the forehead between the eyes). EEG recording began with 1 minute of no stimulation, followed by up to 4 minutes of stimulation, and a final minute without stimulation. The subsequent few sessions were mapping sessions during which 18 seconds of stimulation were administered with monopolar EEG recording at each of 21 sites. This yields approximately 6 minutes of stimulation. If a movement artifact was detected, the time at that site was repeated in order to obtain accurate data. Average amplitude and variability of the EEG were recorded in both delta and alpha frequency bands at each site and used to create a sort sequence from lowest amplitude and variability to highest.

During remaining sessions, FNS treatment was administered following the delta activity sort sequence. Each site was treated in the following way. The reference electrode was applied to the left earlobe, the skin was prepared, and impedance was reduced to 3K Ohm. Then, the active lead was applied to sites successively, as specified in the delta activity sort sequence, and feedback was administered at each site. Although we attempted to standardize the amount of stimulation provided during treatment sessions, the exact duration of feedback during each session was based on participants' reactions. Some participants were quite sensitive to the feedback, and the duration was reduced in these cases. Participants' reactions changed over the course of treatment, and duration of feedback was modified accordingly. Therefore, the duration of stimulation received during an individual session ranged from 5

seconds to 20 minutes. Four participants received feedback for an average of less than 5 minutes per session. For other participants, feedback averaged between 10 and 15 minutes per session.

Results

Between-Groups Analyses

Analyses of covariance (ANCOVAs) were conducted to compare groups after only the immediate treatment group had received FNS treatment (see Time 2 in Figure 1), while controlling for baseline differences. Group means and standard deviations are found in Table 1. Because this was the first controlled evaluation of FNS, we did not want possible effects of treatment to go unnoticed. Therefore, alpha was set at .05 and was not adjusted for multiple tests. For the self-report measures, four ANCOVAs were conducted initially. The treatment group was significantly improved compared to the control group on the individualized rating scale (F=12.38, p<.01), and the Beck Depression Inventory (F=10.01, p<.02). Between-group differences were not significant for the total score on the Multidimensional Fatigue Inventory (p<.09), or the Positive Symptom Distress Index of the SCL-90 (p<.19). However, the MFI was designed with 5 independent subscales, which we analyzed separately to determine if there were between-group differences only for some of them. The treatment group was significantly improved compared to the control group on the General Fatigue (F=8.04, p<.02), and Mental Fatigue (F=9.10, p<.02) subscales. No significant differences were noted for Physical Fatigue (p<.13), Reduced Activity (p<.64), or Reduced Motivation (p<.20).

Insert Table 1 about here

Similar ANCOVAs were conducted for the neuropsychological measures. The treatment group was significantly improved compared to the control group on Digit Span Backwards (F=5.37, p<.05), the interference trial (F=5.54, p<.05), and the delayed recall trial (F=7.47, p<.03) of the AVLT, and the most difficult trial of the PASAT (F=8.08, p<.02). In addition, the results approached significance for Digit Symbol (F=3.64, p<.09) and the first immediate recall trial of the AVLT (F=4.52, p<.07).

Within-Group Analyses

Repeated measures analyses of variance were used to examine changes over time. Data were used from three assessments: pre-treatment (just prior to treatment), post-treatment (just following treatment), and follow-up (the next subsequent assessment). The two groups (immediate treatment and delayed treatment control) were combined for these analyses, because all participants had received treatment before the third assessment. Means and standard deviations are found in Table 2.

Insert Table 2 about here

ANOVAs showed significant improvement over time for each self-report measure except the reduced activity and reduced motivation subscales of the Fatigue Inventory, which were less problematic for participants. Even prior to treatment, they remained motivated to participate in activities, despite their fatigue. Among the fatigue subscales, participants reported the greatest improvement in their mental fatigue. Most neuropsychological measures showed significant improvement over time.

If the repeated measures ANOVA was statistically significant for a measure ($p<.05$), then the within-subjects contrasts were examined to determine when changes occurred. Of particular interest were the hypotheses that improvement would occur following treatment and be maintained at follow-up assessment. Significant improvement was observed following treatment for almost all self-report measures, including the Fatigue Inventory total score and the Positive Symptom Distress Index, for which the differences between the immediate treatment and delayed treatment groups failed to reach significance. Results for the Fatigue Inventory subscales confirmed the results of the between-groups analyses. For the neuropsychological measures, there was significant change from pre-treatment to post-treatment for Digit Span Backwards ($p<.01$), Digit Symbol ($p<.05$), and the first ($p<.05$), third ($p<.01$), and fourth ($p<.001$) trials of the PASAT. Overall, these findings support and extend the results of the between-groups analyses. Treatment gains were maintained from post-treatment to follow-up, and in some cases further improvement was observed. Participants reported even less emotional distress at follow-up on the Positive Distress Symptom Index ($p<.05$). Performance improved on a number of neuropsychological measures, and many scores were significantly better at follow-up than pre-treatment (see means in Table 2). Thus, participants did not experience a reversal of symptoms following the end of treatment, and continued improvement was observed for some measures.

Clinical Observations

Table 3 presents a summary of outcomes and selected participant characteristics. Four of the participants had been through extensive rehabilitation programs, three of them as inpatients. Prior to treatment, all 12 participants reported difficulty with their ability to work or complete academic courses. Following treatment, 7 of them were able to work professionally or engage in full academic work. Two other participants reported improvement in some areas following FNS treatment. Three people did not respond to the treatment. Three participants had very low amplitude resting EEGs, including two of the three who did not report much improvement. Clinical experience suggests that people with severely low amplitude EEG require a different treatment protocol than was used in this study.

With treatment, 2 of 8 participants who had been taking medications were able to reduce the dosage for these prescriptions and 3 were able to eliminate them entirely. Three had no change and 4 were not taking medication. For 15 years, one person had required large doses of pain medications as well as weekly walk-in clinic or emergency room visits to manage post-traumatic migraine headaches. After 9 treatments, the headaches were gone, pain medications were greatly reduced and mild headaches, which were responsive to over-the-counter medication, subsequently recurred less than once a month. One person with post-traumatic fibromyalgia substantially reduced medication by the end of treatment. After eighteen months, she still required only low doses of medication and was working full-time.

Insert Table 3 about here

Safety

FNS is generally safe, however, the most common side effect experienced during treatment was a temporary intensification of symptoms that had previously been problematic. Many of the participants experienced again symptoms that had occurred at the time of the TBI. Symptoms included pressure in the head or headache (3 people), dizziness (4 people), nausea (1 person), tingling sensation (1 person) or physical pain associated with broken bones or other injuries occurring at the time of the accident (2 people). Such reactions usually occurred within the first 6 or 7 sessions and typically resolved within a few days. Adverse reactions may also be caused by over-treatment. At each session, participants were asked about their reactions to treatment in order to determine the length of the next treatment session. Fatigue (3 people) and restlessness (1 person) were the most common indications of over-

treatment and session length was reduced accordingly. Following treatment, one person reported unexplained hair loss.

Discussion

The overall pattern of results from this preliminary investigation strongly suggests that Flexyx Neurotherapy System (FNS) may be an efficacious treatment for people who have experienced a traumatic brain injury. Compared to a wait-list control group, FNS treatment produced significant improvement in depression and a range of other symptoms reported by participants as most problematic. Treatment also produced significant improvement on some measures of cognitive functioning, specifically those involving working memory, immediate memory of new material, and retention of information. Results for other measures also indicated improvement, but failed to reach statistical significance. Longitudinal analyses of all participants receiving treatment supported and extended these findings. With the added statistical power afforded by repeated-measures analyses, significant improvement was observed for additional self-report and cognitive measures. Follow-up assessments showed clearly that improvements were maintained following the end of treatment. Although there were not any substantial delayed effects of treatment, some small continued improvements were noted.

The lack of significant findings for some measures suggests several possibilities. First, if the effect size is smaller for these measures, this sample may have been too small to detect the effect of treatment. This possibility is supported by the observation that a greater number of measures achieved statistically significant results when analyses with more statistical power (e.g. repeated-measures analyses) were used. Second, some of the neuropsycholgical tests used may not have been sensitive enough to detect changes experienced by study participants. Specifically, measures often fail to capture the complexity of a real-world environment that places multiple simultaneous demands on cognitive processing. Third, FNS treatment may be more effective for treating some symptoms than others. Fourth, practice effects on some neuropsychological measures may have been strong enough to obscure improvement produced by treatment. Fifth, variability in location and severity of damage to the brain may have obscured improvement as measured by average group scores, because changes were experienced by only some of the participants.

Efforts were made to reduce practice effects that result from multiple exposure to the same content. Alternate word lists were used for the AVLT. Sequences in digit span backwards and digit symbol cannot be memorized. However, practice effects still occur from increased familiarity with the process of each test. People develop better strategies for handling these tasks, particularly the participants in this study who generally had a high level of functioning prior to their injuries. Therefore, improvement in scores on neuropsychological measures may be due to repeated exposure to tests rather than effects of treatment. This is a difficult issue that impacts any research in which multiple assessments are required. In this study, the results of the within-groups analyses must be considered in the context of the between-groups design, which controls for practice effects by including a wait-list control group.

Because this study was among the first experimental examinations of the effects of FNS, we did not want to overlook any potential benefits of treatment. Therefore, given the small sample size, alpha level was not adjusted for multiple statistical comparisons. Nonetheless, the number of findings that reached statistical significance was greater that would be expected by chance.

The research design used in this study does not eliminate the possibility that participants improved simply because they believed that action was being taken to help them, rather than as a result of the specific treatment administered. This phenomenon of positive response to an intervention regardless of its content has been termed the Hawthorne effect, and was first described in studies with non-injured people performing repetitive low-skill tasks. The Hawthorne effect is almost certainly a minor explanatory factor in this study, however, because simple attention is

unlikely to have a substantial long term effect on individuals who have experienced brain injuries and who have reached a stable performance plateau after receiving prior medical treatment and rehabilitation. Many of these participants experienced improvement with FNS after other interventions had failed to benefit them. Nonetheless, a placebo control group or a control group involving irrelevant attention will eventually be needed to completely eliminate attention as an explanatory cause of improvement, and should be included in future research on FNS.

It is important to note that clinical observations made by participants and therapist during the course of the study indicated that meaningful change occurred in many areas. Several participants were able to return to work or academic study following treatment. Generally, reports indicated improvements in quality of life, some of which were profound. However, there were three people (25%) for whom improvement was minimal. Clinical efforts are already underway to identify those people who may require a different FNS treatment protocol, or for whom FNS may not be appropriate.

Taken as a whole, the findings of this study are strong enough to identify FNS as a promising new treatment for traumatic brain injury, which merits further evaluation. The mechanism of action is unclear, but other research suggests that normalizing EEG activity is associated with benefits in cognitive and behavioral functioning.[3,12] Subsequent studies should use a larger sample and a more comprehensive assessment battery that includes quantitative EEG as an objective measure of change in addition to cognitive and functional measures. A more homogeneous group of people with regard to severity of injury, time since injury, and presenting problems would also be beneficial. Recently developed improvements in FNS technology will also enable the use of a double-blind procedure with a placebo control group, which will increase the quality of subsequent research. Such research will provide a clearer picture of the benefits of FNS in the treatment of traumatic brain injury and help determine which symptoms are most responsive to FNS and what circumstances optimize treatment outcome.

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Table 1

Means and Standard Deviations for Time 1 and Time 2 Assessments by Group

	Immediate Treatment Group		Delayed Treatment Control Group		
	Time 1	Time 2	Time 1	Time 2	
Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F
Symptom average	8.47 (1.31)	3.80 (2.38)	8.49 (0.91)	7.62 (0.96)	12.38**
Beck Depression	22.50 (9.89)	7.00 (5.25)	16.67 (9.81)	16.17 (12.19)	10.01*
Fatigue Inventory Total	74.83 (20.43)	48.50 (20.89)	61.50 (18.85)	61.33 (20.58)	3.68†
General Fatigue	17.17 (4.02)	9.83 (4.83)	14.83 (4.17)	14.00 (4.56)	8.04*
Physical Fatigue	16.00 (6.23)	10.00 (3.52)	10.50 (4.51)	10.83 (5.34)	2.88
Reduced Activity	14.33 (5.57)	11.33 (5.35)	10.67 (4.68)	10.83 (4.96)	0.24
Reduced Motivation	10.17 (4.75)	7.00 (2.83)	10.00 (3.90)	10.00 (4.86)	1.99
Mental Fatigue	17.17 (3.31)	10.33 (6.31)	15.50 (3.83)	15.67 (3.50)	9.10*
PSDI	2.42 (0.58)	1.65 (0.24)	1.96 (0.29)	1.82 (0.40)	2.04
AVLT trial 1	6.83 (2.64)	8.17 (1.94)	5.17 (1.72)	5.33 (1.63)	4.52†
AVLT trial 2	10.17 (3.19)	10.50 (2.26)	8.33 (1.75)	8.17 (2.32)	1.54
AVLT trial 3	11.50 (1.38)	12.00 (2.10)	10.67 (1.21)	10.33 (2.07)	1.40
AVLT trial 4	11.50 (2.74)	13.17 (0.98)	12.00 (1.41)	11.33 (2.16)	3.04
AVLT trial 5	12.17 (2.40)	13.50 (1.22)	11.67 (1.21)	11.67 (1.97)	3.26
AVLT list B	5.83 (2.23)	7.17 (1.72)	4.83 (2.48)	5.33 (0.52)	5.54*
AVLT immediate recall	11.00 (1.79)	11.00 (1.67)	8.50 (1.87)	10.00 (2.45)	1.29

AVLT delayed recall	10.33 (2.94)	12.00 (1.79)	9.00 (1.26)	9.00 (1.67)	7.47*

Measure	Immediate Treatment Group		**Delayed Treatment Control Group**		
	Time 1	Time 2	Time 1	**Time 2**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F
PASAT trial 1	25.00 (6.54)	36.17 (11.09)	27.17 (5.56)	33.50 (8.69)	0.45
PASAT trial 2	26.67 (6.09)	32.83 (8.04)	23.50 (6.44)	29.00 (6.03)	0.94
PASSAT trial 3	21.83 (6.49)	28.67 (6.12)	17.67 (6.71)	25.17 (10.30)	0.01
PASAT trial 4	15.83 (4.40)	24.50 (7.64)	17.33 (3.56)	18.17 (8.86)	8.08*
Trails B (in seconds)	78.17 (15.69)	70.83 (32.71)	79.00 (16.73)	71.00 (31.83)	0.01
Rey figure recall	13.79 (3.53)	17.75 (4.13)	16.50 (4.80)	18.75 (5.20)	1.45
F-A-S total	37.67 (15.19)	44.33 (13.09)	29.83 (8.77)	32.83 (8.08)	2.95
Digit Span Backward	6.00 (0.89)	8.17 (2.14)	5.83 (1.72)	5.67 (1.37)	5.37*
Digit Symbol	50.00 (6.96)	61.67 (13.02)	54.67 (14.04)	53.50 (12.28)	3.64†

Note: PSDI = Positive Symptom Distress Index from the Symptom Checklist 90 – Revised; AVLT = Auditory Verbal Learning Test; PASAT = Paced Auditory Serial Addition Test

†$p<.10$; * $p<.05$; ** $p<.01$

Table 2

Means and Standard Deviations with Groups Combined

Measure	**Pre-treatment** Mean (SD)	Post-treatment Mean (SD)	3-Month Follow-Up Mean (SD)	**F**
Symptom Average	[a]8.04 (1.18)	[b]3.65 (2.04)	[b]3.67 (1.86)	34.42***
Beck Depression	[a]19.33 (11.09)	[b]7.92 (6.91)	[b]7.83 (6.74)	18.29***
Fatigue Inventory Total	[a]68.08 (20.78)	[b]50.08 (19.01)	[b]47.33 (20.03)	8.43**
General Fatigue	[a]15.58 (4.42)	[b]11.17 (4.76)	[b]10.45 (5.05)	6.50**
Physical Fatigue	[a]13.42 (6.16)	[a]9.83 (3.33)	[a]9.27 (4.89)	4.02*
Reduced Activity	12.58 (5.35)	10.08 (4.80)	8.00 (4.20)	3.48†
Reduced Motivation	10.08 (4.58)	8.00 (3.64)	7.73 (4.43)	2.72
Mental Fatigue	[a]16.42 (3.34)	[b]11.00 (4.94)	[b]10.73 (4.36)	14.68***
PSDI	[a]2.12 (0.57)	[b]1.53 (0.38)	[c]1.37 (0.35)	18.83***
AVLT trial 1	[a]6.08 (2.23)	[b]7.08 (1.93)	7.33 (2.06)	3.19†
AVLT trial 2	9.17 (2.86)	10.25 (2.05)	10.50 (3.00)	1.66
AVLT trial 3	[a]10.92 (1.78)	[ab]11.83 (1.90)	[b]12.58 (2.19)	4.32*
AVLT trial 4	[a]11.42 (2.35)	[ab]12.50 (1.31)	[b]13.42 (1.88)	3.93*
AVLT trial 5	11.92 (2.11)	12.33 (2.50)	13.17 (1.85)	1.68
AVLT list B	5.58 (1.56)	6.50 (2.20)	6.83 (1.70)	2.97†
AVLT immediate recall	10.50 (2.11)	10.17 (1.90)	12.25 (2.80)	3.26†
AVLT delayed recall	9.67 (2.39)	11.08 (2.54)	12.00 (2.86)	3.42†
PASAT trial 1	[a]29.25 (8.57)	[b]36.42 (8.99)	[b]40.42 (6.01)	13.97***

PASAT trial 2	[a]27.83 (5.91)	[a]31.67 (9.13)	[b]37.08 (8.76)	12.06***
	Pre-treatment	Post-treatment	3-Month Follow-Up	
Measure	Mean (SD)	Mean (SD)	Mean (SD)	**F**
PASAT trial 3	[a]23.50 (8.39)	[b]29.00 (8.02)	[c]32.75 (9.07)	18.48***
PASAT trial 4	[a]17.00 (6.78)	[b]23.75 (8.36)	[b]27.00 (8.95)	13.75***
Trails B (in seconds)	[a]74.58 (24.22)	[ab]67.17 (26.68)	[b]59.92 (20.67)	3.77*
Rey figure recall	[a]16.27 (4.97)	[ab]17.50 (6.39)	[b]19.02 (6.92)	3.43*
F-A-S total	[a]35.25 (11.87)	[ab]38.83 (11.68)	[b]40.50 (11.37)	3.45*
Digit Span Backward	[a]5.83 (1.11)	[b]7.33 (2.19)	[b]7.75 (2.34)	5.80**
Digit Symbol	[a]51.75 (9.69)	[b]59.00 (11.29)	[b]61.16 (11.62)	6.93**

Note: PSDI = Positive Symptom Distress Index from the Symptom Checklist 90 – Revised; AVLT = Auditory Verbal Learning Test; PASAT = Paced Auditory Serial Addition Test

[†]p<.10; *p<.05; **p<.01; ***p<.001

[a] Means with different subscripts differ significantly from each other (p<.05).

Table 3

Participant Characteristics and Outcome

ID	Time Since Injury (yrs.)	Severity of Injury	Very Low Amplitude EEG	Change in Medication	Functional Outcome
1	9.5	Mild	**No**	Eliminated	From working part-time with great effort to working full-time. Adult child with M.D. reported return to pre-injury functioning.
2	7.5	Moderate	No	Eliminated	Able to complete post-graduate courses with less effort.
3	5.5	Moderate	Yes	Not Taking	Little change. Did report improvement in spatial orientation, and was therefore able to travel by subway and car without getting lost.
4	3.0	Mild	Yes	Not Taking	From working in low-skill job to seeking position in pre-injury field of employment.
5	15.0	Mild	No	Decreased	**From no employment to working full-time.**
6	9.0	Mild	No	Not Taking	From no employment to working full-time with good reviews of job performance. Better social relationships due to decreased irritability.
7	21.0	Moderate	No	Eliminated	Able to complete tasks of daily living and to participate in other activities due to reductions in pain and fatigue.
8	7.0	Mild	No	Decreased	Taking required courses in preparation for return to work in professional field.
9	3.5	Mild	No	No Change	Little change.
10	3.0	Mild	Yes	No Change	Temporary improvement that did not persist.
11	5.5	Mild	No	No Change	Reduced anxiety / panic attacks. Little cognitive change.
12	3.0	Mild	No	Not Taking	From taking few college courses and getting low grades to making the Dean's list (3.5 grade point average with full course load). Better social relationships due to decreased irritability.