Real-Time Changes in Connectivities During Neurofeedback

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ABSTRACT. Introduction. Changes in quantitative EEG during and in response to neurofeedback (NF) training was explored in patients with traumatic brain injury (TBI). Data from 19 adults with a TBI of moderate mechanical nature, non-drug-related, and without severe posttraumatic stress disorder or seizure disorder were analyzed (14 male and 5 female).

Methods. EEG was evaluated before, during, and after ROSHI NF training. Data were collected as duplicate samples of 6 min each during eyes open and eyes closed conditions, but only the eyes closed condition was analyzed.

Results. Significant changes in connectivity occurred during and in response to NF training.

Conclusion. Results showed significant changes in real-time QEEG connectivity. An evaluation of a larger subject population will clarify gender differences in connectivity responses to NF training.

KEYWORDS. Acquired brain injury, brain injury, coherence, connectivity, neurofeedback training, NeuroRep, QEEG, synchrony, traumatic brain injury (TBI)

Traumatic brain injury (TBI), the “silent epidemic of our times” (Cernak, 2006, p. 1371), may lead to chronic disabilities. Based on the North American Centers for Disease Control and Prevention (2006), the incidence of new cases of head injury is 300 per 100,000 per year (0.3% of the population) with 1 in 12 cases resulting in death. According to the Centers for Disease Control and Prevention, 1.4 million people per year suffer TBI and an estimated 80,000 to 90,000 became chronically disabled in the United States. The Pentagon has reported that 320,000, or 19%, of the military personnel developed a TBI since 2001 and blast-injury war veterans develop symptoms of TBI even when there is no evidence of physical impairment (Jelinek, 2008). Head injury may be mechanical in nature or due to complex biochemical modifications, which lead to chronic neurological dysfunctions due to neuronal cell loss or diffuse axonal injuries (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001; Vink & Van den Heuvel, 2004). The consequences of TBI are complex and include physical, motor, or sensory dysfunction (paralysis, epilepsy, pain, visual distortion), emotional dysfunction (depression, anxiety, anger, sleep disturbances), and cognitive dysfunction (attention deficit, lack of concentration, forgetfulness).

A TBI of any severity can cause great disturbance intra- and intercortically due
to the diffuse axonal injuries (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Axonal injuries lead to a set of disturbances in the architecture of the fibrous framework of the brain and lead to disturbances in brain connectivity. Clinical EEGs may not detect these abnormalities; however, quantification of spectral activity (quantitative electroencephalograph, or QEEG), may be used to identify these disconnections (Duff, 2004). Randolph and Miller (1988) showed that variability of QEEG is an important discriminant between normal and brain-injured individuals. Referential EEG coherence was found to be a more sensitive EEG measure of TBI (Thatcher, 2000), a two-dimensional level analysis of electrical activity. An alternative method to measure, analyze, and differentiate regions of dysfunction at the intra- and interhemispheric level of electrical communication uses a three-dimensional analysis of EEG coherence (Hudspeth, 1999).

The treatment of TBI from mechanical, chemical, infectious, or vascular etiology includes a variety of approaches including neurosurgery, occupational therapy, physical therapy, speech therapy, psychotherapy, and hyperbaric oxygen in combination with pharmaceutical treatment. Recently, Cernak (2006) reviewed TBI treatments and suggested that once acute interventions are completed there is still a need to address symptoms to minimize “the multi-factorial secondary cascade” (p. 1376) of TBI. Other alternative neuroprotective approaches that have undergone numerous clinical trials include hypothermia, corticosteroids, barbiturates, magnesium salts, dexamethasol, glutamate antagonists, free radical scavengers, and calcium channel blockers to reduce complications (Bayir, Clark, & Kochanek, 2003). Neurofeedback (NF) training has also been evaluated to modify and stabilize EEG activity after TBI. Past approaches previously focused on enhancing or suppressing the magnitude of specific frequency bands (Laibow, Stubblebine, Sandground, & Bounias, 2001; Thornton & Carmody, 2005; Tinius & Tinius, 2000) or to adjust the theta/beta ratio (Lubar, 1995) and to reduce or eliminate specific symptoms (Hoffman, Stockdale, & Hicks, 1995; Randolph & Miller, 1988). Recently, Walker, Norman, and Weber (2002), and Thornton and Carmody (2005) showed that NF could change the measure of brain connectivity called coherence. These results showed changes after training, but changes in coherence during NF training can also be shown in real time as well (Ibric & Hudspeth, 2004). Connectivity changes produced by NF training observed in TBI patients correlated with subjective and behavioral improvements. For example, TBI patients improved on depression and anxiety scores, pain reduction, and overall reduction of symptoms. In addition, the Integrated Visual and Auditory Continuous Performance Test also significantly improved (Ibric, 2004, 2007). The purpose of the present study was to describe changes in EEG connectivity after real-time coherence training. We hypothesize that the disruption in brain connection measures disrupted by head trauma may be normalized through the use of real-time NF techniques.

**METHOD**

**Participants**

Participants were patients referred for evaluation and for NF training. Forty-two participants were selected from a pool of 105 participants who suffered a TBI. The majority of participants experienced one or more TBIs of varying severities over their lifetime due to traffic accidents, infections, physical or emotional trauma, or drug abuse. Of the 42 motor vehicle accidents (MVA) cases, 19 participants were selected after participants were excluded because of multiple head injuries with loss of consciousness, severe symptoms for an extended period, or prescribed heavy medication at the time of this study.

The remaining 19 participants provided written consent (14 male, 5 female). Table 1 shows the demographic data for the participants (49.05 ± 17.77, range = 17–79). Seven participants who experienced only one recent head injury (no longer than 12 months prior the evaluation) were analyzed using the NeuroRep–Compare program. The range of these participants was 25 to 70 years of age.
TABLE 1. Effect of neurofeedback (NF) training on nZ coherence deviations.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>NF Type</th>
<th>a: nZ Score Pre-NF</th>
<th>b: nZ Score During NF</th>
<th>c: nZ Score Post-NF</th>
<th>a–b: Pre/ During Change</th>
<th>b–c: During/ Post Change</th>
<th>a–c: Pre/ Post Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/49</td>
<td>SYNC</td>
<td>137</td>
<td>103</td>
<td>152</td>
<td>34</td>
<td>–49</td>
<td>–15</td>
</tr>
<tr>
<td>4</td>
<td>M/26</td>
<td>SYNC</td>
<td>200</td>
<td>154</td>
<td>119</td>
<td>46</td>
<td>35</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>F/35</td>
<td>SYNC</td>
<td>192</td>
<td>128</td>
<td>234</td>
<td>64</td>
<td>–106</td>
<td>–42</td>
</tr>
<tr>
<td>7</td>
<td>M/79</td>
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<td>228</td>
<td>226</td>
<td>193</td>
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<td>33</td>
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<tr>
<td>8</td>
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<td>19</td>
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<td>19</td>
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<td>SYNCS</td>
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<td>9</td>
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<td>M/17</td>
<td>AOI</td>
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<td>31</td>
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<td>6</td>
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<td>AOI</td>
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<td>AOI</td>
<td>205</td>
<td>106</td>
<td>175</td>
<td>99</td>
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<td>30</td>
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<tr>
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<td>AOI</td>
<td>139</td>
<td>97</td>
<td>113</td>
<td>42</td>
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<td>26</td>
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<tr>
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<td>AOI</td>
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<td>130</td>
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<td>83</td>
<td>19</td>
<td>102</td>
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<tr>
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<td>AOI</td>
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<td>157</td>
<td>170</td>
<td>63</td>
<td>–13</td>
<td>50</td>
</tr>
</tbody>
</table>

Note. M = male; F = female; SYNCS = synchrony training; AOI = alpha only inhibit.

Apparatus

EEG was acquired from a 19-channel Lexicor digital EEG system (Lexicor, Augusta, GA) using an Electro-Cap (Electro-Cap International, Eaton, OH). Electrode impedances were maintained below 5 KOhm. The active NF electrodes were placed on the frontal areas between the Fp1/F7 and Fp2/F8, and were referred to the bilateral mastoid processes (see Figure 1). NF training was provided by a two-channel EEG ROSHI instrument (ROSHI Corp., Los Angeles, CA). Figure 2 shows a therapist screen during the experiment. The screen displays left/right cortex of each individual frequency, from 1 Hz to 16 Hz, with delta and theta bands in blue, alpha in green, and beta bands in red.

Procedure

Eyes closed (EC) and eyes open (EO) EEG recordings (6 min) were obtained prior to, during, and after training. NF training
protocols was developed based upon the results of a pretraining QEEG assessment and depended upon individual deviation in connectivity measures or alpha activity. During training synchrony (sync) was rewarded or not rewarded or alpha frequency not rewarded frontally (see Table 1). To minimize artifact caused by eye movements during the EO condition (Thatcher, Cantor, McAlaster, Geisler, & Krause, 1991), connectivity changes under stimulation were evaluated primarily in the EC condition. After each exposure to the light closed loop-EEG (LCL-EEG) or electromagnetic stimulation closed loop-EEG (MCL-EEG), other recordings were collected. To compare different sources of stimulation, half where first exposed to LCL-EEG followed by MCL-EEG, the other half exposed to MCL-EEG followed by the LCL-EEG. All EEG recordings were visually edited, excluding artifacts prior to analysis for EEG coherence, phase, amplitude asymmetry, relative power, frequency ratios and high-resolution spectra.

This article presents only the NF effects on coherence measures. Results of the QEEG analyses using the NeuroRep program (Hudspeth, 1999) are presented along with normative comparisons. Total coherence z-score deviations obtained for all frequency bands (delta, theta, alpha, and beta) and total spectra are presented. The Compare program was utilized for the connectivity analysis of the group of seven cases who experienced only one recent head trauma.

RESULTS

The dependent variable in this study was the total number of z-score coherence deviations across all frequency bands (nZ score) from normative values for adults during pre-NF, during NF, and post-NF session. Table 1 shows gender, age, training modality, and nZ-scores for coherence during different stages, as well as the differences across training.

Repeated measurements based on three conditions were analyzed. The total nZ scores and standard deviation for the treated group were calculated pre-NF, during NF and post-NF (see Table 2). There was no control group used in this study.

A single factor for repeated measures design was used (Cody & Smith, 1997). The experiment conditions become a second factor to the subject factor resulting in the use of the two-way analysis of variance (Motulsky, 1995). Findings from a two-way analysis of variance showed a significant within condition ($F = 12.21, p < .001$) as well as a significant subject effect ($F = 13.75, p < .001$).

Pre-NF, during NF, and post-NF data had normal distributions (Dragomirescu & Postelnicu, 2002). Dunnett’s one-tailed $t$ test was used to determine a significant difference between conditions (Dunnett, 1955). There was a significant difference across conditions, $F(2, 36) = 12.21, p < .001$, with significant improvement from during NF to pre NF (41.4 nZ differences, $p < .001$) and from
pre-NF to post-NF (23.7 nZ difference, \( p < .01 \)).

Bartlett’s test for homogeneity of variance was not significant, Bartlett’s \( \chi^2(2) = 0.278 \), \( p = .870 \), indicating that the standard deviations were homogeneous with 95% confidence. In conclusion, these results show that NF produces a statistically significant reduction in nZ score deviations in QEEG connectivity. There is a significant decrease in nZ scores for during NF versus pre NF stage. A residual effect is observed in the post-NF stage, versus pre-NF (see Figure 3). Also, as shown in Table 3, female participants responded to a greater degree than male participants in normalizing brain connectivity with neurofeedback (\( p < .02 \)).

**NeuroRep–Compare Pilot Study**

Finally, using the Compare function of the NeuroRep program, limited to 7 participants, allowed identification of changes in connectivity that occurred during NF to pre-NF and post NF to pre-NF. The mean age for this sample analyzed was 51 years. The analyses included the comparison of the nZ scores obtained pre-NF, during NF, and post-NF, and the differences between the connectivity aspects for during to pre and post to pre.

The nZ score for the pre-NF phase, from the sample was 14 (see Figure 4). During the NF training the nZ score was reduced by half, to 7 (see Figure 5). Post NF the nZ score bounced back to 15 (see Figure 6).

The NeuroRep–Compare program was used to analyze changes in coherence that occurred during and post-F. Data points were normalized with a Fisher z-transformation (Fisher, 1921). A False Discovery Rate statistical procedure was also applied (Miller et al., 2001). It is important to note that NF training produced changes at the deficit locations. For example, Figure 7 shows that during NF there is a significant increase in beta coherence (\( p < .02 \)). The changes are primarily over frontal and left temporal-parietal regions, for intrahemispheric comparisons (the highest values for connectivity [+3.2 to +3.0] are at F4-C4 and C4-T4) and interhemispherically between the left and right frontal, and central-parietal areas (Figure 8, lower panel). Post-NF there is a significant decrease in the alpha connectivity over the right frontal cortical area (Fz-F8) and intercortically frontal areas (Fp2-Fp1, Fp1-F4; Fp1-T4 and F3-F8; F3-F4, see Figure 8, lower panel; \( p < .01 \)), whereas beta coherence has become normalized (False Discovery Rate, \( p < .001 \)). NF training changed beta and alpha coherences.

**DISCUSSION**

Results of this study revealed real-time changes in EEG coherence during a single

| TABLE 3. Effect of neurofeedback training on coherence deviation for males and female participants. |
|---|---|---|---|---|
|  | No. | Pre–During | During–Post | Pre–Post |
| Female | 5 | 46.0 | -48.8 | -2.8 |
| Male | 14 | 39.7 | -6.5 | 33.2 |
| \( \rho \) of one-tailed t test | \( \rho \) of one-tailed t test | \( \rho \) of one-tailed t test | \( \rho \) of one-tailed t test | \( \rho \) of one-tailed t test |
| | .33 | .02 * | .04 |
| Bartlett’s \( \rho \) value | .30 | .53 | .56 |

*Significant for one-tailed t test (\( \rho < 0.025 \))
NF training session. Enduring changes in alpha coherence, specifically a decrease of alpha coherence, may have therapeutic indications. When one compares pretraining to posttraining EEG, some coherence abnormalities disappear and new ones appear,

FIGURE 4. Compare function of NeuroRep applied to seven cases at pre-NF shows an nZ score equal to 14.

FIGURE 5. Compare function of NeuroRep applied to seven cases during NF shows an nZ score equal to 7.
FIGURE 6. Compare function of NeuroRep applied to seven cases at post-NF group shows an nZ score equal to 15, a likely rebound effect after training.

FIGURE 7. Compare program reveals from pre-NF to during-NF a significant increase in beta coherence over the left frontal, temporal-parietal regions of intracortical, and inter-cortically between left and right frontal and central-parietal regions ($p < .02$).
though the new abnormalities did not reach significance.

Numerous spectral parameters may be evaluated with reference to a QEEG database (e.g., Thatcher, 2000), and a number of researchers have examined the effect of neurofeedback on TBI in terms of magnitude or coherence abnormalities (Tinnius et al., 2000; Thornton & Carmody, 2005). The TBI patients were also treated with visual and/or auditory guided exercises and results evaluated using cognitive tests, such as IVA (Sandford & Turner, 1995; Sandford, Turner, & Brown, 1993). Alternatively, the NF experience was enhanced by adding sub-threshold photic-stimulation in TBI patients (Schoenberger, Shif, Esty, Ochs, & Matheis, 2001). Improvement or complete elimination of symptoms over time, using the enhanced type of NF by LCL-EEG or Magnetic-EEG stimulation, have been reported and published (Ibric & Davis, 2007).

Widespread loss of cerebral connectivity is considered to underlie the failure of brain mechanisms that support communication and goal-directed behavior following severe traumatic brain injury (Schiff et al., 2007). Disrupted connectivity may be corrected or improved through the use of NF techniques.

The information collected as electrical activity of the brain can be processed and Eigenimages (NEI) analyzed against a normative database. The analysis is enhanced by using the Compare function of the NeuroRep program applied to groups of individuals treated similarly.

The results are based on the neuroplasticity of the nervous system. NF contributes to the neuro-neuronal rehabilitation (Hudspeth, 2001). By changing connectivities between specific working modules (Luria, 1973; Walker, Kozlowski, & Lawson, 2007) of the brain that have been impaired by TBI, NF contributes to the correction of those particular associated impaired functions. This has been proven in the past by others who evaluated the modification of coherence after a group of NF sessions (Thornton, 2000). We are now showing that the changes produced by NF, measured in real time, appear to

FIGURE 8. Compare program reveals from pre-NF to post-NF a significant decrease in beta coherence overall ($p < .001$) and a significant decrease in alpha coherence over the right frontal area and intercortically for frontal and temporal-parietal regions ($p < .01$).
produce permanent changes even after only a single session. Changes in connectivity, after repeated NF sessions, also correlated to symptom reduction such as correction of cognitive, emotional and physical dysfunctions, as previously reported (Ibric, 2006; Ibric & Hudspeth, 2004).

More invasive techniques, such as deep brain stimulation have shown an acceleration of recovery or improved functional outcome in TBI patients who had “disorders of consciousness that persisted for longer than 12 months after severe traumatic brain injury” (Schiff et al., 2007, p. 602). By comparison, NF is a noninvasive technique that can aid in the rehabilitation of the central nervous system posttrauma and its results based on operant conditioning. To draw a conclusion regarding gender influence on the NF outcome in TBI participants, a larger sample population must be evaluated.

The present study presents real-time changes in coherence, an important parameter of brain functionality. Dysfunctions associated with head trauma were partially normalized through NF for this small group; however further studies of larger sample populations are warranted.

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