alzheimer's association

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INTERIM

Scientific Progress Report

Institution	Brown University
Project Title	Efficacy of qEEG Neurocognitive Training in Early-Stage Alzheimer's Disease
Principal Investigator	Elena Festa Martino
Alz. Assoc. Grant #	IIRG-07-59553
Institution Grant #	5-29223
Grant Period	9/1/07 – 8/31/08
Reporting Period	9/1/07 – 8/31/08
Year	1
Report Due	9/1/08

REQUEST FOR SCIENTIFIC PROGRESS REPORT

The scientific progress report due to the Alzheimer's Association should contain the sections highlighted below. When compiling the report, please use the previous page (top sheet of this request). Questions should be addressed to the applicable Post-Award Specialist:

IIRG, **Hatfield** and **Temple** Awards contact:

Mary Grilli, Post-Award Specialist, at 312-335-5727, e-mail: Mary.Grilli@alz.org

ETAC, **NIRG**, and **Zenith** Awards contact

Rita Freeman, Post-Award Specialist, at 312-335-5727, e-mail: Rita.Freeman@alz.org

CONTENTS

1. NARRATIVE

Provide a clear, concise narrative account (3-5 pp.) of the overall progress of the project, including results obtained to date and a comparison of actual accomplishments with the proposed goals for the reporting period. A discussion of any problems encountered or significant research developments should be included. The narrative should be written at the "Scientific American" level; technical detail, tables, figures, video tapes, CDRoms may be included/attached as Appendices. *Number the first page of the narrative as* page 1. **At the end of the narrative, include** a **section with Future Aims. This same section should also be included as the first section of the following year's interim/final report, providing continuity of grant progress.**

Overview

The overall goal of this project is to investigate the efficacy of quantitative electroencephalographic (qEEG) neurofeedback training (NFT) as a rehabilitative behavioral intervention for patients with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). Findings from this project should provide information about the potential of this intervention to not only delay progressive deterioration but also make real improvements in current cognitive functioning of MCI and AD patients. The data from this project should also contribute to our understanding of the relationship between changes in neurocognitive function and in the underlying neural activity associated with aging and the progression of MCI to AD.

For this project, we proposed to examine MCI and AD patients over a one-year period, in order to evaluate the relative effectiveness of two different NFT protocols: 1) a coherence reinforcement schedule specifically targeting the cortical disconnectivity associated with AD and 2) a power spectra ratio schedule that has been previously used effectively to ameliorate cognitive deficits in other patient populations. Outcome measures include changes in: 1) qEEG measures of targeted brain activity; 2) standard neuropsychological tests of cognitive function and mental status; and 3) neurocognitive tasks developed in our lab to assess specific cognitive processes (i.e., sensory integration, spatial orienting of attention, alerting, and working memory). Participants are assigned either to an experimental real-NFT group or to a demographically-matched mock-NFT control group.

In this first year of the project, we determined that it was necessary to first evaluate and establish the short-term effectiveness of the proposed NFT protocol before initiating the year-long longitudinal study. We therefore received approval from Brown's IRB for an addendum to our project to test participants on a shorter-term study in which 8 NFT sessions are administered across a 4-6 week time period. Changes in the outcome measures are then evaluated prior to and after the training. To date, we have tested a total of 26 participants in this study; the demographic characteristics of these participants are presented below. The participants in the pilot groups received an earlier version of the training protocol which was subsequently modified and administered to the participants in the real and mock-feedback groups. The summary of results described below is from data obtained for these latter two healthy elderly groups.

Demographic information of participants in Year 1 of the project

Group	n(m, f)	Age, y (SD)	Ed, y (SD)	MMSE (SD)	RBANS (SD)
Pilot EC	3(0,3)	59.0 (5.3)	18.3 (0.6)	29.3 (0.6)	116.3 (11.7)
Pilot MCI	3(0,3)	71.7 (10.7)	11.3 (1.2)	27.0 (1.4)	79.7 (4.0)
Pilot AD	4(2,2)	74.8 (12.5)	14.0 (1.6)	17.5 (4.2)	56.7 (4.0)
Real EC	9(1,8)	72.1 (8.3)	16.4 (3.9)	28.7 (1.3)	107.1 (12.4)
Mock EC	7(1,6)	71.3 (9.4)	15 (2.4)	29.1 (0.9)	109.1 (11.5)

Note: MMSE = Mini-mental state examination; RBANS = Repeatable battery for the assessment of neuropsychological status; GDS = Geriatric depression scale

<u>Results Obtained to Date</u>

Normal aging is accompanied by a slowing or decline in cognitive functioning, with a particular decline in attentional processes. The present validation study specifically examined the efficacy of our proposed neurofeedback training protocol in improving neurocognitive measures of attention in normal aging. Sixteen healthy elderly participants participated in this study: Nine received real-time feedback linked to their individual brain activity *(real-NFT group)* and seven received playback recording of the feedback from the recording of the actual feedback obtained from a demographically matched participant in the real-NFT group *(mock-NFT group)*. The neurofeedback was based on a global z-score protocol through which participants trained to normalize quantitative brainwave parameters that existed outside of a threshold as determined by a normative database. All participants were administered 8 NFT sessions across a 4-6 week time period and changes in the outcome measures were evaluated prior to and after the training

In the assessment sessions, a battery of neuropsychological tests, neurocognitive tests of attention and sensory integration, and 5-minute EEG recordings of resting brain activity (closed eyes) were obtained. Within each training session, mood and arousal measures and 5-minute EEG recordings of resting brain activity were obtained immediately before and after the 10-minutes of training. We are currently still analyzing a number of the outcome measures obtained within the assessment and training sessions. The data reported in this report include changes in the behavioral assessment measures obtained from: 1) Visual Search tasks examining selective attention and the integration of featural information both within (i.e., luminance and motion) and across (i.e., color and motion) cortical visual streams; 2) A hybrid Covert Orienting/Simon Interference task examining the component attentional processes of alerting, orienting, and executive control; and 3) the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a standardized neuropsychological assessment tool measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory;

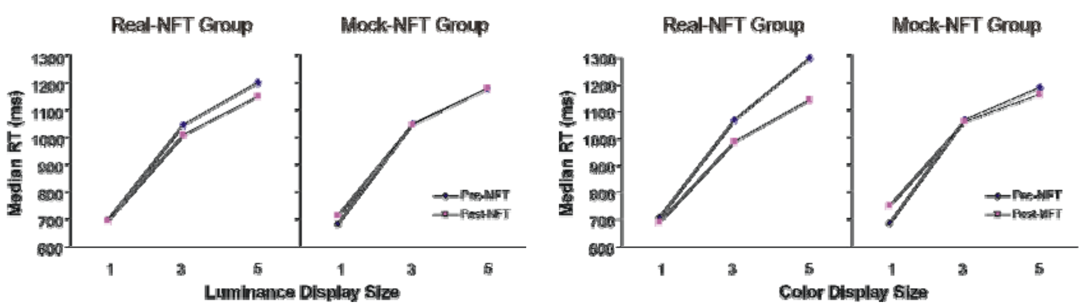
As described below, neurofeedback did not simply produce a general improvement across all tasks (e.g., improvement in overall reaction time), but rather selectively improved specific component cognitive processes. In particular, participants' performance was significantly enhanced under conditions that were primarily sensitive to the efficiency of processing within posterior sensory and attentional cortical networks, while no changes in performance were seen under conditions which relied upon selective attention and executive control processes associated with more anterior cortical networks.

1. Visual Search: Selective Attention and Sensory Integration

The status of selective attention was assessed in a visual search paradigm in which subjects must search for and detect the presence of a target embedded within an array of irrelevant distractor items. When the location of the target within the display is uncertain, the response time to detect the target typically increases with increasing number of distractor items. The magnitude of this increase reflects the efficiency of subjects' selective attentional processes.

Two visual search tasks identical in selective attention demands but differing in sensory integration demands based on the nature of the features defining the target (i.e., motion + luminance vs. motion + color) were administered. Because motion and luminance are processed within the same dorsal visual pathway while color is processed in the ventral visual pathway, the binding of motion with color information requires greater integration demands than the binding of motion with luminance information. In both tasks, search displays consisted of 1, 3, or 5 items randomly positioned on an imaginary circle around a fixation point. Half the displays contained a target; subjects were instructed to press a response key only when they found a target in a display.

As expected, response times increased for both groups and for both search conditions as the attentional demands increased with increasing display size. More importantly, there was a significant selective improvement in response times for the real-NFT group in the color task but not in the luminance task, suggesting that NFT selectively enhanced sensory integration but not selective attention per se in these search tasks. (See Figures below.)

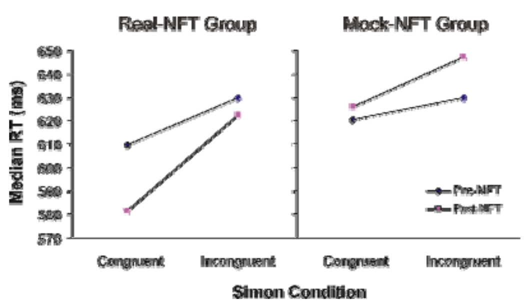


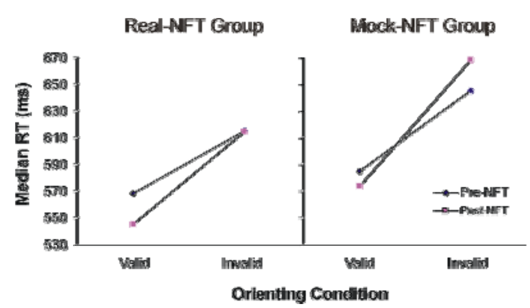
2. Covert Orienting/Simon Interference Task

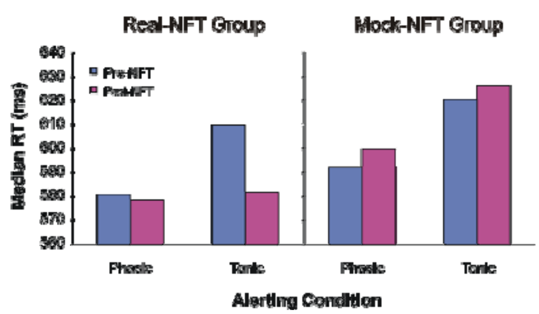
The Covert Orienting task assesses: 1) subjects' efficiency in automatically shifting spatial attention to a valid peripheral cue and disengaging attention from an invalid peripheral cue; and 2) the integrity of the phasic and tonic arousal attentional systems in detecting targets under non-predictive neutral and no cue conditions, respectively. The Simon task provides measures of executive control by comparing performance on trials in which the correct response is either spatially congruent or incongruent with a prepotent response. The hybrid Covert Orienting/Simon Interference task developed in our lab provides an efficient means for assessing these processes.

Subjects were shown a series of trials in which the target spatial word (LEFT or RIGHT) was presented in one of two boxes on either side of the fixation cross. They were instructed to respond to the spatial word, not the spatial location of the target (which could be either congruent or incongruent with the word information), by pressing one of two response buttons as quickly but as accurately as possible. To examine the effects of orienting on responses latencies under congruent and incongruent target conditions, subjects were presented with valid, invalid, neutral, or no cue information regarding the spatial location of the subsequent target stimulus in each trial.

For the real-NFT group, there was a selective improvement in the congruent trials of the Simon task and the valid trials of the Covert Orienting task, but no change in either the incongruent or invalid trials of the two task conditions. The opposite pattern emerged with the mock-NFT group, with participants demonstrating instead a selective impairment in the incongruent and invalid trials, but no change in either the congruent or valid trials. Finally, a selective enhancement in the tonic alerting cue condition, but no change in the phasic alerting cue condition was observed in the real-NFT group (See Figures below.)

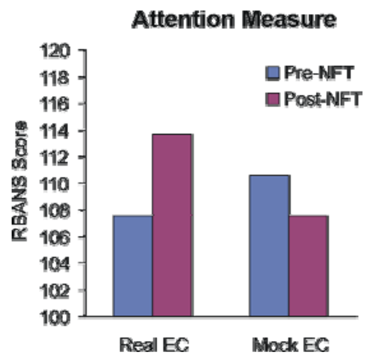






3. RBANS

This standardized neuropsychological test is designed to be a stand-alone assessment battery for the detection and characterization of dementia in the elderly. Versions A and B of the test were administered to each participant both before and after neurofeedback training, with the order counterbalanced across subjects. There was no effect of training on the overall total score. However, when we examined the specific components of the RBANS test, we found a significant selective improvement in the Attention sub-score measure for the real-NFT group (See Figure below).



Summary of Results

The proposed NFT protocol was found to selectively improve some but not other component cognitive processes in healthy elderly subjects: Performance was significantly enhanced under conditions that were primarily sensitive to the efficiency of processing within posterior sensory and attentional cortical networks, while no changes in performance were seen under conditions which relied upon selective attention and executive control processes associated with more anterior cortical networks. Taken together, these results indicate that the proposed NFT protocol is indeed effective in inducing improvements in specific aspects of cognitive functioning in healthy elderly.

Future Aims

Overall, we have made substantial progress during the past year. Having now demonstrated the efficacy of our proposed neurofeedback training protocol in selectively improving several neurocognitive outcome measures of attention in normal aging, we are ready to begin enrolling patients in the longer version of the study. In this way, we will be able to evaluate both the short-term and long-term effectiveness of this behavioral intervention within the targeted patient population. In Year 2, we plan to complete data collection and analyses of the other outcome measures from the short-term NFT study in order to submit these findings for publication. We also plan to begin enrollment of patients in the longer protocol. In order to achieve our goals for the next year, we intend to hire a full-time research assistant to work on the project. In anticipation of this need to hire a full-time assistant in Year 2, we reserved funds from year 1's budget to cover the additional costs associated with Year 2. The hiring of a qualified research assistant responsible for patient scheduling, patient testing, and data management for the longer longitudinal protocol is critical for the success of this project, and we are requesting that the remaining Year 1 funds to be carried forward into Year 2.

2. OTHER SUPPORT AND PERSONNEL CHANGES

Provide current information about other research support for senior personnel and personnel changes on this form.

OTHER SUPPORT

Agency	Title	Amount	Project Period	% Effort
NIH	Naturalistic assessment of the driving ability of cognitively impaired elders	$273,733	4/1/07 – 3/31/11	16.7%

PERSONNEL CHANGES

Changes which occurred over the past year should be listed first. Planned changes should be listed next. Indicate the % effort of personnel departing with a "-" and those being added with a "+" .

Name	Degree(s)	Role on Project	% Effort
T.B.A.		Research Assistant	+ 100%

3. NON-TECHNICAL SUMMARY

Summarize your research progress during the reporting period in language suitable for an educated layperson (500 - 750 words). For second-year interim reports, briefly reiterate the progress of the first year. Explain all terms that cannot be simplified. Include background information in the first paragraph. Attach the non-technical summary to the narrative following the "Other Support and Personnel Changes " page.

The overall goal of this project is to investigate the efficacy of quantitative electroencephalographic (qEEG) neurofeedback training (NFT) as a rehabilitative behavioral intervention for patients with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). NFT is a form of biofeedback in which the subject trains to control attributes of brain wave activity through operant conditioning. Given the neuropathological and cognitive changes observed in MCI and AD, NFT may prove to be particularly effective in both populations, and therefore represent a substantial advancement in the treatment of these disorders. Findings from this project should not only provide information about the potential of this novel intervention to both delay the progressive deterioration and make real improvements in patients' current cognitive functioning, but should also provide a better understanding of the relationship between changes in neurocognitive function and the underlying brain activity associated with aging and the progression from MCI to AD.

In the first year of this project, we determined it was necessary to first evaluate and establish the short-term effectiveness of the proposed NFT protocol before initiating the year long longitudinal study. We received approval from IRB for an addendum to our project to test participants on a shorter-term study in which 8 NFT sessions are administered across a 4-6 week time period. Changes in outcome measures are then evaluated prior to and after the training. To date, we have tested a total of 26 participants; 10 were piloted in an earlier version of the training protocol which was subsequently modified. Of the remaining participants, nine received real-time feedback linked to their individual brain activity and seven received playback recording of feedback from a demographically matched participant in the real-NFT group. In the assessment sessions, a battery of neuropsychological tests, neurocognitive tests of attention and sensory integration, and 5-minute EEG recordings of resting brain activity (closed eyes) were obtained. Within each training session, mood and arousal measures and 5-minute EEG recordings of resting brain activity were obtained immediately before and after the 10-minutes of training. In this report, we described the analyses for the behavioral assessment measures obtained from two of the neurocognitive tests assessing sensory integration and attentional processes and the RBANS standardized neuropsychological test measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory.

We found that neurofeedback did not simply produce a general improvement across all tasks. Rather, NFT was found to selectively improve those measures that are sensitive to the efficiency of processing within the posterior sensory cortical network, but not those that relied upon selective attention and executive control processes associated with more anterior cortical networks. Specifically, we found a selective improvement in response times in Visual Search conditions that required greater sensory integration demands and in the conditions of the hybrid Covert Orienting/ Simon Interference task that were associated with consistent sensory-response stimulus mapping, as well as overall tonic arousal level. In addition, we saw a selective improvement in the attentional sub-score measure of the standardized RBANS task. Taken together, these results indicate that the proposed NFT protocol is indeed effective in inducing improvements in specific aspects of cognitive functioning of healthy elderly.

Having now demonstrated the efficacy of our proposed neurofeedback training protocol in selectively improving several neurocognitive outcome measures of attention in normal aging, we are ready to begin enrolling patients in the longer version of the study. In this way, we will be able to evaluate both the short-term and long-term effectiveness of this behavioral intervention within the targeted patient population. In Year 2, we plan to complete data collection and analyses of the other outcome measures from the short-term NFT study in order to submit these findings for publication. We also plan to begin enrollment of patients in the longer protocol. In order to achieve our goals for the next year, we intend to hire a full-time research assistant to work on the project. In anticipation of this need to hire an assistant, we reserved funds from Year 1's budget to cover the additional cost associated with Year 2. The hiring of a qualified research assistant to administer patient testing and to assist in the data analyses for the proposed longer protocol will greatly ensure the ultimate success of this project.

4. PUBLICATIONS

Cite each publication (including abstracts) that has resulted from this grant. *Upload each publication to the pcCentral website**.*
If there are no publications, explain in the publications section of this report. If you have published other AD-related research articles during the reporting period and wish to make us aware of them, please include that information and related publications in an appendix list.

Preliminary findings from this project were presented at an invited talk at the *Association for Applied Psychophysiology and Biofeedback* conference held in Daytona, Florida in May 2008. Findings from this project were presented as senior honors thesis project by an undergraduate Neuroscience concentrator at Brown University. We anticipate submitting the results of the study described in this progress report for publication in Year 2 once we have obtained sufficient number of participants in the study groups.

Presentations:

Heindel, W.C. & Festa, E.K.; Assessing the efficacy of neurofeedback training in aging and Alzheimer's disease: A cognitive neuroscience approach; Association for Applied Psychophysiology and Biofeedback; Daytona, Florida; May 2008.

Posa, A.; The efficacy of neurofeedback training on behavioral and electrophysiological measures in normal aging; Neuroscience Undergraduate Honor's Defense Presentations, Brown University; April 2008.

5. IRB CERTIFICATION, IACUC CERTIFICATION and RECOMBINANT DNA(rDNA) CERTIFICATION

For all grants involving human subjects or vertebrae animals or rDNA an updated annual certification(s) is/are required by the Association as an appendix to the progress report if protocols have been changed substantively from those originally proposed and approved.

In order to first evaluate and establish the short-term effectiveness of the proposed NFT protocol before initiating the year long longitudinal study with patients, an addendum to the protocol was made from that originally proposed. The revised protocol, approved by the Brown University IRB, proposes to evaluate both the long- and short-term effects of neurofeedback training on cognitive and physiological measures in both MCI/AD patient and healthy elderly populations.

6. REPORT SUBMISSION – only online Uploads accepted

INSTRUCTIONS FOR REPORT/PUBLICATION SUBMISSION(S)

To access your award online, download templates for the required reports, and to submit your annual reports; go to the same location that you used previously to submit your application:

https://v2.ramscompany.com/Login.asp

A tutorial for the submission of annual reports as well as other capabilities of the online system for grantees is available at the login page. Scroll down to the tutorial called "Grantee Instructions to access award information" or use the following link in your web browser to download the tutorial directly:

https://v2.ramscompany.com/Instructions_Award_Info.pdf

Follow the instructions in the tutorial to download the REQUIRED scientific progress report and financial report forms to be used for the submission of your annual reports and to attach the completed documents prior to the deadlines listed in your award.

IMPORTANT NOTE: Delinquent reports may cause funding to be terminated on your grant. **It is extremely important that the reports are uploaded on time.

Hard copies of the reports are no longer required. Reports must be uploaded using the new online system.

Questions pertaining to **IIRG**, **Hatfield** or **Temple** Awards contact Mary Grilli, Post Award Grant Specialist

e-mail:	Mary.Grilli@alz.org
Phone:	1-312-335-5727
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Questions pertaining to **ETAC**, **NIRG**, or **Zenith** Awards contact Rita Freeman, Post Award Grant Specialist

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