

Methodology and preliminary data on feasibility of a neurofeedback protocol to improve visual attention to letters in mild Alzheimer's disease[☆]

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ABSTRACT

Background: Brain-computer interface (BCI) systems are controlled by users through neurophysiological input for a variety of applications, including communication, environmental control, and motor rehabilitation. Although individuals with severe speech and physical impairment are the primary users of this technology, BCIs have emerged as a potential tool for broader populations, including delivering cognitive training/interventions with neurofeedback (NFB).

Methods: This paper describes the development and preliminary testing of a protocol for use of a BCI system with NFB as an intervention for people with mild Alzheimer's disease (AD). The intervention focused on training visual attention and language skills, as AD is often associated with functional impairments in both. This funded pilot study called for enrolling five participants with mild AD in a six-week BCI EEG-based NFB intervention that followed a four-to-seven-week baseline phase. While two participants completed the study, the remaining three participants could not complete the intervention phase because of COVID-19 restrictions.

Results: Preliminary pilot results suggested: (1) participants with mild AD were able to participate in a study with multiple assessments per week and complete all outcome measures, (2) most outcome measures were reliable during the baseline phase, and (3) all participants with mild AD learned to operate a BCI spelling system with training.

Conclusions: Although preliminary results demonstrate practical feasibility to deliver NFB intervention using a BCI to adults with AD, completion of the protocol in its entirety with more participants is needed to further assess whether implementing NFB-based cognitive intervention is justified by functional treatment outcomes.

Trial registration: This study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03790774).

1. Introduction

Language deficits, including impairments in comprehension and reading, are often present in early Alzheimer's disease (AD) [1]. Given the complex relationship between language and other cognitive domains, difficulties with language comprehension and expression affect

many areas of daily living and are important contributors to social exclusion [2]. Impairments in reading comprehension affect many functional activities such as taking in news from a newspaper, understanding a book or email, or even working with a computer. Reading difficulties are strongly related to attention and executive function deficits [3]. Since attention is one of the earliest non-memory domains

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affected in AD [4], interventions targeting attention may improve functional areas, such as reading, in people with mild AD.

There is a breadth of behavioral interventions for improving cognitive function both in older adults without known disabilities and in adults with AD. Reviews of intervention practices for cognition in older adults have usually demonstrated domain-specific improvements [5–7], such that training in one cognitive domain (e.g., working memory) does not appear to transfer to untrained domains (e.g., episodic memory) [8]. According to two systematic reviews, training targeting multiple cognitive domains for people with AD has produced mixed results, with some studies demonstrating improvements and others showing no functional change [9,10]. With advancements in technology, computer-based cognitive training approaches that feature interactive components for participants (e.g., video-gaming elements) have been proposed as a possible intervention modality [11–13]. Historically, cognitive interventions train and measure behavioral responses as indices of cognition. A limitation of current behavioral interventions is the lack of real-time neurophysiologic metrics to objectively measure and guide the user's learning.

BCI is a technology that has been developed to enhance, restore, or replace physical or cognitive functioning using real-time invasive or noninvasive recordings of brain signals as an input method to control the technology [14]. For example, the sensorimotor rhythm has been used in BCIs for control of computers, robotic arms, and wheelchairs by individuals with tetraplegia [14]. While much BCI research has involved healthy adults, people with disabilities [15] may directly benefit from BCIs designed to restore or replace physical function. For individuals with severe speech and physical impairments secondary to incomplete locked-in syndrome, spelling BCIs have been designed to use the P300 signal, an endogenous event-related potential (ERP) following a salient stimulus, as a 'keystroke' (intended selection) for communication [16, 17]. In this paradigm, target letter presentations are interspersed with non-target presentations. Perception of the salient target results in an attentional neurophysiological ERP (e.g., P300) signaling the intended target. This task requires the user to employ many cognitive skills, including (but not limited to) sustained visual attention to the screen, remembering the target throughout the task (working memory), selective attention to the targets on the screen amidst non-targets, and divided attention between the presented letters and feedback. As such, training with a P300 spelling paradigm may be beneficial across multiple cognitive domains.

NFB is the delivery of real-time electroencephalography-based (EEG) feedback in response to an elicited behavior. Few clinical NFB studies present cognitive tasks; most of these studies simply provide feedback to a user based on ongoing EEG frequencies such as alpha or theta band power [18,19]. Some NFB studies have used simplistic recording methods, such as a 2-channel forehead strap system that may even be providing feedback based on the frequency of scalp muscle activity rather than brain activity [20]. Other NFB systems may be giving NFB based on simple alertness [21], which is known to affect ERPs [22] and BCI performance [21]. To improve cognitive performance, the use of NFB during performance of a cognitive task can be hypothesized as better than using NFB during a simple rest state. To this end, the described protocol has made efforts to merge aspects of NFB and BCI research. This merger of BCI and NFB is also relevant to BCI research in a broader sense than utility for functional behavioral intervention, since training people to use a BCI system may be facilitated by NFB during BCI use.

While the P300 may be used to guide a BCI's decision-making process for inferring user intent, most P300 speller systems require numerous stimulus presentations to generate a classifiable P300, and thus cannot reliably provide NFB quickly enough on attention to a task. One study has used presentation of a selected letter during use of a P300 speller as a type of behavioral feedback to improve performance at fast presentation speeds, though this approach is an indirect metric of electrophysiological signals [23]. In a later study, the same type of

feedback was used to demonstrate changes in alpha activity at Pz that were suggestive of increased attention during feedback training compared to no-feedback training [24]. As such, utilizing measures of EEG spectra may be a way to improve attention to BCI cognitive demands, particularly for alpha-band activity which has been successfully leveraged for NFB during tasks in previous studies [25,26]. Therefore, calibrating with EEG-based NFB to enhance attention may be an important research direction for improving cognitive performance [27].

There is some evidence of benefits of this training delivery method, including increased visual attention in young adults without disabilities [24] and improvement of attention deficit hyperactivity disorder symptoms in children [28]. Most studies based on recent systematic reviews have focused on healthy older adults [29,30]. One randomized wait-list controlled study of adults without disabilities ($n = 39$), including 24 half-hour sessions of BCI training using a Stroop task, noted slight improvements on the Repeatable Assessment of Neuropsychological Status [31]. A follow-up study with 240 healthy elderly participants did not demonstrate clear improvements in the same cognitive outcomes, but did demonstrate a sex moderation effect such that male participants who completed the intervention improved more than male controls whereas female participants who completed the intervention did not improve more than female controls [32]. The limited number of studies included in systematic reviews that involved people with cognitive impairments (mild cognitive impairment or AD) all had significant weaknesses, including inclusion of NFB as one component of a more general lifestyle intervention [33], use of only a single channel of EEG [34], lack of a control group or multiple baseline assessments to control for learning effects [26,35,36], or use of a simple retrospective analysis of a poorly-characterized group of people of mixed ages with cognitive dysfunction treated with NFB [37]. One study with 65 women with amnesic mild cognitive impairment and 54 female control participants who received NFB in a gamified interface demonstrated significant increases in rapid visual processing and spatial memory tasks compared to those using a gamified interface without NFB [25]. There were two control groups: a treatment as usual (passive control) and an exergame done as frequently as the NFB sessions (active control). The NFB and the active control group both demonstrated improvements in some, but not the same, cognitive outcomes.

This protocol was developed to adapt an existing BCI system, BciPy [38], in order to provide NFB and explore its application to facilitate improvement in attention and reading skills in people with mild AD. Outcome measures were selected to assess targeted skills within the domain of the proposed intervention: selective attention to letters, speed of processing while reading, and working memory while manipulating letters. We hypothesized that NFB training would improve attention to letter processing and other attention-dependent measures related to functional reading. This paper reports on the methodology and preliminary feasibility of utilizing a novel NFB training method for individuals with mild AD.

2. Materials and methods

2.1. Participants

Six individuals with possible or probable AD were recruited as study participants for this protocol funded by the US National Institutes of Health (NIH). Five participants were enrolled in the protocol. One additional participant completed screening but did not enroll in study because of rigor of study visits and activities. The participant number for this study was small but is typical for the planned analysis: a non-experimental within-subject A-B single case research design (SCRD) [39,40]. A conventional randomized controlled trial would be best for demonstrating efficacy of a NFB intervention, given concerns such as motivation to please research personnel in a non-blinded study, payments to participants, and placebo or expectancy effects, a smaller feasibility study was selected [41,42]. Due to safety concerns involved in

continuing to conduct home visits for data collection with vulnerable populations after the start of the COVID-19 pandemic, the study was concluded with complete data from only two participants. These participants, #1 and #2, will be referred to as “completers”. Data collection for the other three participants was discontinued after completion of the baseline phase of the protocol, either before or shortly after the beginning of the intervention phase. Please refer to [Table 1](#) for a description of participants and demographic information.

Participants were recruited from the Oregon Health & Science University (OHSU) Layton Aging and Alzheimer’s Center, which is funded in part as an NIH Alzheimer’s Disease Research Center. Recruitment procedures included chart review, communication with the treating neurologist regarding eligibility criteria for diagnosis of mild possible or probable AD (AD), and a phone screening that consisted of approximately 30 min of questioning to determine eligibility. During this phone screening, participants completed the judgment subtest of the Neurobehavioral Cognitive Status Examination (NCSE) in order to assess capacity to consent to the study procedures [43]. Inclusion criteria were as follows: (1) adults aged 50–100 years old; (2) a diagnosis of AD by their treating neurologist at the Layton Aging and Alzheimer Disease Center, consistent with conventional criteria [44]; (3) a Global Clinical Dementia Rating (CDR) of 0.5 or 1.0 [45]; (4) a Montreal Cognitive Assessment (MoCA) score of ≥ 14 [46] or a Mini Mental State Examination (MMSE) score of ≥ 18 [47] within the previous two months; (5) a mild language impairment attributable to cognitive challenges assessed through clinical impression by either an ASHA-certified speech-language pathologist from the research team (DGM) or behavioral neurologist at the Layton Center; (6) absence of EEG-altering medications (e.g. benzodiazepines); (7) no significant motor, vision, or hearing impairment; and (8) greater than 80% accuracy on at least one of four trials of a practice RSVP task (described below). Study activities were approved and overseen by the OHSU Institutional Review Board (IRB #18984) and registered with [ClinicalTrials.gov](#) (NCT03790774). All methods were performed in accordance with the relevant governmental and institutional guidelines and regulations.

To ensure compliance with the study procedures and facilitate communication and scheduling of study activities, participants were required to enroll with a study partner who also consented to participation in the study. Both participants and study partners provided written informed consent. Study participants were paid at each visit, with a completion bonus paid after follow-up; study partners were not paid for their participation. In order to qualify as a study partner, an individual needed to: (1) have a close relationship with the participant (i.e., spouse, adult child, parent, sibling, or close friend), (2) interact an average of at least 5 hours per week with the study participant, either in person or over the phone, (3) demonstrate capacity to consent as evidenced by a score of ≥ 3 on the NCSE Judgement subtest, and (4) demonstrate low risk of cognitive impairment, as measured by a score of ≥ 31 on the modified Telephone Interview for Cognitive Status (TICS-m) [48].

2.2. Procedure

The study protocol consisted of a within-subject A-B design with multiple data collection sessions both before and during administration

Table 1
Participant demographics.

Participant	Age	Years of Education	MoCA	# Baseline Sessions	# Intervention Sessions
#1	79	16	21	4	18
#2	66	17	29	5	18
#3	53	18	22	4	—
#4	72	18	24	7	6
#5	76	13	19	7	—

All participants were white and non-Hispanic.

of the intervention (hereafter “baseline” and “intervention,” respectively). In the baseline phase, participants received RSVP Keyboard training without NFB. In the intervention phase, the training incorporated NFB. A single follow-up session was conducted 4–5 weeks following the intervention phase. The intervention in the follow up session did not incorporate NFB. All sessions were conducted at either the participant’s home, the Oken Laboratory at OHSU, or a neutral location (e.g., a public library meeting room), according to the participant’s preference. Consistent days of the week, start times, and visit durations were maintained for each participant. Please see [Fig. 1](#) for an outline of study phases and the activities and assessments conducted at each visit; these are described in more detail below.

2.2.1. Study entry visit and outcome measures

The first visit included informed consent procedures, study eligibility questions, and administration of initial summative outcome measures. The summative outcome measures, given once prior to the baseline sessions and once at the final follow-up session, were: (1) the Discourse Comprehension Test (DCT) [49], a measure of listening comprehension, and (2) the forward and backward digit span subtests of the Wechsler Adult Intelligence Scale IV (WAIS-IV), a measure of phonological working memory and attention [50]. The DCT requires a participant to listen to a 150 to 200-word short story and respond to comprehension questions [49]. There are five short stories per test form with eight questions about each story [49]. The digit span subtests in the WAIS-IV require a participant to listen to a sequence of numbers read aloud and repeat that sequence back to the examiner in the same order (forward), in reverse order (backward), or in numerical sequence from smallest to largest (sequencing) [50]. The number of digits in each sequence ranges from two to 16 [50]. Participants answered questions about their health, demographics, and the nature of their relationship with their study partner. Additionally, participants completed a computer-based practice RSVP Keyboard task without use of EEG equipment. This practice task was designed to familiarize them with the demands of the experimental task and to confirm they could demonstrate the requisite skills, including: (1) attending to targets, (2) responding if targets were present on screen, and (3) inhibiting responses to non-targets. Participants were presented with a target letter and asked to attend to the letters in a series of 10 letters in order to answer the question: “Was the target letter in the sequence?”. Five out of 10 sequences contained the target and five did not. Participants were trained from slowest presentation speed (1 Hz) to fastest presentation speed (4 Hz) in four steps (i.e., 1, 2, 3, 4 Hz). At each step, participants were trained to criterion, defined as getting eight out of 10 items correct at a given presentation rate (1 Hz, 2 Hz, 3 Hz, 4 Hz). Participants were provided with up to four chances to train to criterion at a given presentation rate. An exclusion criteria of study enrollment was not achieving 80% accuracy at the 4 Hz presentation rate. No participants were excluded for this reason. This practice RSVP task was repeated at the beginning of each baseline, intervention, and follow up session in order to ensure that participants maintained an ability to complete the task with a presentation rate of 4 Hz.

2.2.2. Baseline visits and outcome measures

Baseline sessions were planned to begin one week after the initial visit and to occur once per week afterward. Participants completed four to seven baseline sessions until there was stable performance of the outcome measures as assessed by visual analysis [51]. During each baseline session, participants completed RSVP Keyboard calibration and copy-spelling tasks [52] using the BciPy software [38] version 1.4.2, as well as repeated measures outcome tasks to monitor progress. The repeated measures tasks were: (1) letter cancellation task; (2) letter span task; and (3) Woodcock Johnson Test of Achievement 4th edition (WJTA-IV) Sentence Reading Fluency Subtest (form A, B, or C) [53]. A description of each task follows. Participants were not excluded due to their performance on these metrics.

For all RSVP Keyboard tasks (with the exception of the practice task),

Study Entry	Baseline							Intervention							Follow-Up
	1	1	2	3	4	5	6	7	1	2	3	4	5	6	1
Consenting	X														
DCT (raw score)	X														
WAIS-IV digit span (raw score)	X														
Practice RSVP task	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RSVP calibration – no NFB		X	X	X	X	X	X	X							X
RSVP calibration – NFB									X	X	X	X	X	X	X
RSVP copy-phrase		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Letter cancellation		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Letter span task		X	X	X	X	X	X	X	X	X	X	X	X	X	X
WJTA sentence reading fluency		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Fig. 1. Study Activities

This infographic depicts the assessments conducted at each visit type and the frequency of their measure across phrases of the study. The dashed lines in the baseline phase represent the variability in number of baseline visits that varied between 4 and 7 visits based on stability of baseline performance from week-to-week.

participants wore a dry electrode cap (Wearable Sensing; San Diego, CA) that measured EEG responses to target and non-target letters (see section on Electrophysiological Recordings and Processing below for more details on EEG recording).

Data were collected on a 17.3-inch ASUS Vivobook Pro N705F laptop (1920x1080 resolution) with a refresh rate of 60 Hz (Windows 10 Pro) with an Intel(R) Core (TM) i7-8565U CPU @ 1.80 GHz CPU, 16 GB RAM, and a dedicated 2 GB NVIDIA graphics card.

In the calibration task, participants were shown a single target letter and asked to search for it in a rapidly-presented series of letters containing nine non-target letters and one target letter. Each letter was presented centrally on the screen, one at a time, at a rate of 3 Hz. The temporal position of the target letter in each sequence was randomly assigned. For each of 100 sequences of letters, participants mentally responded when they saw the target letter on the screen. The intention of this paradigm was to elicit a P300 signal in response to target letter presentations, and to gather data for training a classifier to be used in the copy-spelling task. The calibration task lasted approximately 13 min. The main outcome measure in calibration was Area Under the Curve (AUC), a measure of classification accuracy. Software and specifics related to the BciPy classifier are more fully outlined in Memmott and colleagues (2021). For classification, the software uses a regularized discriminant analysis with 10-fold cross validation to evaluate EEG in the 500 ms epoch following each task stimulus.

In the copy-spelling task, participants were asked to copy a phrase letter by letter (“HELLO_” followed by a word of their choice) by selecting each target letter in the phrase from a stream of non-target letters. Participants were instructed to mentally react to a target letter, as in the calibration task. For each sequence, the system combined EEG evidence with probabilities determined by an integrated language model [52] repeating sequences until one letter reached a probability threshold of 0.80 and was selected for typing. This task demands vigilance to the target for several sequences, as the target letter typically must be selected more than once before the system comes to a decision.

The main outcome measure for the copy-spelling task was whether or not the target word was successfully copied.

The letter cancellation task in this study was adapted from the letter cancellation task used in Baddeley and colleagues (2001), and measured selective attention. Participants were instructed to cross out all instances of a target letter, “Z”, as quickly as possible, in a grid of upper-case letters presented on a standard letter size sheet of paper in 14-point Arial font [54]. There were two forms that varied in difficulty: an easier version with a combination of 10 curved letters as foils (e.g., “B”, “P”, and “R”) and a harder version with a combination of 10 straight letters as foils (e.g., “K”, “M”, and “Y”). Baddeley and colleagues (2001) found that participants with AD took significantly longer on a version with straight letter foils, and proposed that this effect was attributable to the similarities of visual features between the non-target letters and the target letter “Z” [54]. There were 20 “Z” targets on each form out of a total of 150 letters. Target positions were randomized and plotted by assigning random x and y values to a 10 by 15 grid using R version 3.6.1 [55]. Randomly-generated form versions with more than three adjacent targets in a row, column, or corner were rejected. The outcome measure for this task was total completion time (in seconds) corrected for task accuracy (total time/accuracy), as used in other studies.

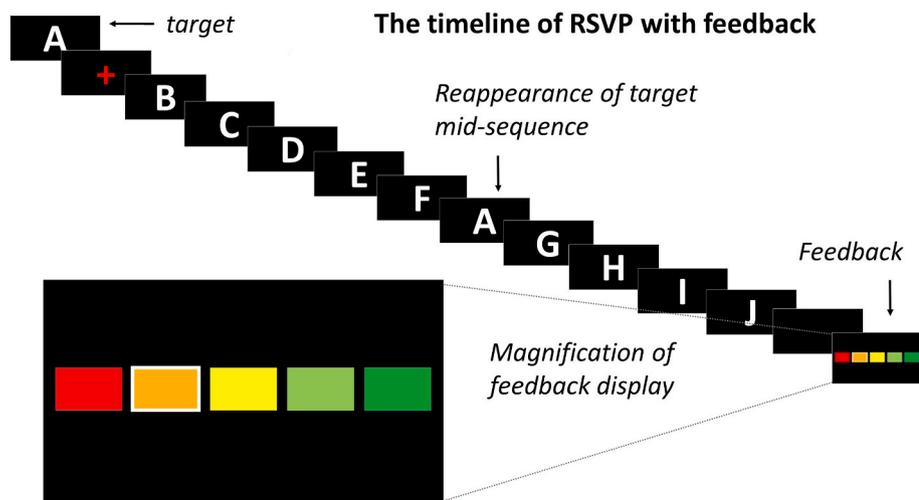
The letter span task in this study, which measures working memory, was adapted from the letter span task used by Conrad and Hull (1964) with task considerations modeled from the WAIS digit span subtest [50, 56]. Participants attended to a sequence of two to eight letters, presented one at a time at a rate of one per second on a monitor, and recite the sequence back to the examiner either in the same order (forward condition) or in reverse order (backward condition). There were two items for each sequence length in the task. The task was discontinued when the participant answered both items for a given sequence length incorrectly. The letter span task was programmed in Python using PsychoPy3 v3.0.0b11 [57]. Strings consisted of only consonant letters to reduce the ability for participants to use a word encoding strategy. Sequences were reviewed by three researchers to remove any consonant

combinations commonly used as acronyms or abbreviated phrases in English (e.g., BRB, HQ, RSVP). Stimulus order was randomized and 15 unique versions were generated to reduce the chance of a repetition learning effect across baseline, intervention, and follow-up weeks for each condition. Participants received unique versions in a randomized order. The outcome measure for this task was maximum sequence length, defined as the longest sequence length where a participant recited at least one of the two sequences correctly.

The well-validated WJTA-IV Sentence Reading Fluency subtest [53] was used to measure processing speed. This subtest requires participants to read as many sentences as possible and answer whether the sentence is generally “True” or “False” in 3 min. Example items include: “Fire is hot”, “Dogs can eat”, and “A school bus has a driver”. To minimize a repetition learning effect over baseline, intervention, and follow up sessions, the order of the three unique test forms was randomly permuted for each participant (e.g., C, A, B, repeating). The outcome measure for this task was the number of items answered correctly in a 3-min period.

2.2.3. Intervention visits and outcome measures

The decision to begin the intervention phase was determined by observation of stable baseline performance on the three repeated outcome tasks and the BCI calibration task as assessed by visual analysis [51], or by the participant reaching the pre-determined maximum of seven baseline sessions. Intervention sessions occurred three times per week for a six-week period, and required participants to complete a calibration task with NFB and a copy-spelling task. In this phase, the standard RSVP Keyboard calibration task from baseline was adjusted to feature an additional NFB display after each 10-letter sequence (about every 3.3 s). This display was onscreen for 2 s and included five colored boxes ranging from dark red (poor attentional performance) to dark green (excellent attentional performance; see Fig. 2). A thick white border around one box was used to indicate to participants their attention rating on the most recent sequence. This feedback display (defined in software as Level Feedback) and task (defined as RSVP Inter-Inquiry Feedback Calibration) were written for this experiment and may be accessed freely in BciPy version 1.4.2. Participants were asked to try and achieve as many dark green (excellent) ratings as possible during each session and to pay increased attention to the RSVP Keyboard sequences if they were given dark red, orange, yellow, or light green ratings. NFB was individualized for each participant and updated weekly based on data from the previous week’s calibration task (see Calculation of Neurofeedback below). To monitor progress, participants completed repeated measures tasks before the calibration and copy-spelling tasks during the third session of each week.



2.2.4. Calculation of Neurofeedback

To quantify attention to the RSVP Keyboard display for NFB, posterior parieto-occipital alpha power was used to measure engagement of visual attention. This signal was used for NFB because: (1) event-related alpha attenuation during visual tasks is associated with mental effort [58,59], (2) alpha power has been used in prior NFB experiments during rest states to improve visual cognition [60], and (3) results of an alpha power pilot study supported its utility for this purpose.

In the alpha power pilot study, participants without known disabilities ($n = 8$, age range 21–65 years) performed a one-back task that required them to press a button to indicate whether a target sequence was present within a longer sequence of ten letters. The target sequence was always the letter N followed by any random letter, followed by the letter A. Non-target sequences were included to increase difficulty, and consisted of the letters N and A separated by either two or zero other characters. While performing this task, participants wore a 24-channel wet electrode EEG system (BioSemi, Amsterdam). Average button-press error rate for the task was 10%, although three participants made fewer than two errors and were excluded from these analyses. For the five remaining participants, EEG frequency analysis of the 2.5-s epoch including each ten-letter sequence revealed a 17% increase in posterior rhythm (alpha) amplitude when participants made errors compared to when they made no errors ($p = 0.013$, Fig. 3). For the three participants who made no errors on the behavioral task, visual inspection of EEG data revealed that they had the lowest amplitude posterior alpha rhythm of the eight participants, further supporting the relationship between visual attention and posterior alpha rhythm.

In the NFB feedback protocol, calibration recordings from all available baseline sessions were reviewed to determine which of five candidate electrode sites (Pz, Oz, P4, PO7, or PO8) recorded the greatest amount of resting artifact-free alpha activity for each participant. Due to poor contact at sites Pz and Oz and excessive electromyography (EMG) artifact at sites Oz, PO7, and PO8 for the first two participants, P4 was selected as the channel of interest for calculating NFB during intervention for the completers, participants #1 and #2. Both participants who completed all study visits consistently demonstrated peak resting alpha activity at approximately 9.0 Hz in both baseline and intervention sessions, therefore, a target frequency band of 8–10 Hz was chosen for NFB. All EEG feedback data were bandpass filtered at 7–20 Hz to minimize interference of both EMG and a 6 Hz harmonic related to the 3 Hz steady-state visually evoked potential elicited by the RSVP Keyboard letter stream. Relative power spectral density (PSD; $\mu V^2/Hz$) was calculated using BciPy’s signal decomposition module with Welch’s method [61] and defined as the PSD of the target band (8–10 Hz) compared to PSD of the wider band (7–20 Hz). From aggregate baseline

Fig. 2. Schematic of the RSVP task and the neurofeedback to the participant.

Following presentation of the target letter there is a sequence of 10 letters presented following a red cross-hair fixation cross. Neurofeedback is based on individualized alpha Power Spectral Density (PSD) percentiles at a pre-specified occipitoparietal electrode. Colored boxes range from upper 15th percentile alpha power in red, 15th - 30th percentile, 30th - 45th, 45th to 70th, and the least alpha power in green from the 70th - 100th percentiles. The current feedback the participant sees is highlighted with the white edges around one colored rectangle. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

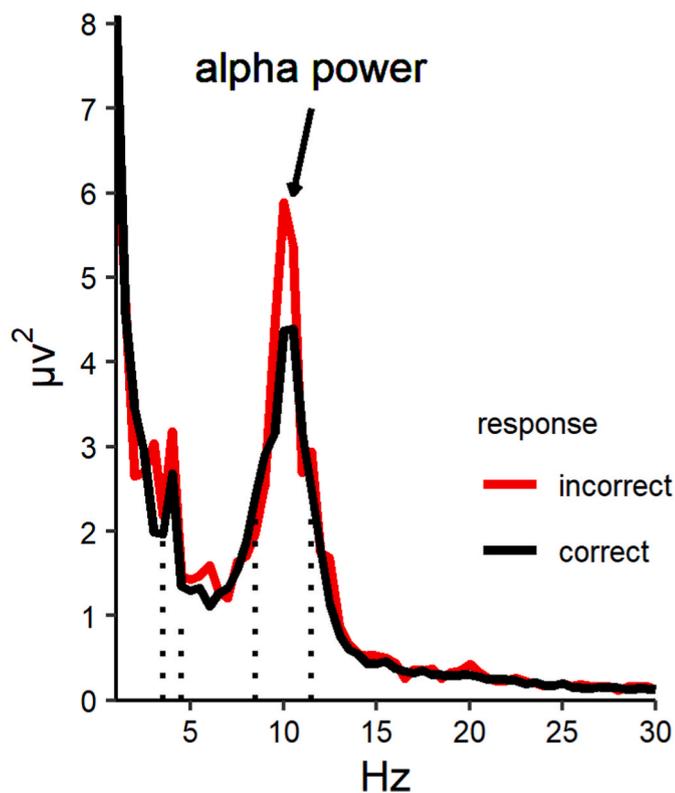


Fig. 3. EEG frequency data from 5 of 8 participants who made errors during pilot task

Spectra are from site Oz, averaged across 2.5 s epochs during sequences where participants either made or did not make recognition errors. Besides the increased alpha power during error trials, note the steady-state visual evoked potential aligned with presentation rate of 4 Hz, which did not change based on error status. The three participants not included in this average because they did not make errors had even lower levels of alpha than the “correct” condition illustrated in the figure.

data within-participants, the 70th, 45th, 30th, and 15th percentiles of relative PSD were set as the NFB cutoffs for the first week of intervention. Specifically, the delineation of the lowest 30% of relative alpha amplitude responses (70th percentile; lower alpha power corresponds to improved attention, so our percentile representations have been inverted) was used to demarcate dark green “excellent” feedback; the next lowest 25% of relative alpha PSD values (45th percentile cutoff) marked the range of light green “good” feedback, and the remaining 45% of relative PSD values were equally divided into orange (“medium”), yellow (“poor”), and dark red (“bad”) ranges, respectively (see Fig. 2). These thresholds were chosen in order to provide a positive bias to the feedback and encourage participant engagement. The feedback was presented after each ten-letter sequence (with letters shown at three per second), so approximately every 3 s. After each week of intervention, these cutoffs were recalculated from the most recent week of calibration data.

2.2.5. Follow-up visit

Approximately one month after the final intervention session, participants completed one follow-up session to assess maintenance of performance on the repeated measures tasks, as well as a final RSVP Keyboard calibration and copy-spelling session without NFB.

2.2.6. Electrophysiological Recordings and Processing

EEG data were recorded using an adjustable DSI VR300 dry-electrode system (Wearable Sensing; San Diego, CA) with linked-ear references, ground at A1 (left earlobe), and scalp electrodes at 10/20

sites FCz, F7, Pz, P4, PO7, PO8, and Oz. Data were sampled at 300 Hz and digitized at 16 bits. The inclusion of an electrode at F7 was a modification of the standard VR300 design (the original location was P3), made to allow for monitoring of eye-related activity (e.g., blinking). Though field recordings of EEG are sometimes more susceptible to noise than data collected in a more controlled laboratory setting (e.g. ambient 60 Hz electrical noise from power sources in US; mechanical artifact related to appliances or home-medical equipment, etc.), all electrodes were calibrated to be within operating ranges as specified by the manufacturer guidelines. Additionally, experimenters monitored real-time EEG during the tasks (displayed using 2–45 Hz bandpass and a 60 Hz notch filters) in order to identify and minimize high amplitude artifacts and ambient noise.

All recordings were down-sampled to 150 Hz and filtered 2–45 Hz for analysis by the classifier. N200 and P300 potentials at site Pz were later quantified offline in Brain Vision Analyzer (Brain Vision LLC; Morrisville, NC, U.S.A.) in order to explore target discrimination and identification processes, respectively. Offline data were band pass filtered 1–45 Hz with a 60-Hz notch before use of Independent Component Analysis (ICA) to remove eye blinks. These data were segmented –200 ms–1000 ms relative to target and non-target letters before baseline correction using the 200 ms prior to letter presentation. These segments were subjected to artifact rejection and epochs were flagged for review if they contained voltage steps $>50 \mu\text{V/ms}$, amplitude changes $>125 \mu\text{V}$ over 50 ms, amplitude values $> \pm 75 \mu\text{V}$, or sustained amplitude values $< 0.5 \mu\text{V}$ for longer than 100 ms. N200, and P300 peaks were cursoried using semiautomatic peak detection windows of 250–400, and 350–500 ms, respectively. N200 and P300 peaks were quantified for analysis using peak-to-trough, or by measuring the change in voltage from the most recent peak of the opposite polarity.

2.3. Data analysis

One planned analysis component for this non-experimental single case research design, as is typical for all SCRd studies, was graphical analysis [40]. Graphical analysis is particularly useful for heterogeneous populations as it allows for iterative improvements during ongoing intervention. However, the fact of multiple repeated baseline and intervention-phase measurements makes conventional longitudinal statistical analyses possible as well. To evaluate the stability of the measures of interest, we calculated within-subject coefficients of variation (CVs) and intraclass correlation coefficients (ICCs) using the baseline measurements only. The CV is a metric of overall volatility in a longitudinal setting, expressing the equilibrium standard deviation as a fraction of the long-run mean for each participant. Lower CVs are better, and, as a rule of thumb, values of $\sim 5\%$ or lower are indicative of good stability and values in excess of 10% are indicative of poor stability. We estimated an average within-subject standard deviation as the root-mean-square error from an absorbing regression [62] on the baseline measurements of the cohort (absorbing participant effects), and calculated the average within-subject CV as this value divided by the overall baseline mean. (Note that this is a population-level estimate, not a strict average of the individual CVs.) The standard error of the CV was approximated using the formula $\frac{CV}{\sqrt{(2 \times df)}}$, where $df = \frac{(n \times m)}{(1 + (m-1) \times r)}$, for $n = 5$ (the number of participants), $m = 4.4$ (the average number of included baseline measurements per participant), and r (an estimate of the average correlation among longitudinal values for a participant) different for each outcome. ICCs and their corresponding confidence intervals were estimated using a restricted-maximum-likelihood linear mixed-effects model [63] of the outcome measure adjusted for session time, specifying random intercepts for participants. The ICC is an estimate of the average proportion of total variance attributable to true differences in the outcome measure.

Within- and between-subject correlations of median relative alpha power and other EEG-derived metrics (e.g. average P300 amplitude

across all target letter events) were planned to be explored if all participants completed the study with a fixed-effects longitudinal model [64] using Bland and Altman’s method [65] for the within-subject correlation estimate and the complementary "between-effects" longitudinal estimator (used in the calculation of the fixed-effects model) for the between-subject estimate. Degrees of freedom for the within-subject correlation were estimated using the df formula noted above, and using the sample size $n = 5$ for the between-subject correlation, in each case subtracting 3 when calculating Fisher’s approximation of the z-score of the correlation [66].

Stata version 16.1 [67] was used for the statistical analyses listed above, and R version 3.6.1 [55] was used for data management and to generate descriptive summaries.

3. Preliminary results

Five participants with mild AD were enrolled in this feasibility study (See Table 1 for demographic information). All five participants completed their respective baseline sessions. One of the five completed both their baseline sessions and two full weeks of intervention; and two of the five completed all baseline, intervention, and all follow-up sessions. Baseline repeated measure results for each participant are included in Table 2. As the protocol could not be implemented in its entirety due to the COVID pandemic, the following section reports baseline session results from all participants’ and from the intervention sessions of the two completers. Future studies will be needed to more thoroughly evaluate the protocol.

The stability of the outcome measures across baseline sessions is shown in Table 3. In particular, performance on WJTA-IV Sentence Reading Fluency, letter cancellation with curved foils, and AUC was reasonably stable, with CVs less than 10%. Some measures demonstrated a learning effect within the baseline phase for some participants,

Table 2
Repeated measures at baseline phase by participant.

Participant	# of Sessions	Measure	Baseline (M ± SD)
# 1	Baseline: 4	Letter Cancellation	
		Curved Letters	52.03 ± 5.42
		Straight Letters	54.19 ± 2.65
		Letter Span	
		Forward	4.25 ± 0.5
		Backward	3 ± 0
# 2	Baseline: 5	WJTA-IV SRF	54 ± 4.9
		Letter Cancellation	
		Curved Letters	31.76 ± 2.74
		Straight Letters	47.5 ± 5.79
		Letter Span	
		Forward	4 ± 1
# 3	Baseline: 4	Backward	3.4 ± 0.89
		WJTA-IV SRF	77.2 ± 7.08
		Letter Cancellation	
		Curved Letters	47.55 ± 16.90
		Straight Letters	57.21 ± 14.24
		Letter Span	
# 4	Baseline: 7	Forward	5.25 ± 0.5
		Backward	4 ± 0
		WJTA-IV SRF	61.25 ± 8.18*
		Letter Cancellation	
		Curved Letters	35.8 ± 2.48
		Straight Letters	40.01 ± 3.31
# 5	Baseline: 7	Letter Span	
		Forward	4.86 ± 0.9
		Backward	4.43 ± 0.53
		WJTA-IV SRF	49.43 ± 3.26*
		Letter Cancellation	
		Curved Letters	39.67 ± 2.35
		Straight Letters	50.44 ± 4.54
		Letter Span	
		Forward	3.71 ± 0.49
		Backward	2.85 ± 0.38
		WJTA-IV SRF	56.2 ± 3.27

Table 3
Stability metrics of Baseline Performance.

Measure	CV ± SE (%)	ICC [95% CI]
AUC	9.23 ± 2.57	0.68 [0.28,0.92]
Median Relative Alpha PSD	24.90 ± 6.68	≈0
WJTA-IV: Sentence Reading Fluency Raw Score	6.50 ± 1.98	0.90 [0.65,0.98]
Maximum Letter Span: Forward	19.01 ± 4.11	0.22 [0.02,0.80]
Maximum Letter Span: Backward	16.04 ± 4.20	0.57 [0.18,0.89]
Letter Cancellation (sec): Curved	5.19 ± 1.59	0.92 [0.71,0.98]
Letter Cancellation (sec): Straight	13.38 ± 3.17	0.37 [0.06,0.83]

which can be seen in the outcome measure results for participants #1 and #2 (completers) in Fig. 4. On the RSVP Keyboard calibration task, participants achieved a mean correct classification rate (AUC) across their baseline sessions of 0.72 ± 0.03 (mean ± SE). In the baseline phase, AUC for participants #1, #2, and #3 ranged from 0.67 to 0.80, 0.69 to 0.83, and 0.58 to 0.76, respectively. Participants #4 and #5 (both non-completers) exhibited consistently low AUC values near 0.6 across their baseline sessions (Fig. 4). Illustrations of representative EEGs and ERPs taken from the 1st week of intervention for participants #1 and #2 (completers) and participant #4 (non-completer) are presented in Fig. 5 In the outcome measures tasks, letter cancellation tasks for both participants (Fig. 4A, B, 4F, and 4G) and WJTA-IV Sentence Reading Fluency for participant #2 (Fig. 4J) demonstrated baseline variability.

For both completers, preliminary intervention results were mixed. Fig. 4 includes examples for which there was no change in performance with the introduction of the intervention (Fig. 4D), a sustained learning effect continuing through the baseline and intervention phases (Fig. 4J), a learning effect only during the baseline phase (Fig. 4G), and an apparent improvement from the intervention (Fig. 4A). Participant 1 demonstrated a decrease in performance in the intervention phase for the letter span forward condition but not the letter span backward condition. As the letter span backward condition is of higher complexity and may be a better index of working memory, it is possible that motivational factors or fatigue related to the difficulty of the task may have influenced this participant’s performance.

4. Discussion

The current study demonstrated feasibility of a NFB intervention using posterior alpha power during performance of an RSVP Keyboard task. Participants with mild AD were able to participate in an intensive study with up to three intervention visits per week. All chosen baseline and outcome measures were able to be completed by participants with mild AD and most outcome measures were reliable during the baseline phase. Preliminary data from initial implementation of this protocol suggest that adults with mild AD can perform a complex and cognitively-taxing BCI calibration task (RSVP Keyboard), with one participant achieving AUC values up to 0.94. One participant with an exceptionally low AUC (0.5) appeared engaged and completed the letter discrimination task, but had no classifiable P300 (see Fig. 5B, participant #4). There is some concern that this is at least partly due to the age-related decline in P300 amplitude and prolongation of P300 latency, as well as AD further increasing those changes [68,69]. The task required participants to attend to 100 sequences of letters and look for a target while minimizing distractions to non-targets and artifact-inducing movements. This relies heavily on attention, a domain of cognition that is affected in early stages of AD. Additionally, the two participants who completed the intervention correctly typed a word in a copy spelling task. This preliminary result demonstrates that adults with impairments in attention, a domain of cognition, may be able to operate a BCI for communication.

Results for all five participants demonstrated that some, but not all, outcome measures were stable during the baseline phase. For instance, the WJTA-IV Sentence Reading Fluency, letter cancellation with curved

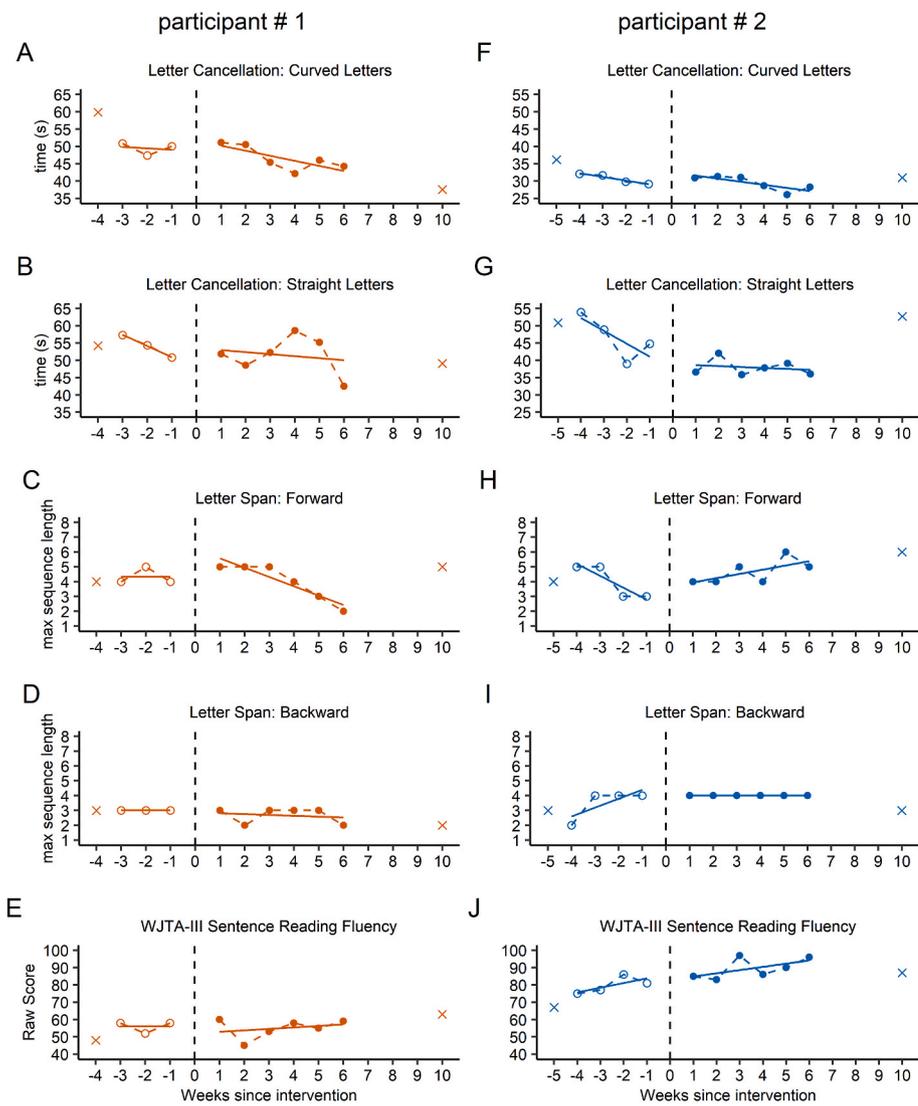


Fig. 4. Outcome Measures for Completers
 In general, the WJTA IV Sentence Reading Fluency, Letter Cancellation with curved foils, and AUC (Fig. 2) were the most reliable. Note examples of outcome measures in for which there was: no change in the intervention (Letter Span Backward) (d and i); a sustained learning effect continuing through the baseline and then through the intervention periods (Sentence Reading Fluency) (j); a learning effect only during the baseline (Letter cancellation with straight foils) (b and g); an apparent improvement from the intervention (Letter Cancellation with curved foils) (a), and a decrease in performance in treatment phase (Letter Span forward) (c).

foils, and AUC had CVs less than 10%. The novel letter span task with scoring similar to the WAIS Digit Span had worse baseline stability with higher CVs (19% for forward and 16% for backward). This demonstrates the stability of some measures for future studies that might be more robust to test-retest effects.

This proof-of-concept study had limitations. EEG recordings obtained in a natural environment, such as the participant’s home, may be more susceptible to artifacts. However, the purpose of this study was to assess the feasibility of an intervention that could be delivered in participants’ homes. Conducting study visits in participants’ homes also served to facilitate participant compliance, limit attrition, and to allow opportunities to observe real-life contributors to the efficacy of intervention (e.g., typical environmental noise, dry electrode system fitting challenges, discomfort, differences in alertness etc.). As with other behavioral research, future NFB studies will need to control for non-specific aspects of improvement that may have occurred with the additional social interaction and cognitive stimulation associated with data collection visits, independent of the NFB. Ideally, future investigations would make use of an active control with comparable stimulation and interactions with the research team (e.g., viewing health and wellness videos that we have previously used as a control in mind-body interventions trials) [70]. Although, at a minimum, a wait-list control could be used. It is possible that the baseline version of the RSVP Keyboard tasks provided stimulation that could even be

considered an active control. The preliminary data suggest that the specific target for the NFB in this study (i.e., alpha level) may not be optimal for the NFB as expected changes in the EEG measure used for the NFB were not demonstrated. Alpha feedback was used in this study due its common use in the neurofeedback field. Alpha amplitude varies significantly across participants and, as such, it is possible that the feedback will not be reliable if alpha amplitude is very low. To this point, a threshold for minimum alpha amplitude may need to be established. Additionally, alpha has both a tonic aspect related to global state of alertness and attention as well as a state aspect in terms of relatively immediate alpha attenuation following presentation of visual stimuli with rapid return to baseline. Klee and colleagues (2022) recently analyzed alpha attenuation during RSVP letter presentations and observed greater alpha attenuation following target letters compared to non-target letters [71]. This attentional measure of alpha attenuation following target may be better than simply averaging alpha over several secs for the purposes of generating neurofeedback. Finally, the sample size was small, and homogenous in socioeconomic status, race, and education. Larger studies with control conditions and more diverse participant samples are needed to further explore this neurofeedback intervention.

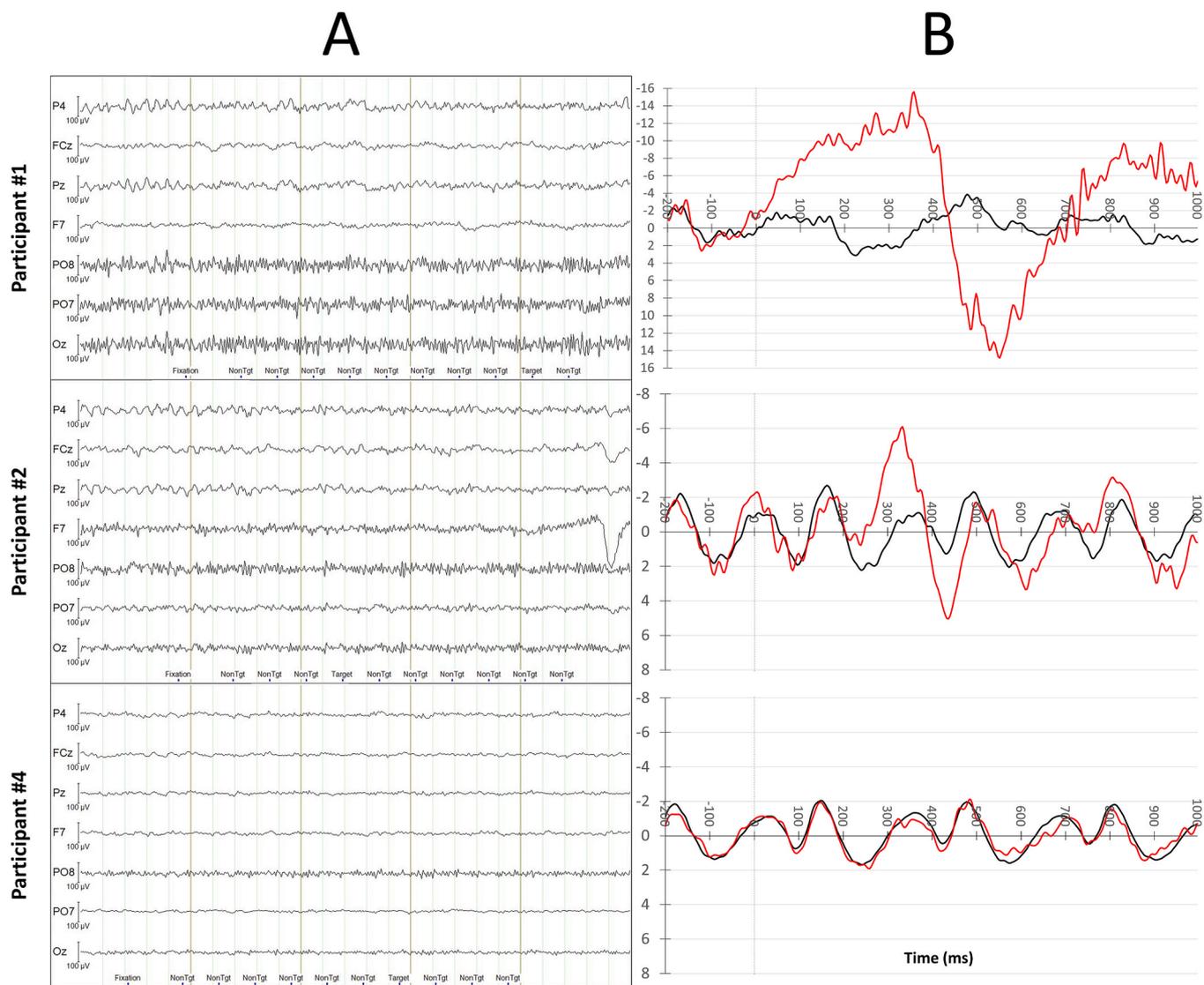


Fig. 5. Examples of Electrophysiological Data for 3 participants

(A) 5-s of representative EEG data taken from week #1 of intervention. The presented windows each include one full sequence of 10 letters (1 target; 9 non-targets) during the RSVP neurofeedback calibration task. Parieto-occipital alpha is clearly visible at sites P4 and Pz prior to fixation. Participant #1 demonstrates neck EMG contamination at posterior sites Oz, PO7, and PO8. (B) Demonstrative ERP averages of target and non-target responses at Pz, derived from week #1 of intervention (3 sessions; neurofeedback calibration). Participant #1 shows EMG contamination, but a large N2/P3 response. Participant #2 exhibits alpha signal but also a small yet clear ERP response to the target. Participant #4 demonstrates no visible target-related response.

5. Conclusions

This NFB protocol brings novel contributions to the field of AD and BCI. First, the results of this study demonstrated the feasibility of this intervention for participants with mild AD. While this project required significant programming and signal processing expertise, the use of open-source software [38] and the availability of clinical NFB devices dramatically increases the feasibility of further research and eventual clinical application. Single case design studies with multiple assessment before and during an intervention [40,51] are a potential approach for AD pilot studies. Second, and perhaps most importantly, preliminary results demonstrated that participants with cognitive impairments such as mild AD can use a P300 based BCI speller.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

DGM, DK, TM, BP, JW, MFO, and BO contributed to the writing of the manuscript including text, figures, and tables. DGM, DK, BO, TM, JW, and BP contributed to the design of the experiment. DGM and DK collected and processed data. DGM programmed analysis scripts and behavioral tasks in R and PsychoPy. TM provided software development needed in BciPy for use as NFB intervention. JW performed statistical analyses. All authors have read and approved the manuscript.

Declaration of competing interest

All authors received a salary for their work from their respective institutions.

Data availability

Data will be made available on request.

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