# Neurofeedback based enhancement of single trial auditory evoked potentials: Feasibility in healthy subjects

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## Abstract

Previous studies showed a global reduction of the event-related potential component N100 in patients with schizophrenia, a phenomenon that is even more pronounced during auditory verbal hallucinations. This reduction assumingly results from dysfunctional activation of the primary auditory cortex by inner speech, which reduces its responsiveness to external stimuli. With this study, we tested the feasibility of enhancing the responsiveness of the primary auditory cortex to external stimuli with an upregulation of the event-related potential component N100 in healthy control subjects. A total of 15 healthy subjects performed eight double-sessions of EEG-neurofeedback training over two weeks. The results of the used linear mixed effect model showed a significant active learning effect within sessions ($t = 5.99$, $p < 0.001$) against an unspecific habituation effect that lowered the N100 amplitude over time. Across sessions, a significant increase in the passive condition ($t = 2.42$, $p = 0.03$), named as carry-over effect, was observed. Given that the carry-over effect is one of the ultimate aims of neurofeedback, it seems reasonable to apply this neurofeedback training protocol to influence the N100 amplitude in patients with schizophrenia. This intervention could provide an alternative treatment option for auditory verbal hallucinations in these patients.

The study is registered at the WHO approved ISRCTN registry (ISRCTN23930628– Neurofeedback treatment of auditory verbal hallucinations).



## Keywords

N100, event-related potentials, neurofeedback, auditory verbal hallucinations, learning, habituation

**Introduction**

Of all mental disorders, schizophrenia is one of the most disabling and psychologically straining diseases. Auditory verbal hallucinations (AVH) are a common symptom in schizophrenia. Due to hallucinations, patients often feel strongly disturbed in their daily activities. Social and working life is largely affected. In 25-30% of patients, AVH cannot be sufficiently treated with antipsychotic drugs [1]. Therefore, alternative strategies are needed: Specialized psychotherapeutic approaches [2] and non-invasive brain stimulation methods, like repetitive transcranial magnetic stimulation (rTMS) [3, 4] or transient direct current stimulation (tDCS) [5, 6], have been applied. However, similar to the response to pharmacological interventions, the response to these novel forms of treatment varies, maybe due to different underlying phenotypes [7, 8]. Since tolerable dosages of these interventions do not guarantee a sufficiently strong and lasting clinical response, further treatment alternatives with low side effects and which potentially induce longer-lasting effects are needed. One such alternative may be neurofeedback (NFB).

*Theories of AVH*

There has been a wide range of approaches searching for the origin of AVH. An explicit review can be found in Ćurčić-Blake and colleagues [9].Shortly, psychological models point out the importance of the subjective experience of the context and the emotion expressed in the AVHs [10]. These models assume an emotional trauma as cause of the perception of AVHs. This hypothesis is supported by cognitive models of aberrant memories, where a failure of inhibition of unintended memory activation leads to the appearance of intrusive memories [10, 11]. Further, neurobiological models support the hypothesis of the misattribution of inner speech to an external source [9, 10, 12-16]. In this hypothesis, a self-monitoring deficit is emphasized through a lack of “self-attributes” of internally generated events like i.e. thoughts or inner speech [9].

*Neurophysiology of AVH*

*The role of the auditory cortex and the auditory evoked potential (AEP) N100.* Two decades of research into the neurobiological basis of AVH have identified a network of brain areas involved in the perception of AVH, from primary and secondary auditory sensory cortices and premotor cortex, to more complex cortical structures like the prefrontal cortex or the anterior cingulate cortex (ACC), up to subcortical and cerebellar regions [12, 16, 17]. Focusing on the involvement of the primary auditory cortex (PAC), Dierks and colleagues found an abnormal activation in hallucinating patients [18]. Further, Hubl et al. confirmed the involvement of the PAC during AVH and showed its reduced responsiveness using auditory evoked potentials (N100) [13]. The N100 is an event-related potential (ERP) that has its peak between 80 to 120 ms after an auditory signal [19]. In a first study, Saletu et al. showed in 1971 a reduction of the N100 amplitude in schizophrenia patients [20]. After that, various studies confirmed the N100 amplitude reduction in schizophrenia patients compared to healthy subjects. Ford and colleagues showed a decreased N100 specifically in schizophrenia patients compared to epileptic patients [21]. Hubl and colleagues further revealed a stronger reduction of the N100 during phases of auditory hallucinations compared to non-hallucinating phases [13]. Evidence of the source underlying the N100 was mainly found in primary and secondary auditory cortices, but other parts of the temporal lobe, frontal areas, insula as well as the ACC also showed a link to the N100 amplitude [22-24]. Despite a variety of hypotheses about the origin of AVHs and their neurobiological fundament, there seems to be a consensus that the reduced N100 is a good marker of the functional abnormalities in schizophrenia patients with AVH. Further evidence for the importance of the N100 in the genesis of AVH is given by the reduction of the N100 in healthy adults during inner speech [25]. The N100 component is dependent on selective attention and can thereby be influenced through a shift in attention [26]. This was shown in a study with tinnitus patients, who are hypothesized to display a selective attention deficit towards external sounds, seen in a reduction of the N100 component [27]. Rosberg et al. summarized in a review different aspects which might influence the N100 component, whereat selective attention towards a stimulus on the attended compared to the non-attended ear is mentioned to increase the AEP [28].

*Neurofeedback as a treatment option*

The aim of the present study was to test the feasibility of learning to control the N100 amplitude by NFB with the perspective to gain a novel treatment option for patients with AVH. NFB is a method enabling subjects to self-regulate their ongoing brain activity. Therefore, a positive feedback is given on the desired brain state and thereby reinforces the subject in its performance [29-34]. It allows the modulation of brain states that are not voluntarily accessible. Typically, no concrete instruction on how to achieve the desired state is given [31]. NFB has been successfully applied in different psychiatric disorders, e.g. ADHD [35, 36], and also in patients with schizophrenia to generally lower psychopathology [36-39]. Gruzelier and colleagues showed in 1999 the ability of schizophrenia patients in learning a control task and demonstrated the feasibility of operant conditioning based on the electroencephalography (EEG)-NFB [38]. Some more evidence is found in fMRI-NFB studies, where subjects modulated either the ACC or the insula [17, 37, 39]. Recently, Dyck and colleagues tested the self-regulation of the activity of the ACC in treatment-resistant patients with AVH using real-time functional magnetic resonance imaging (rtfMRI). They reported an upregulation of the ACC along with an improvement in some aspects of AVHs [17].

In terms of the modification of the AEP N100, it has been shown that subjects may actively manipulate the amount of phase-locking onto an auditory stimulus by varying selective attention to competing auditory stimuli [27, 40] and that rtfMRI NFB of the PAC may reduce symptoms in patients with tinnitus [41]. However, no study investigated whether the subjects may learn to increase the amplitude of the N100 evoked by a simple auditory stimulus by means of EEG-NFB.

So far, research on NFB training has shown that in general not everybody is able to learn equally successful to modulate one's own brain function. Furthermore, in NFB context, learning may involve various aspects, such as learning across sessions, learning within single-sessions, or increments in passive conditions [42]. Apart from the basic aim to show the feasibility to learn to modulate N100 by

NFB, we were also interested in defining the dynamics of this process in a healthy population, as this may serve as a reference for the evaluation of NFB-related changes to the N100 (and to AVH) in patients with schizophrenia.

## Materials and methods

*Subjects*

In total, 16 subjects were recruited through advertisement to participate in the NFB training. For participation, a monetary reward of 300 CHF was given. As inclusion criteria, subjects had to be between 18 and 65 years old and had to be able to engage in two weeks of continuous NFB training. Participants with any psychiatric or neurological diseases, hearing or non-corrected vision problems, or pregnancy were excluded. All participants completed a questionnaire to screen for psychopathological diseases (table 1). One subject had to be excluded after this pre-screening due to verbal aggressive behavior against a clinician. A total of 15 young healthy subjects fulfilled the handedness questionnaire [43] of which 14 were right-handed and one was left-handed. All participants were fully informed about the study procedure, and gave written informed consent. Time of the training was kept constant within subjects. Subjects were instructed to avoid caffeine at least two hours and smoking at least 30 minutes before the training sessions. All procedures were in accordance with the declaration of Helsinki and approved by the local ethics committee ("Kantonale Ethikkommission Bern", Reference-Number: 193/13).

**table 1**

*Design and experimental procedures*

In total, participants completed a pre-session (1), NFB training over 2 weeks including 8 double-sessions in total (2), and a post-session (3) (figure 1A).

**figure 1**

In the pre-session (1), subjects were informed about the experimental procedure and all inclusion and exclusion criteria were checked. Subjects were informed about the task and that the upward move of the balloon (visual feedback) was coupled with an increase of an AEP. For proofing normal hearing, we used an audiometry measure (Diatec Screening Audiometer, AS 608) to test the hearing threshold in the norm range (based on WHO defined threshold for hearing loss – hearing threshold of 25dB or better). Then, a series of psychological tests were conducted to ensure mental health and a normal cognitive functioning level. These included a) the BSI: Brief Symptom Inventory [44] assessing psychological distress and psychiatric diseases; b) the HVLT-R: Hopkins Verbal Learning Test-Revised of the MATRICS Consensus Cognitive Battery [45, 46] to assess the ability of verbal learning; c) the NAB-Mazes: Neuropsychological Assessment Battery of the MATRICS Consensus Cognitive Battery [45, 46] to reproduce executive functioning; and d) the D2 Test of Attention [47] to evaluate selective and sustained attention. Furthermore, a series of EEG recordings were taken (for details see section *Recording of pre-session*).

The NFB training (2) consisted of 8 double-sessions in total distributed across 2 weeks with 4 training days weekly and 2 single-sessions daily. The first and second session per day were performed consecutively, each one lasting about 22 minutes with a short break in between. After each single-session, the subjects were asked to describe the strategies used and their subjective feeling of control in terms of the NFB performance.

In the post-session (3), again the BSI psychological screening to control for psychological distress and psychiatric diseases was assessed to ensure the absence of any changes due to the NFB training in terms of mental health in healthy participants.

*EEG-ERP recording and feature extraction.* During all EEG recordings, subjects sat in a comfortable resting position in front of a computer monitor (distance from monitor to chair was 1.30 m) in a sound shielded EEG cabin. All recordings were video-monitored to control for body movements. For the EEG, a 32-channel ActiCap system with active electrodes (layout based on the 10-10 system) was used (Brain Products GmbH, Germany). The reference electrode was placed at FCz and the ground electrode at AFz. Impedances were kept below 20 kΩ. Signal recordings were amplified by a BrainAmp 32-channel amplifier (BrainAmp, BrainProducts GmbH) at a sampling rate of 500 Hz and band pass-filtered between 0.3 and 70 Hz. The ERP N100 was evoked with a series of simple 1000 Hz sinusoidal tones with a duration of 70 ms (increase 10 ms, plateau 50 ms, decrease 10 ms) which were presented with an inter-stimulus interval of 1430 ms ± 140 ms through a standard hi-fi audio amplifier (Technics V300 Mark 2, Panasonic, Japan) according to Hubl et al. [13].

*Recording of the pre-session.* An overall scheme of the recordings and analysis steps is shown in figure 2. In the pre-session, three EEGs were recorded. First, a resting-state EEG with eyes-open/eyes-closed lasting 8 minutes in total was performed where subjects were instructed by the NFB trainer to rest and alternately open and close their eyes during 2 minutes (item a. in figure 2). Second, an EEG with voluntary eye movements (blinks, left-right and up-down movements) was recorded (item b. in figure 2). In a later offline analysis, this data was used to build a spatial filter to remove ocular movements (item c. in figure 2). Third, an EEG of 4 minutes was recorded while the simple 1000 Hz tones, later used in the NFB training to evoke the N100 amplitude, were presented (item d. in figure 2). Therefore, subjects were instructed to rest in a thought-free state, listen to the beep tone, and focus on the screen with the visual feedback symbol as a static frame.

**figure 2**

*Offline analysis of the pre-session*. In order to maximize the signal-to-noise ratio of the EEG feature used for the NFB training, i.e to optimally extract the amplitude of the N100 component on a single trial level, the elimination of artifacts and the extraction of the target parameter was based on individualized spatial, temporal and frequency filters. These filters were extracted from the EEG data of the pre-session as follows: an individual filter to suppress ocular movement artifacts was built based on the EEG with voluntary eye-movement artifacts by means of an independent component analysis (ICA) procedure [48] (Item c. in Fig. 2) using Vision Analyzer (Version 2.0, BrainAmp, BrainProducts GmbH). Thereby, factors representing eye-movements were identified through visual inspection based on topography and waveform and excluded (out of the 32 factors, on average 4 factors (range 2 – 5) were excluded). These spatial eye movement filters were applied to all subsequently analyzed EEGs and were applied during the online quantification of the single trial N100 amplitude. Then, individual temporal and spatial filters (items e. & f. in figure 2) for the extraction of the single trial N100 amplitude (based on an average of 173 segments with a range from 163 – 198 segments) were applied to the eye movement-corrected EEG data of the pre-session with the auditory stimulation. First, the data was band pass-filtered from 1 to 30 Hz and recomputed to the average reference. In addition, the data was segmented from 0-500 ms post-stimulus onset, and a baseline correction (0-500 ms) was applied. These single trial ERPs were wavelet transformed using real Gabor-functions, and one-sample t-tests were computed across trials for all electrodes, time-points, and wavelet layers. In order to obtain an index of the overall signal-to-noise ratio across time and frequency, the absolute values of these t-values were collapsed across channels and visualized. The optimal individual latency and frequency layer for the detection of the N100 was then chosen at the peak of these t-values, based on the visual inspection of this display in Vision Analyzer (Version 2.0, BrainAmp, BrainProducts GmbH). The spatial filter to isolate the amplitude of the N100 component (item g. in figure 2) was obtained from the averaged wavelet transformed single trial data at the frequency and latency found to be optimal. Using

this filter, the amplitude of the N100 component was defined as the weighted sum of all electrodes of the wavelet filtered EEG at the individually defined N100 latency, where the weights were defined by the spatial filter. The waveform distribution of the averaged AEP of the pre-session between subjects is depicted in figure 3.

**figure 3**

*Online analysis of NFB training.* The online extraction of the N100 amplitude for each single trial was implemented using the build-in and in-house developed plug-ins for RecView (Brain Products GmbH). The raw data was filtered online with the prior built spatial filter for ocular movement, and the EEG was recomputed to the average reference. Then, the individually built spatial filter, a temporal wavelet filter corresponding to the optimal frequency, and the obtained optimal latency were applied to this EEG to extract the ERP component N100 on a single trial level (item h in figure 2). No baseline correction was used for the extraction of single trials on the online analysis, because of the usage of a wavelet filter. The visual feedback in the NFB training was given based on the extracted single trial N100 amplitudes (item i in figure 2).

*Neurofeedback training protocol*

As displayed in figure 1B, the NFB training protocol consisted of 1 passive condition and 2 active conditions (training and transfer) with 8 repetition blocks in total lasting 2 minutes 20 seconds in duration with 100 beep tones each. The beep tones were presented during all conditions. To visualize any modifications of the N100 amplitude, visual feedback, implemented in PsychoPy[49] with a balloon rising according to the N100 amplitude, was used. The following rule was used to update the position of the balloon:

$$y_t = y_{t-1} + (s - y_{t-1}) * k$$

where $y_t$ is the value fed back to the subject at trial *t*, s is the value of the single trial quantifier of the N100 amplitude at trial *t*, and k is a constant. During the pilot phase, the value k = 0.2 was found to produce a dynamic of the feedback that was subjectively responsive to each single trial while not moving to abruptly, and was thus used for all subjects.

In the first block of the passive condition, subjects were instructed to rest and try to stay in a thought-free state while fixating on the screen with a static frame (static balloon, no feedback) while the beep tones were presented. The distribution of the single trial N100 amplitudes during this passive condition session was then used to calculate a threshold for receiving positive feedback during 60% of the trials. Subsequently, 4 training blocks followed with the instruction "*Try to let the balloon fly as high as possible.*" For the upregulation, subjects were instructed to use mental strategies, e.g. mentally singing a song or solving an equation. Strategies could be changed during and/or across the repetition blocks and were assessed after each single-session. The balloon started rising at the level of the individually recorded threshold and reached its maximum with an increase of 15% from the initial threshold of the N100 amplitude. After each training repetition, subjects could individually define a short break. The third condition called transfer, was surrounded by two blocks of the passive condition, one before and one after the transfer block. In this transfer condition, subjects heard the instructions "*Try to reproduce the same state as before in the training blocks where the balloon was flying high by using the same mental strategies*". For the transfer condition, subjects fixated the screen during the absence of any feedback (no balloon on the screen).

*Statistical analysis to assess learning in NFB*

The statistical analysis quantified the effect of our NFB training protocol on the amplitude of the N100 component as quantified for the feedback across sessions and within single-sessions, between subjects on a group level, as well as within subjects on the individual subject level (see word index). By using linear mixed modeling, the N100 amplitude performance was accounted for by a constant, by a time

factor (i.e. session or repetition), by condition (passive or active: training and transfer), as well as by the interaction of these factors [29]. Some of these factors were included as random variables to account for between-subject differences (see table 2).

For both across- and within-session NFB performance, we assessed (1) the general ability to increase the N100 amplitude, named aptitude (training-aptitude and transfer-aptitude); (2) non-voluntary improvement as a passive response, assessed in the passive condition and named carry-over; and (3) voluntary improvement as an active response, assessed in training and transfer conditions separately and named learning (training-learning and transfer-learning) (see word index).

In the linear mixed model, (1) aptitude was captured by a constant difference of the N100 amplitude between the passive and an active condition (training and transfer). Therefore, training-aptitude stood for the constant difference of the N100 amplitude between training and the passive condition, and transfer-aptitude represented the constant difference of the N100 amplitude between transfer and the passive condition independent of time. (2) Learning in the passive response as a non-voluntary improvement represented N100 amplitude modulation in the passive condition across time. Further, (3) voluntary learning in the active condition was defined as the interaction between condition (active: training/transfer vs. passive) and time (session and repetition) of N100 amplitude modulation (figure 1).

As figure 1B shows, the passive condition had 3 repetitions, the training conditions had 4 repetitions, and the transfer condition was not repeated. To analyze any training effects, the 4 training repetitions were compared to the surrounding passive condition blocks (repetition 1 and 2). However, for any transfer effects, repetitions 2 and 3 of the passive condition were included as contrast conditions.

**Results**

*Subjects*

A total of 15 healthy subjects completed the neurofeedback training. We measured 11 females and 4 male with a mean age of 27.7 (SD = 7.6) and an age range between 21 – 45 years.

*NFB training*

*Across-session and between-subjects.* Table 2 section A gives an overall overview of the across-session and between-subject results. In a first step, a very simple model with a random effect for time (time offset) was tested and showed a significant reduction of the N100 amplitude due to time ($\beta = -0.04$, $t = -5.27$, $p < 0.001$) independent of the condition (table 2 section A2). The effect of time was also tested across the session to control for a systematic decrease (see *Within-session and between-subjects)* across the training sessions. However, this effect was not significant ($\beta = -0.001$, $t = -1.54$, $p = 0.13$). Given our hypothesis, the effect for time was of no interest for our experiment. Therefore, data were corrected for the factor of time by computing a regression of the data against time after the beginning of each session, and subtracting this regression line from the data. All further analyses were performed on this time-corrected data.

**table 2**

A visual inspection of the across-session results shown in figure 4 indicated a systematic difference between the first and second sessions per day. In a second step the analysis of the most complete linear model (table 2 section A3) across sessions, including *Session, Session half* (first against second session per day) and *Condition* (passive or active: training or transfer), as random effects confirmed the visually inspected characteristics: The model yielded a significant main effect of session (first against second sessions per day: $\beta = 0.70$, $t = 2.86$, $p < 0.01$) as well as a significant interaction between session and day ($\beta = -0.11$, $t = -2.33$, $p = 0.02$). Due to this interaction, a separation of the first and second session for each day was carried out (table 2 section A4). The division of the data into first and second sessions per day showed a significant carry-over effect for day ($\beta = 0.13$, $t = 2.42$, $p = 0.03$) and a tendency for training-learning ($\beta = -0.11$, $t = -1.94$, $p = 0.06$) in the first session of each day. For a

graphical overview, see figure 5A for the first session each day and figure 5B for the second session of each day. Further, no significant effects were found in training-aptitude, transfer-aptitude, or transfer-learning. None of the time-corrected data for the second sessions per day showed any significant results. Further, a N100 peak analysis to check the effect of latency yielded no significant shifts, neither between conditions (passive condition vs. training) nor within condition in the pre-post comparison.

**figure 4**

**figure 5 A & B**

*Within-session and between-subjects.* Table 2 section B shows an overview of the within-session and between-subject results. The most complete linear mixed effect model for within-session included random effects for *Repetition* and *Condition*. As for the across session analysis, data was corrected for a time effect, which was of no interest and showed a significant reduction of the N100 amplitude across time and within sessions (table 2 section B1). Figure 6 shows the time-corrected data of the most complete within-session model (table 2 section B2) with a significant negative carry-over effect ($\beta = -0.96$, $t = -7.17$, $p < 0.001$) as well as training-aptitude ($\beta = -1.59$, $t = -6.24$, $p < 0.001$) and a positive training-learning effect ($\beta = 0.84$, $t = 5.99$, $p < 0.001$) (difference between carry-over and training).

The division of the data into first and second sessions for each day also showed comparable results to the prior analyses (table 2 section B2). In the first session per day, a significant negative effect for carry-over ($\beta = -1.02$, $t = -5.29$, $p < 0.001$) as well as for training-aptitude ($\beta = -1.65$, $t = -4.52$, $p < 0.001$) and a positive training-learning effect ($\beta = 0.88$, $t = 4.78$, $p < 0.001$) were found. In the second session per day, a significant negative effect for carry-over ($\beta = -0.90$, $t = -4.83$, $p < 0.001$) as well as for training-

aptitude ($\beta$ = -1.53, t = -4.39, $p < 0.001$) and a positive training-learning effect ($\beta$ = 0.79, t = 4.07, $p < 0.001$) were found.

**figure 6**

## Discussion

The present study tested the feasibility of regulating the N100 component through NFB in healthy subjects. The motivation was given by the fact that schizophrenia patients show a reduction of the N100 component [19, 50, 51], a phenomenon that is even more pronounced during acute phases of AVH [13].

The results showed a significant learning effect within sessions despite an observed unspecific habituation effect that lowered the N100 amplitude over time. Across sessions, a significant increase, named as carry-over effect, was found.

*Neurophysiological learning parameters*

Gruzelier [42] argued that EEG-NFB learning contains possible improvements across and within sessions as well as carry-over. We modeled the N100 amplitude as linear responses to these learning categories and time, subdividing them into (1) aptitude: general ability to increase the N100 in the active condition (training or transfer) compared to the passive condition, (2) carry-over: non-voluntary learning in the passive condition, and (3) voluntary learning: as an increase in one of the active conditions (training or transfer) compared to the passive condition across time. This subdivision was used to account for individually different learning patterns by linear mixed effect models. Overall, we separated our data into across-session and within-session between subjects.

Our findings suggest that the N100 amplitude cannot be described as a static or constant component. As evident in figure 4, the N100 amplitude decreased from the first to the second session per day and

also within each session. This motivated a first, very simple model that merely accounted for the time offset from the beginning of the training. Given our hypotheses, this unspecific time effect was not of our primary interest and, therefore, was eliminated for all further analysis.

*Across-session*

*Carry-over effect.* Using the time-corrected data, we first used the most complete model for across-session including random effects for *Session* and *first and second session per day* and *Condition* (passive and active: training, and transfer) as seen in table 2 section A1. The significant interaction between *Session* and separation into *first and second session per day* justified the differentiation into first and second session per day in a further step. The most relevant finding across-session was a carry-over effect in the passive condition in the first session; subjects showed a significant increase in the passive condition across the sessions, which constituted a non-voluntary and passive response of the N100 amplitude to NFB training. Gruzelier [42] described passive increments as learned changes that manifest in the pre-training period of consecutive sessions. So, despite the instruction to rest and try not to think of anything specific, subjects seemed to be more capable of increasing the N100 amplitude in this state on a non-conscious or non-voluntary basis.

*Neurofeedback as operant learning.* NFB is often described to involve operant learning as an underlying mechanism [33]. The passive condition seemed to show these operant and unconscious learning effects. Especially in clinical patient studies, an improvement in the passive condition is advantageous, since the goal in this group is to change a certain brain state over a stable time that then might lead to a behavioral change.

*N100 and attention dependency.* Contrary to the results of the passive condition, and both for the first and second session per day, neither training-aptitude nor transfer-aptitude showed a significant effect across sessions. Thus, across subjects' sessions, we found no consistent evidence of learning when voluntary and active participation of the subject was required. A possible explanation for our intriguing finding that N100 increases were found to be selectively present during periods when the subjects

were not actively trying to learn may be that the N100 is attention-dependent [52]. Forty years ago, Hink et al. [53] showed in a task that required selective attention an enhanced N100 amplitude evoked by stimuli presented to the attended ear. A newer study even showed that healthy subjects could adjust their AEPs by the amount of attention paid to the competing auditory stream [40]. Our data, therefore, suggest that in our type of NFB training, attention on the mental strategies suppressed the N100 amplitude but at the same time facilitated long-term plastic changes that affected the N100 amplitude the following training day (carry-over effect).

*Within-Session*

Within-session results showed a consistent and stable effect in the non-separated data as well as in the data divided into the first and second sessions per day. Overall, there were two main findings: First, a significant decrease of the N100 amplitude (carry-over) in the passive condition, and second, a significant learning effect with voluntary learning (active training vs. passive condition).

*Habituation effect of the N100.* A systematic decrease of the N100 amplitude across sessions can be seen with repetitions. Despite a number of studies that investigated response decrements of AEP components after repeated stimulus presentation, there is still an ongoing discussion about the underlying mechanism that leads to this decrease. Mainly two systems have been discussed: (1) a decrease of the AEP component through habituation as a simple learning process and (2) a response decrease due to refractoriness, which describes the recovery time for neurons to AEP responses before fully being able to respond again. While for refractoriness the response decrease is completed after the second stimulus, habituation shows an asymptotic response decrease over a longer time period [28]. For repeated stimuli and what was earlier described as long-term habituation, Näätänen and Picton [26] illustrated the phenomenon of a decrease of the N100 across time  In our study, the presentation of repeated stimuli of the same frequency showed a reduction within one session as well as a reduction from the first session to the second session per day. However, the decrement could not be seen in the consecutive training sessions performed on different days. On the contrary, subjects even showed a

carry-over effect (increase of the passive condition) across the sessions. According to the definitions above, a habituation process might thus explain these results best, given that it is not a long-term effect and recovers from one day to the next. Interestingly, despite this habituation effect within one session, our subjects were able to voluntarily modify the N100 amplitude in the training condition within one session and, therefore, withhold the habituation effect over several minutes. Thus, within sessions, subjects seemed to be able to voluntarily differentiate between the passive condition (where subjects rested without modifying the N100 component) and a training condition (where subjects were instructed to increase the visually presented balloon and thereby modify the N100 amplitude). However, this habituation effect was not found across session. Therefore, it seems that the N100 recovers from the habituation from one training session to the next.

*Neurofeedback under the scope of learning theories.* These within- and across-session results showed the ability to modulate the N100 within a certain time period on a voluntary level as an active response and, during a longer time, as a non-voluntary passive response. These results support basic motor learning theories according to Fitts [54], who stated three consecutive stages of motor skill acquisition: First, in the cognitive stage at the beginning of skill acquisition, the explicit knowledge is gained. This phase supposedly requires a high amount of attention, and the correct behavior is identified by trial and error. Second, in the associative phase, the new behavior is practiced by focusing on specific details of the learned sequence. The third and final stage is the autonomous stage, where the desired action can be practiced automatically with less attention [55]. An additional model that has been used to explain NFB learning results from the dual process theory by Lacroix [56]. According to this model, the subject analyzes successful strategies in a first cognitive commanding phase, which then leads in the second step to an association between the interoceptive stimuli and the given feedback. Transferring these models to our findings, within-session learning seems to reflect the active cognitive state of voluntary learning by trial and error and is assumed to be attention-consuming. The advanced and more automatized stage of learning a new behavior can be observed in the across-session passive condition increment across time. According to our definition, the passive increase mirrors a passive

response to a non-voluntary learning level. Importantly, this baseline increase of the N100 amplitude as automating learning reflects a carry-over effect manifesting after the training sessions in the consecutive session [42]. We can conclude from these findings that successful learning has to be adapted depending on the investigated time period (within or across sessions).

*N100 and its role in pathology.* Heinks-Maldonado and colleagues [57] linked the ERP reduction of the N100 to hallucinations and to a dysfunction of perceptual processes. To discuss whether NFB training of the N100 amplitude might be a possible treatment for auditory hallucinations, some evidence is available from NFB studies on tinnitus. Patients with tinnitus also showed dysfunctional auditory perception processes that are biologically reflected as a reduction of the N100 component. In tinnitus, the N100 has been successfully modulated through NFB. Delb et al. [27] showed alterations of the ERP component in association with distress and attention. Attention could be modulated in controls in only one NFB session [40]. Given the hypothesis that the N100 amplitude and the primary auditory cortex are underlying neurophysiological features that play an important role in misperception of auditory events, Haller and colleagues [41] used rtfMRI training to affect the responsiveness of the primary auditory cortex in patients with tinnitus. The disease-related increased responsiveness of the auditory cortex was reduced after the training, which led to a symptom reduction in some of the patients with tinnitus. Importantly, patients with tinnitus showed a comparable pattern in the underlying neurobiology of the N100 to patients with schizophrenia. These studies might, therefore, be an important model for future schizophrenia studies to investigate AVH. In regard to schizophrenia and learning to self-regulate the own brain activity by means of a neurofeedback task, Gruzelier et al. revealed that schizophrenia patients were able to learn to control slow potential interhemispheric asymmetry and thereby demonstrated the feasibility of patients being able to improve in such a task despite often displaying cognitive deficits. Looking at regions important to treat AVHs, Cordes and colleagues showed in a fMRI-NFB study the capability of schizophrenia patients to modulate their ACC [37]. Further, Dyck and colleagues reported a successful training of the ACC in AHV patients with an improvement in some AVH symptoms [17].

*Limitations*

The study has several limitations. First, the small sample size of 15 subjects restricted statistical power. Second, this study did not include a control group with a placebo or sham-training. The primary interest was to test the feasibility of a N100 component modulation. However, in neurofeedback studies, we suggest to include a placebo or sham-training to control for unspecific neurofeedback processes (e.g. attention from the trainer) that might influence training success. Third, in neurofeedback, there is no gold-standard in the use of a training protocol. Our protocol was designed and used for the first time. Given the decrease of the amplitude across time and the deterioration of training performance in the second session per day, a shorter training protocol might be equally successful.

*Conclusion*

In this study, we tested the feasibility of healthy subjects to modulate the N100 amplitude and counteract the known decrease of the N100 amplitude over time through NFB training. Given these results and the above described knowledge about schizophrenia patients with AVH and their connection to the N100 amplitude as a possible underlying neurophysiological feature, it seems reasonable to perform NFB training in patients with hallucinations. EEG-NFB has the advantage of a high temporal resolution allowing to give feedback in real time. Further, it empowers patients to achieve changes on their own and thus enhances the feeling of control. However, it has to be noted, that learning to modulate the N100 can only be interpreted in an indirect way due to the observed habituation effects. For future perspectives, in N100 neurofeedback trainings, the common instruction in neurofeedback to use mental strategies should be more controlled due to the N100 suppression by inner speech [25]. Further, according to our results, a cutback to one session per day might be justifiable and might even further lead to a higher compliance in the patients due to the reduced time effort needed. Other methods like rTMS showed positive effects by targeting similar regions [58]. However, effects only lasted for one month. Allowing to transfer the learned behavior in any situation, NFB might be a possible alternative or a supplementary treatment for AVH with more long-term effects compared

to rTMS [35]. Despite the lack of NFB feasibility studies in schizophrenia patients, a few encouraging studies showed that patients with schizophrenia are able to learn with NFB [37-39, 59].

**Word index**

**Mixed effect model terms**

**Across-session:** compares the mean of the passive condition to one of the active conditions (training or transfer repetitions) across the 8 double-sessions.

**Within-session:** compares passive condition and training repetitions within one session averaged across 8 double-sessions.

**Double-session:** reflects the effect of the 8 neurofeedback training days (2 single-sessions per day) independent of the condition.

**Session half**: means the division into first and second session per day.

**Time offset:** time offset when a new task repetition starts. Due to a natural decrease of the N100 amplitude across time and an irregular distribution of passive condition and training within one session, time offset controls for this additional variable *time.*

**Condition**: shows neurofeedback N100 amplitude responses separated by passive and active condition (training and transfer).

**Repetition:** shows carry-over effects from one block to the next (2.5 minutes of training each).

**Learning indices**

**Passive condition carry-over:** reflects the repetition effects in the passive condition across- or within-session.

**Training-aptitude:** shows the general ability of a subject to increase the amplitude N100 in the training condition compared to the passive condition.

**Training-learning:** reflects the difference between the training condition and passive condition across time. Across sessions, it shows the interaction between session and condition; within sessions, it shows the interaction between repetition and condition. Reflects either an increase or decrease of the N100 amplitude across session or repetition.

**Transfer-aptitude:** shows the general ability of a subject to perform an increase of the amplitude N100 in the transfer condition compared to the passive condition.

**Transfer-learning:** reflects the difference between the transfer condition and passive condition across time. It shows the interaction between session and condition across sessions and reflects either an increase or decrease of the amplitude N100 across sessions.

**tables**

**table 1** Demographic, clinical and cognitive variables

| **Healthy subjects (N = 15)** | **mean** | **SD** |
|---|---|---|
| age (years) | 27.7 | 7.6 |
| education (years) | 16.6 | 3.4 |
| **BSI** | | |
| pre (t-value) | 39.9 | 9.4 |
| post (t-value) | 39.3 | 9.5 |

| | | | |
|---|---|---|---|
| **MATRICS** | | | |
| | NAB-Mazes | | |
| | t-value | 47.9 | 9.8 |
| | perc | 46 | 30.3 |
| | HVLT-R | | |
| | t-value | 55.1 | 11.5 |
| | perc | 61.8 | 32.1 |
| **D2 attention** | | | |
| | total | | |
| | raw | 525.6 | 80 |
| | perc | 68.2 | 28.2 |
| | total nr corr | | |
| | raw | 503.2 | 78.6 |
| | perc | 66.7 | 26.4 |
| | concentration | | |
| | raw | 216.7 | 40.7 |
| | perc | 75.7 | 22 |

*BSI = Brief Symptom Inventory; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia NAB-Mazes = Neuropsychological, Assessment Battery; HVLT-R = Hopkins Verbal Learning Test - Revised; D2: total = Total number processed, total nr corr = total number correct; raw = raw score; perc = percentile*

**table 2** Between-subject responses of the different linear mixed effect models for the N100 amplitude neurofeedback training. A) across-session responses, B) within-session responses

| A) Across-session | fixed effect | estimate | SD | t-value | p-value | random effect for subject | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *Time Offset* | *Session** Session half | *Session*Condition* |
| **1) Session * Session half * Condition** | | | | | | | x | |
| | Intercept | 7.31 | 0.91 | 8.07 | < 0.001 *** | | | |
| | Session : Session half | -0.01 | 0.05 | -2.00 | 0.05 * | | | |
| **2) Time Offset** | | | | | | | | |
| | | -0.04 | 0.01 | -5.27 | <0.001 *** | x | | |
| **3) Session * Session half * Condition** | | | | | | | x | |
| | Intercept | 7.78 | 0.96 | 8.13 | < 0.001 *** | | | |
| | Passive – carry-over | 0.09 | 0.05 | 1.74 | 0.09 | | | |
| | Session half | 0.70 | 0.24 | 2.86 | 0.005 ** | | | |
| | Session : Session half | -0.11 | 0.05 | -2.33 | 0.02 * | | | |
| **4) Session * Condition** | | | | | | | | x |
| 1st session per day | | | | | | | | |
| Training | | | | | | | | |
| | Intercept | 7.84 | 0.98 | 8.02 | < 0.001 *** | | | |
| | Passive - carry-over | 0.13 | 0.05 | 2.42 | 0.03 * | | | |
| | Training - aptitude | 0.03 | 0.30 | 0.10 | 0.92 | | | |
| | Training - learning | -0.11 | 0.05 | -1.94 | 0.06 | | | |
| Transfer | | | | | | | | |
| | Intercept | 7.47 | 0.85 | 8.81 | < 0.001 *** | | | |
| | Passive - carry-over | 0.08 | 0.06 | 1.43 | 0.17 | | | |
| | Transfer - aptitude | -0.24 | 0.44 | -0.55 | 0.59 | | | |
| | Transfer - learning | 0.01 | 0.08 | 0.08 | 0.94 | | | |
| 2nd session per day | | | | | | | | |
| Training | | | | | | | | |
| | Intercept | 8.63 | 1.06 | 8.11 | < 0.001 *** | | | |
| | Passive - carry-over | -0.03 | 0.06 | -0.47 | 0.65 | | | |
| | Training - aptitude | -0.53 | 0.31 | -1.72 | 0.10 | | | |
| | Training - learning | 0.02 | 0.05 | 0.34 | 0.74 | | | |
| Transfer | | | | | | | | |
| | Intercept | 8.18 | 0.94 | 8.69 | < 0.001 *** | | | |
| | Passive - carry-over | -0.18 | 0.05 | -0.39 | 0.70 | | | |
| | Transfer - aptitude | -0.15 | 0.34 | -0.43 | 0.67 | | | |
| | Transfer - learning | 0.01 | 0.07 | 0.18 | 0.86 | | | |

| B) Within-session | fixed effect | estimate | SD | t-value | p-value | random effect for subject | |
|---|---|---|---|---|---|---|---|
| | | | | | | *Time Offset* | *Condition* |
| **1) Time Offset** | | | | | | | |
| | | -0.04 | 0.01 | -5.27 | < 0.001 *** | x | |
| **2) Repetition * Condition** | | | | | | | x |
| | Intercept | 9.90 | 1.00 | 9.90 | < 0.001 *** | | |
| | Passive - carry-over | -0.96 | 0.13 | -7.17 | < 0.001 *** | | |
| | Training - aptitude | -1.59 | 0.26 | -6.24 | < 0.001 *** | | |
| | Training - learning | 0.84 | 0.14 | 5.99 | < 0.001 *** | | |
| 1st session per day | | | | | | | |
| Training | | | | | | | |
| | Intercept | 9.97 | 1.01 | 9.90 | < 0.001 *** | | |
| | Passive - carry-over | -1.02 | 0.19 | -5.29 | < 0.001 *** | | |
| | Training - aptitude | -1.65 | 0.37 | -4.52 | < 0.001 *** | | |
| | Training - learning | 0.88 | 0.20 | 4.38 | < 0.001 *** | | |
| 2nd session per day | | | | | | | |
| Training | | | | | | | |
| | Intercept | 9.83 | 1.04 | 9.47 | < 0.001 *** | | |
| | Passive - carry-over | -0.90 | 0.19 | -4.83 | < 0.001 *** | | |
| | Training - aptitude | -1.53 | 0.35 | -4.39 | < 0.001 *** | | |
| | Training - learning | 0.79 | 0.19 | 4.07 | < 0.001 *** | | |

**figures**

**figure 1.** A) Design and experimental procedures across sessions. B) Neurofeedback training protocol of a single session with 8 repetitions lasting 2.5 minutes each.

**figure 2**. Schematic overview of the pre-session (resting state, ocular movement and EEG auditory evoked potential extraction) and the neurofeedback training circle. *AEP = auditory evoked potential*

**figure 3**. Averaged waveform distribution (between subjects) of the N100 amplitudes for each channel position, recorded in the pre-session.

**figure 4**. Across session results between subjects uncorrected for time (n = 15): N100 amplitude depicted as weighted mean responses per session and condition. *a.u. = arbitrary unit*

**figure 5.** Across session results between-subjects corrected for time (n = 15): N100 amplitude depicted as weighted mean responses per session and training condition compared to passive condition A) first sessions per day and B) second sessions per day*. a.u. = arbitrary unit*

**figure 6**. Within session learning between subjects (corrected for time, n = 15): N100 amplitude depicted as weighted means for passive condition repetitions (left) and training (right) repetitions. *a.u. = arbitrary unit*

**Conflict of interest:** The authors declare that they have no conflict of interest.

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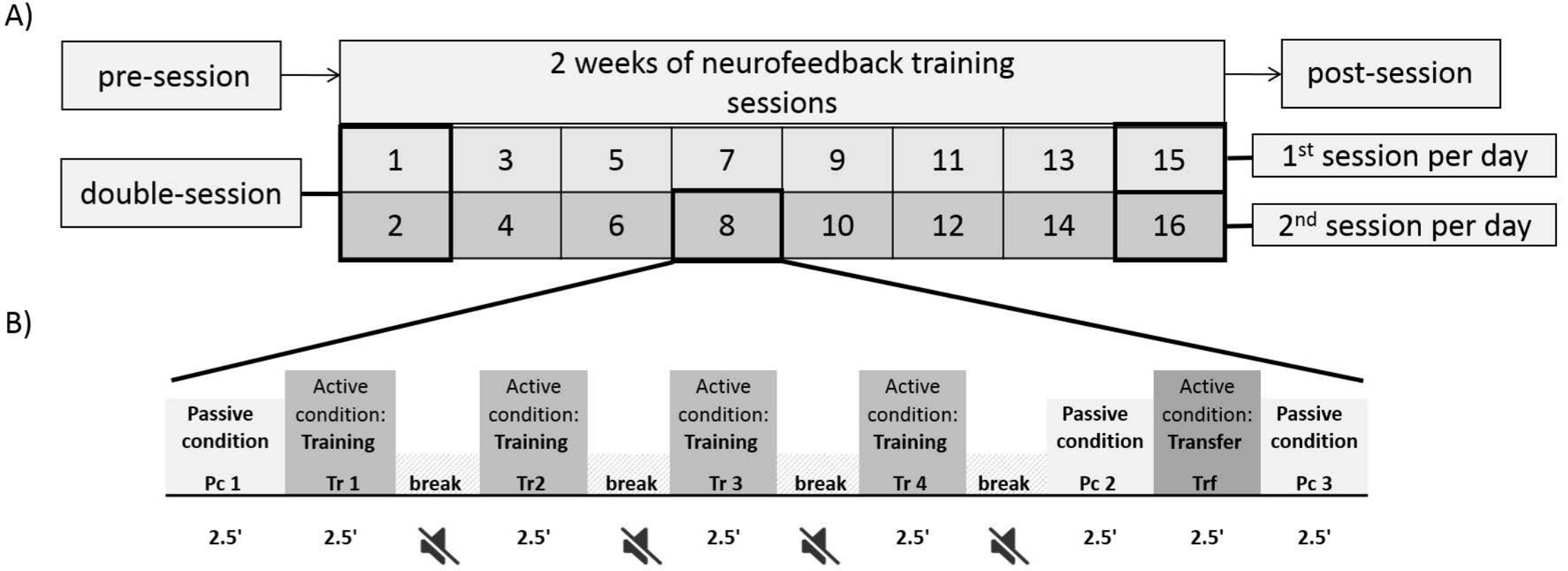
A)
pre-session
2 weeks of neurofeedback training sessions
post-session
double-session
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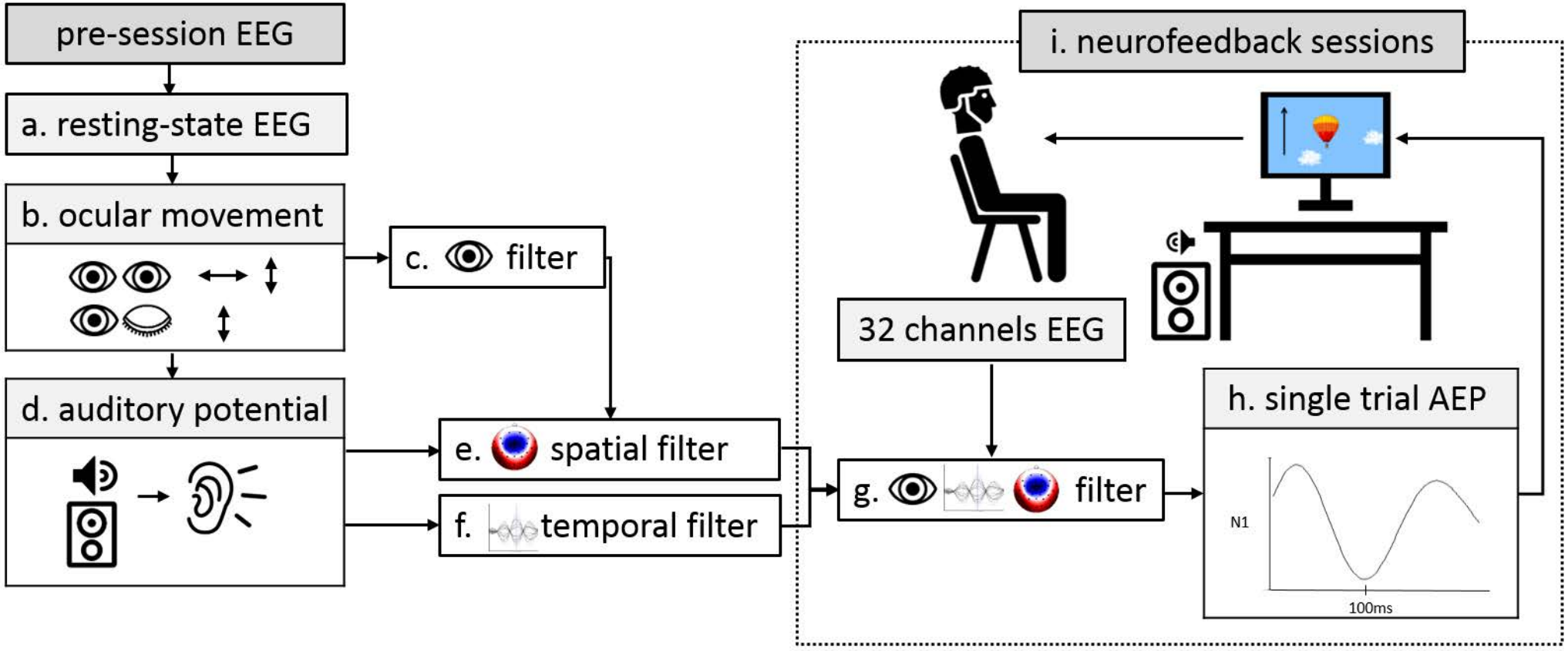
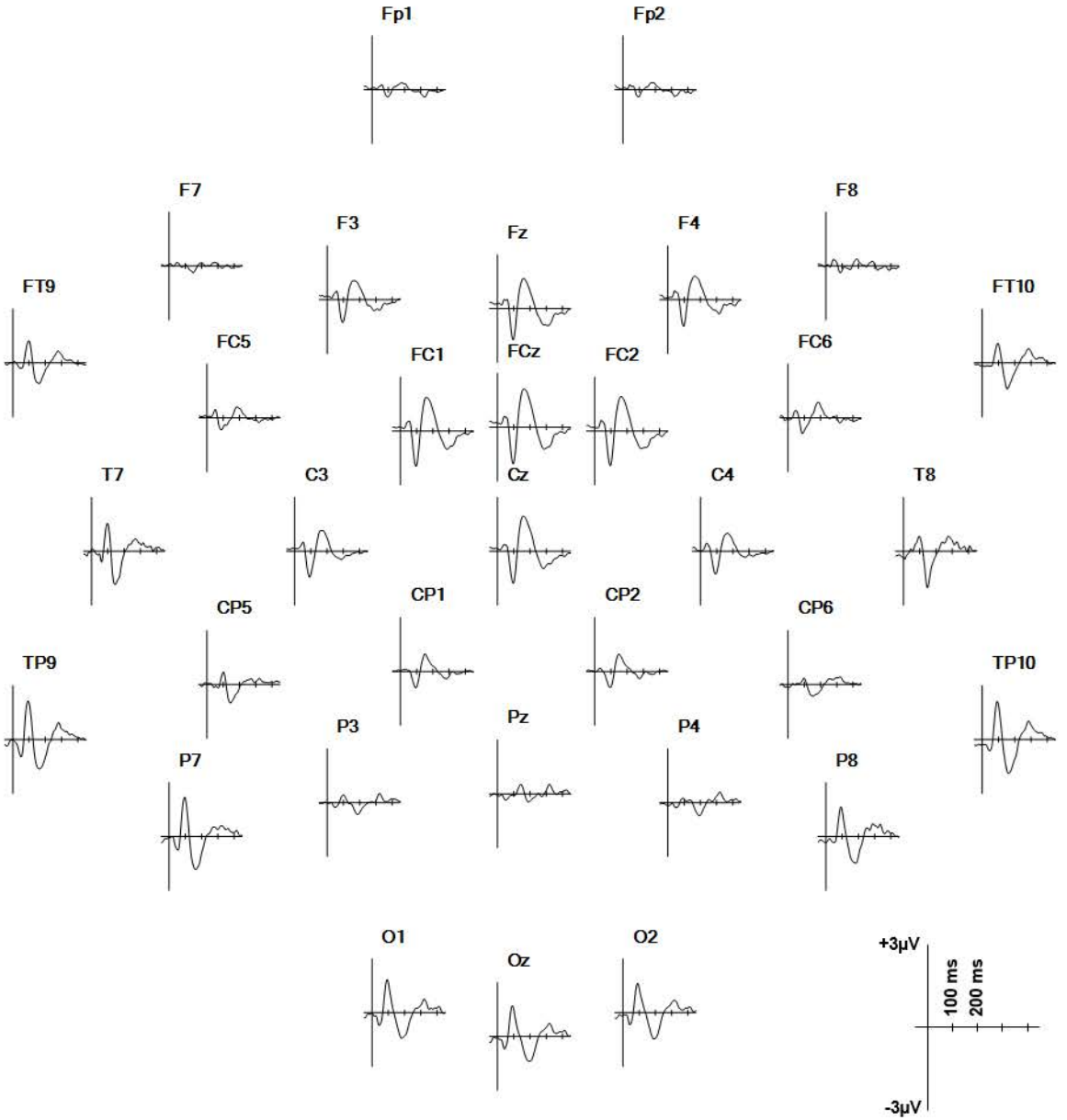
3
5
7
9
11
13
15
2
4
6
8
10
12
14
16
1st session per day
2nd session per day
B)
Passive condition
Pc 1
2.5'
Active condition: Training
Tr 1
2.5'
break
Active condition: Training
Tr2
2.5'
break
Active condition: Training
Tr 3
2.5'
break
Active condition: Training
Tr 4
2.5'
break
Passive condition
Pc 2
2.5'
Active condition: Transfer
Trf
2.5'
Passive condition
Pc 3
2.5'


pre-session EEG
a. resting-state EEG
b. ocular movement
c. filter
d. auditory potential
e. spatial filter
f. temporal filter
i. neurofeedback sessions
32 channels EEG
g. filter
h. single trial AEP
N1
100ms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C3
Cz
C4
T8
CP5
CP1
CP2
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+3µV
100 ms
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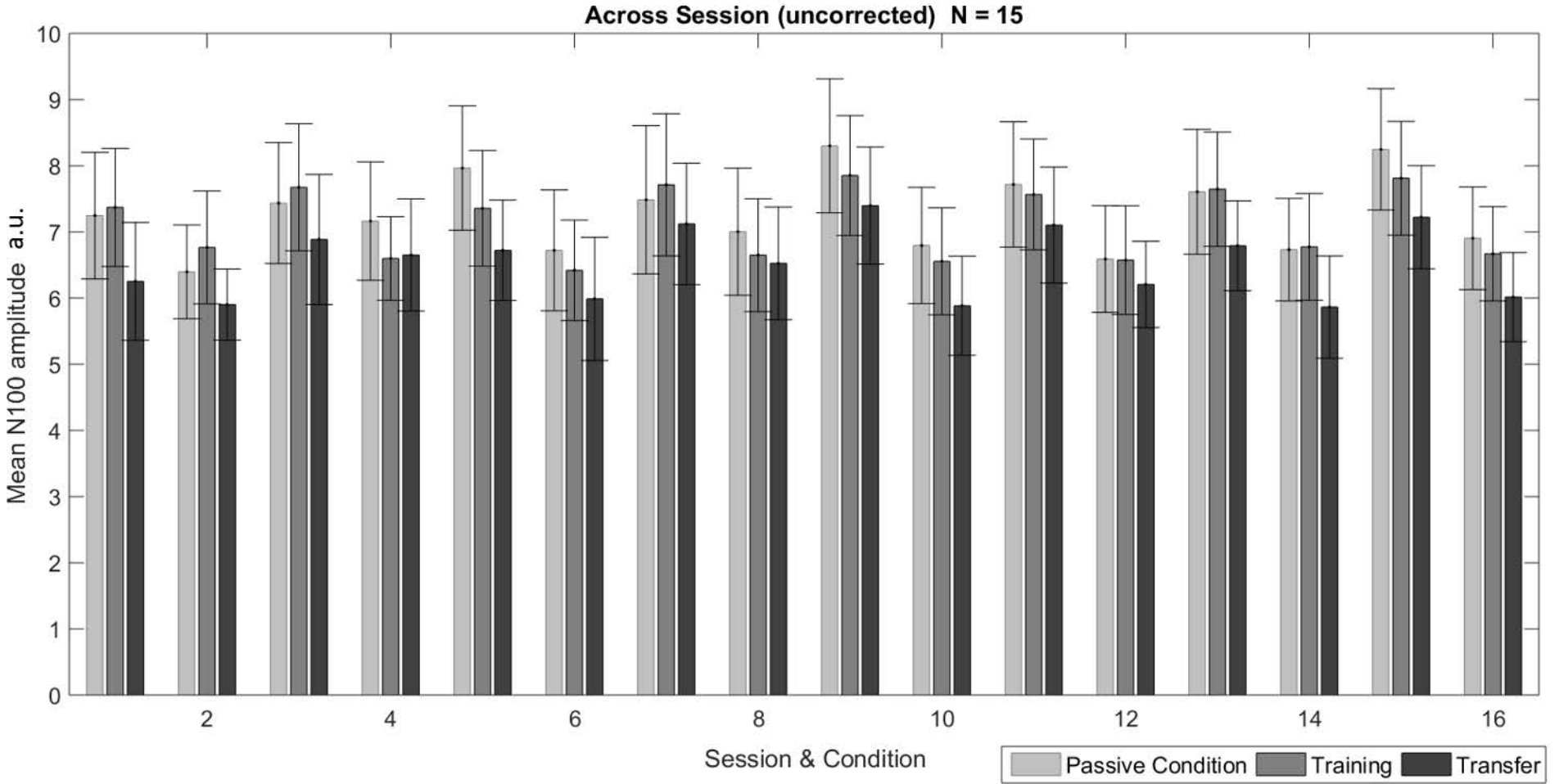
Across Session (uncorrected) N = 15
Mean N100 amplitude a.u.
0
1
2
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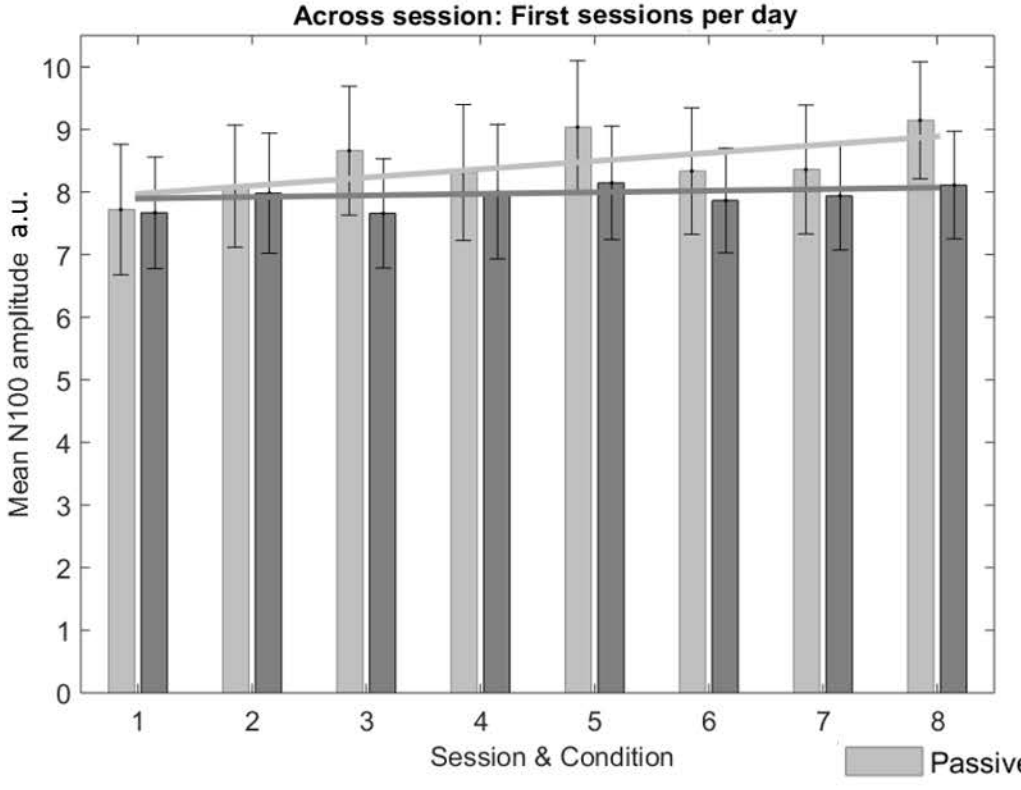
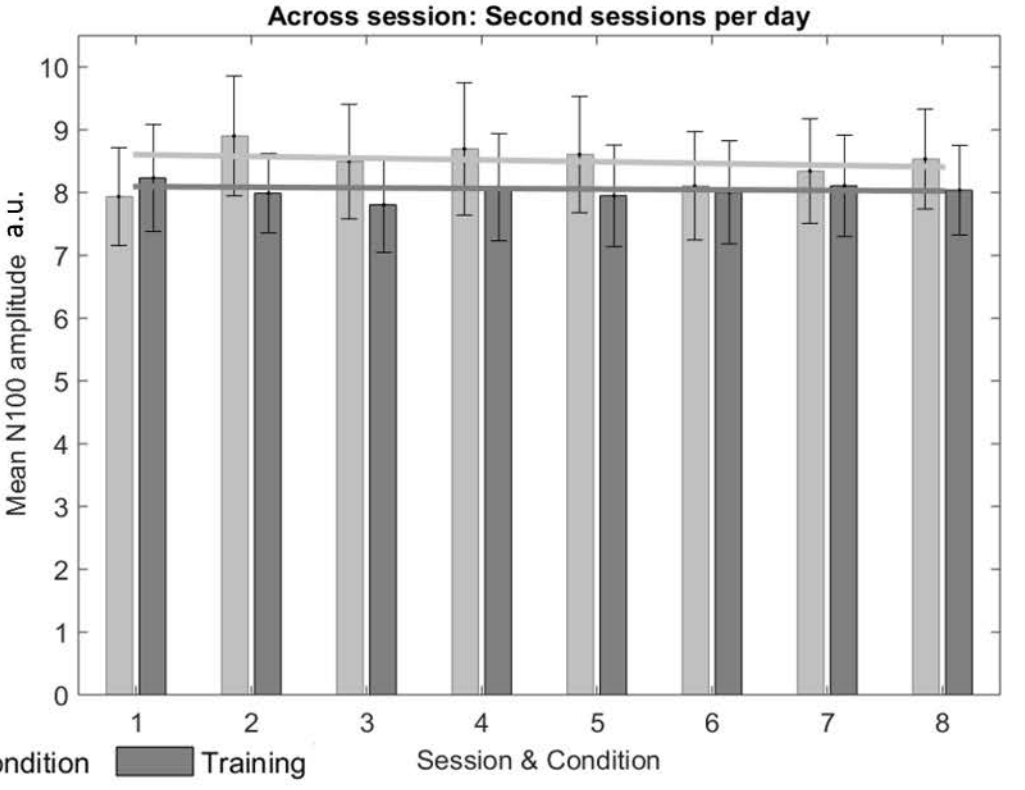
14
16
Session & Condition
Passive Condition
Training
Transfer

A)

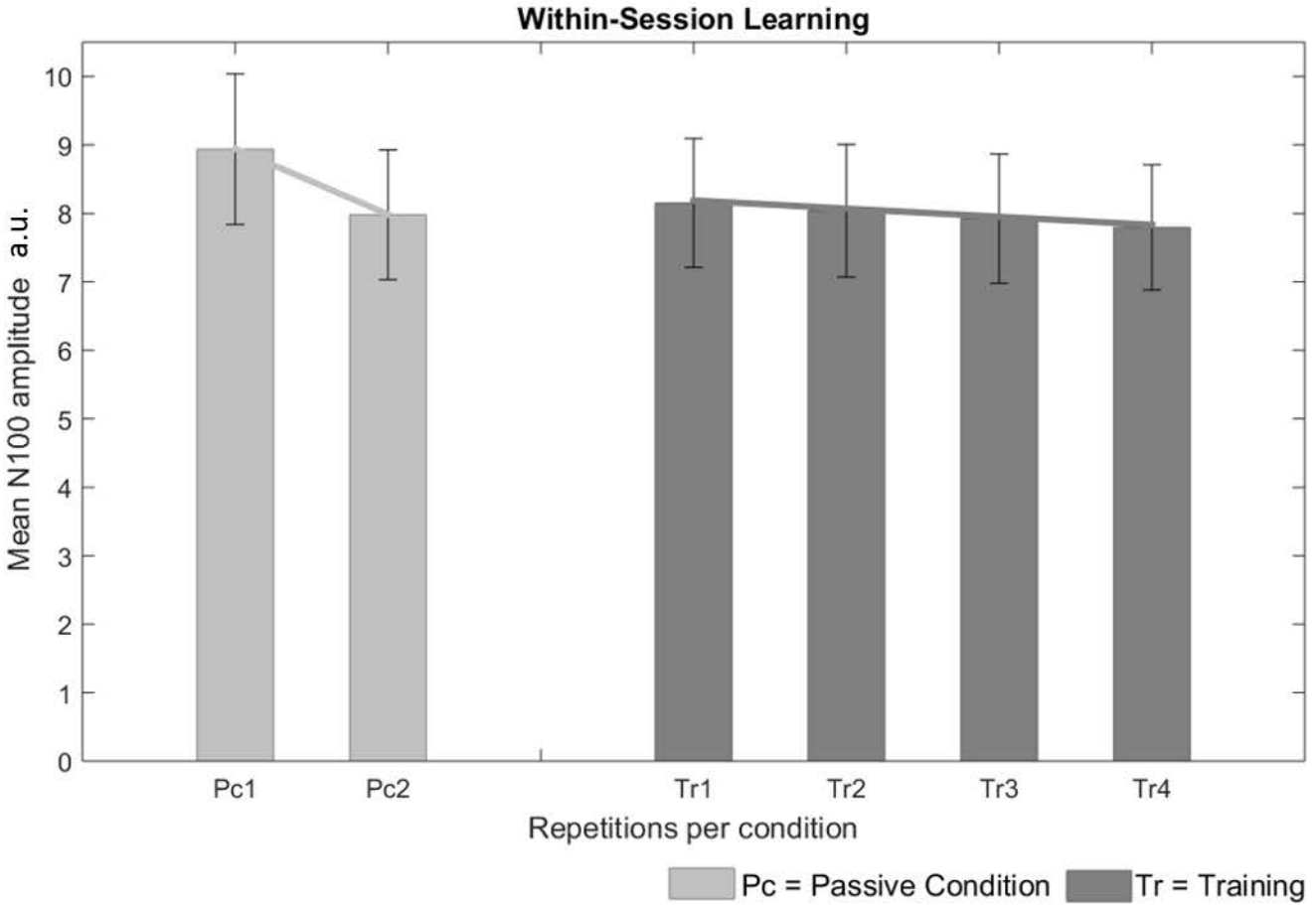



B)




Passive Condition

Training


Within-Session Learning
Mean N100 amplitude a.u.
0
1
2
3
4
5
6
7
8
9
10
Pc1
Pc2
Tr1
Tr2
Tr3
Tr4
Repetitions per condition
Pc = Passive Condition
Tr = Training