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Quantification of Adverse Events Associated with Functional MRI Scanning and with Real-Time fMRI-Based Training

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Abstract

Background—Although functional magnetic resonance imaging (fMRI) is in widespread research use, the safety of this approach has not been extensively quantitatively evaluated. Real-time fMRI (rtfMRI)-based training paradigms use fMRI neurofeedback and cognitive strategies to alter regional brain activation, and are currently being evaluated as a novel approach to treat neurological and psychiatric conditions.

Purpose—The purpose of this study is to determine the incidence and severity of any adverse events that might be caused by changes in brain activation brought about through fMRI or through rtfMRI-based training paradigms.

Method—Quantitative adverse event self-report data were obtained from 641 functional imaging scans in 114 chronic pain patients participating in a research clinical trial examining repeated fMRI scans and rtfMRI-based training. Participants recorded potential adverse events during non-scanning baseline, fMRI scanning, or rtfMRI-based training sessions.

Results—There were no significant increases in the number of reported adverse events following fMRI or rtfMRI scanning sessions compared to baseline non-scanning sessions in a chronic pain trial ($N=88$). There were no reported adverse events of any kind for over 90% of sessions during the course of rtfMRI-based training. When adverse events were reported, they were almost exclusively mild or moderate in severity and similar to those observed in a non-scanning baseline session. There was no increase in adverse events reported by participants receiving feedback from any of four brain regions during repeated rtfMRI-based training scans compared to non-scanning baseline sessions. For chronic pain patients completing the rtfMRI-based training paradigm including up to a total of nine scan sessions ($N=69$), neither the number nor severity of reported events increased during the fMRI or rtfMRI scanning portions of the paradigm. There were no significant increases in the number of reported adverse events in participants who withdrew from the study.

Conclusion—Repeated fMRI scanning and rtfMRI training, consisting of repeated fMRI scanning in conjunction with cognitive strategies and real-time feedback from several regions of interest in multiple brain systems to control brain region activation, were not associated with an increase in adverse event number or severity. These results demonstrate the safety of repetitive

fMRI scanning paradigms similar to those in use in many laboratories worldwide, as well as the safety rtfMRI-based training paradigms.

Keywords

Safety; Adverse events; Functional MRI; Real-time fMRI

Introduction

Functional magnetic resonance imaging (fMRI) studies are generally conducted to measure regional changes in brain activation associated with changes in blood flow in conjunction with a stimulus or task [1]. Real-time fMRI (rtfMRI)-based training is a recent neuroimaging paradigm that involves monitoring fMRI activation as data are being collected (with a short lag, typically 5–8 s due mainly to hemodynamic delay), allowing the training subjects to control brain activation through cognitive processes assisted by neurofeedback-augmented learning. rtfMRI uses fast imaging pulse sequences and greater computational power for rapid image reconstruction to build upon fMRI technology [2–4], which detects the blood oxygen level-dependent (BOLD) signal as a measure of brain activation. In the current study, training tasks consisted of cognitive strategies to increase or decrease the level of brain activation by attempting to modulate the level or quality of perceived pain, in conjunction with neurofeedback from relevant regions of interest (ROIs). rtfMRI-based training has recently been proposed as a novel, potentially clinically relevant approach in the treatment of chronic pain, addiction, and other conditions [2, 3].

Real-time fMRI-based training may pose additional safety concerns relative to routine clinical diagnostic MRI scans and standard fMRI studies. Concern has been raised over the potential health risks associated with this approach, which has the potential to induce long-term plastic changes in the level of activation of targeted brain regions [2, 3]. The potential for inducing seizures or other serious neurological consequences has been a source of appropriate concern for the field. It is important to verify the safety of rtfMRI-based training paradigms involving repeated fMRI scanning and repetitive cognitive task performance to control brain regional activation using real-time feedback.

Since its emergence as a clinical modality in the early 1980s, MRI has become a mainstay of diagnostic medicine and biomedical research. Given the rapid increase in human exposure to MRI over the years, its tolerability and safety profile have been extensively studied [5]. Studies of MRI safety have investigated the biological effects of static and gradient magnetic fields and radiofrequency (RF) pulses used to construct images of the body. There is no confirmed health hazard associated with strong, static magnetic field exposure in subjects who do not have ferromagnetic implants such as pacemakers, and no evidence for hazards associated with increasing exposure [6]. Lifetime studies in animals exposed to radiofrequency electromagnetic fields show no cumulative adverse effects in endocrine, hemato-logical, or immune systems, and cardiovascular tissue is not adversely affected in the absence of heating or electric currents [7]. Moreover, while gradient magnetic fields have been known to stimulate nerves or muscles by inducing electrical fields in patients, current safety standards for gradient magnetic fields associated with present-day MR systems appear

to adequately protect patients from potential hazards or injuries [8, 9]. In an extensive review of the safety of MR procedures, Shellock concluded that most reported cases of MR-related injuries, and the very few fatalities that have occurred, resulted from the failure to follow established safety guidelines for MRI scanning and the use of biomedical implants and devices [5]. According to the most recent guidelines from the US Food and Drug Administration, clinical MRI systems using magnetic fields up to 8.0 T are considered a “non-significant risk” for adult patients [10].

Since the early 1990s, measurement of the BOLD signal using fMRI has come to dominate the field of functional neuroimaging because it is non-invasive, does not require ionizing radiation, and is relatively widely available. In addition to exposure to the magnetic and RF fields in the MRI environment, fMRI studies often employ the use of mental or physical tasks performed by participants while they are in the scanner. Repeated fMRI scanning with higher magnetic field strength scanners is becoming more commonplace, for example, to assess neurologic change over time in longitudinal studies of degenerative diseases or in studies evaluating therapeutic interventions, including clinical drug trials. While fMRI experiments might be expected to have a similar safety profile to other types of MRI scanning that have been investigated extensively, it is worth noting that fMRI scans typically have much longer scan durations. To our knowledge, this is the first study to directly investigate the safety of extended fMRI scans.

In this report, detailed adverse effect data from 641 scanning sessions in 114 chronic pain patients participating in a research clinical trial investigating the use of rtfMRI-based training for treating chronic pain is presented. We hypothesized that participants would not report a significant increase in number or severity of adverse events following repeated fMRI or rtfMRI scan sessions relative to the baseline non-scanning office visit. In addition, we hypothesized that adverse events would not lead to participant withdrawal from the study, and therefore that participants who withdrew from the study during the fMRI or rtfMRI scanning phase of the study would not show a greater increase in adverse events over baseline compared to participants who did not withdraw. Data from a subset of study participants who completed up to nine scan sessions including up to six rtfMRI training sessions, approximately one per week, were analyzed to determine if the number of adverse events and their severity accumulate with repeated rtfMRI-based training. The information obtained in these studies provides the largest and most comprehensive safety dataset yet reported for the use of repeated fMRI and rtfMRI-based training scans and includes four distinct ROIs for real-time feedback.

Methods

Participants

Chronic pain patients refractory to prior pain treatment modalities participated in a clinical trial designed to evaluate the therapeutic potential of rtfMRI-based training to produce a reduction in pain. Inclusion criteria for the clinical trial were: (1) 6 months or more prior history of chronic pain refractory to at least 3 months of physician-prescribed pain therapy; (2) maximum daily pain level averaging at least 5 out of 10 on a visual analog scale during a 1-week monitoring period, (3) age between 21 and 65 years, and (4) capability to understand

and sign informed consent, as well as perform study experimental tasks. Additional criteria for inclusion in this report were: (5) patients were randomized to experimental groups receiving rtfMRI-based training rather than sham control training, (6) patients completed at least one fMRI scan session, and (7) patients whose data were available (i.e., not missing) for both baseline and at least one fMRI scan session ($N=114$). These additional criteria were established to remove potential analysis bias between the baseline, fMRI, and rtfMRI groups.

Of the 122 participants who received at least one fMRI scan and would therefore have otherwise been included in the analysis, eight participants were excluded because of missing adverse events data at baseline, accounting for 6.6% of the sample. For the 114 participants included in this report, three participants had missing data from a fMRI session (accounting for 1.3% of all fMRI visits), and nine participants had missing data from a rtfMRI session (accounting for 2.2% of rtfMRI scanning visits), although for each of these 114 participants adverse events data was available for the baseline session at least one fMRI scan session. Reasons for missing data included noncompliance by the participant to complete the questionnaire at the visit following the request by the investigator, and lack of request by the investigator to complete the questionnaire (baseline visit only). The number of participants that withdrew during each phase of the study is indicated in Fig. 1. All participants were required to provide informed consent prior to entry into the study and all study designs were approved by an institutional review board.

Adverse Event Reporting

Participants completed a detailed, 37-item adverse event questionnaire developed for rtfMRI-based training studies to cover all anticipated potential adverse events. Adverse events were grouped into digestive, sensory, or nervous system effects, changes in emotion or mood, or physical sensations, and were rated by participants as mild, moderate, or severe. Adverse events reports were collected from participants enrolled in chronic pain rtfMRI-based training studies between August, 2007, and July, 2009, immediately following each non-scanning baseline session, fMRI scan, and rtfMRI-based training scan.

Real-Time Training Paradigm

Three similar but distinct real-time training protocols in use during the period of these studies are included together in this report to broaden and maximize the size of the adverse event dataset. Participants completed a baseline office visit followed by one of three scanning protocols: (1) one fMRI scan followed by five rtfMRI scans ($N=49$), (2) three fMRI scans followed by six rtfMRI scans ($N=55$), or (3) four fMRI scans followed by five rtfMRI scans ($N=10$). These three scanning/training protocols were developed to optimize the balance between the number of localizer scans required, the number of real-time training sessions needed, expense of the training paradigm, and subject visit load, and are combined into a single participant flow scheme (Fig. 1).

The baseline session consisted of questionnaire completion, a structured interview regarding chronic pain onset and all medical interventions, a relaxation breathing exercise, and practice of the cognitive tasks for later use in conjunction with both fMRI and rtfMRI scans.

Participants were provided with written cognitive strategies to increase or decrease brain activation. For example, suggested strategies included cognitively manipulating attention to pain and perceived stimulus quality and severity. Participants lay in a supine position on a padded table while practicing the cognitive tasks and rated their pain verbally after employing each cognitive strategy.

During both fMRI and rtfMRI scans, participants employed cognitive strategies to increase or decrease their level of pain. Pairs of strategies in which participants attempted to increase and decrease their perceived pain intensity or brain activation level in a target ROI were repeated up to 10 times in each fMRI or rtfMRI scan session. One to four functional localizer fMRI scans were used to select an individually determined target region for rtfMRI feedback from one of four regions: rostral anterior cingulate cortex (rACC), dorsal anterior cingulate cortex (dACC), or left or right anterior insula (LINS and RINS). Table 1 provides average Talairach coordinates [11] for the four target regions selected as training ROIs.

During rtfMRI scans, participants attempted to use the cognitive strategies in conjunction with real-time feedback to control their level of brain activation in a target ROI. Real-time feedback was presented using a virtual reality display that provided the level of activation measured as the BOLD signal from the selected target brain region. Participants received continuous information about the ongoing level of activation in their target ROI, presented via MRI-compatible VisualSystem goggles (NordicNeuroLab, Bergen, Norway). This information was presented in the form of a virtual reality “fire on the beach” scenario in which the height of the fire is proportional to ongoing target ROI activation and as a scrolling line chart showing a quantitative representation of their brain activation. This signal was computed following real-time 3D motion-correction of whole brain data.

MRI Imaging Parameters

All scanning took place on a GE Signa 3.0 T scanner with CV/NV/i gradients (40 mT/m, slew rate 150 T/m/s); three-plane localizer anatomical scan: T1-weighted three-axis scout (sagittal, axial, and coronal, nine slices, 10 mm thick, FOV=24); 8 s sagittal localizer anatomical scan: T1 FLAIR (TR 1700, TE min, eight slices, 3 mm thick, 0 skip, 512×256 matrix, NEX 1.0, interleaved, FOV=25 cm), 2 min; high-resolution anatomical scans: T1-weighted SPGR, 1.2-mm in-plane resolution; medium-resolution anatomical scans: 2D T1 FLAIR, 4-mm in-plane resolution, in the same space as functional scans; functional scans: T2* sensitive echo planar images; 64×64×28, FOV 210×210×112mm. TR=2 s, TE=30, flip angle=70°, 28 slices, 4 mm thickness; up to six runs of 186 TRs or up to 10 runs of 106 TRs.

Data Analysis

Questionnaire-based self-report data collected following each session were analyzed for each participant as the number (incidence) of adverse events associated with each type of visit (baseline non-scanning, fMRI, and rtfMRI). The total number of adverse events was averaged for each visit type for each participant ($N=114$). In addition, for rtfMRI-based training sessions, the average number of adverse events was determined for four distinct feedback ROIs for each participant. A separate set of analyses were performed on data from patients who completed the repeated rtfMRI-based training paradigm to identify changes in

the number of adverse events between baseline, fMRI scan, first rtfMRI scan, and last rtfMRI scan (fifth or sixth depending upon the protocol; $N=69$). The number of adverse events classified by participants as mild, moderate, or severe were also determined for each of these sessions. To identify a change in incidence of any individual adverse event, the average incidence of each adverse event during the fMRI and rtfMRI portions of the training paradigm was compared with the baseline condition for the 69 participants completing the study. To determine the effects of participant attrition, the incidence of adverse events was compared between visit types for participants that withdrew prior to the first rtfMRI scan ($N=26$) and those that completed at least one rtfMRI scan ($N=88$), and for participants that withdrew prior to completion of the final rtfMRI scan ($N=19$) and those that completed the study ($N=69$). Data were analyzed using non-parametric tests in SPSS 16.0. The Wilcoxon signed-ranks test was used for within-participant comparisons across two visit types. The Friedman test was used for within-participants comparisons across greater than two visit types, with post-hoc tests performed using the Wilcoxon signed-ranks test. The Mann–Whitney U test was used for between-participants comparisons for completers and withdrawn participants. All data are expressed as mean $\pm$ SEM.

Results

A total of 114 participants (44 males, 70 females; mean age 49, SD 8 years) provided adverse events questionnaire information from a non-scanning baseline session and at least one fMRI scan session (Fig. 1). Adverse event data from 114 baseline sessions, 235 fMRI scans, and 406 rtfMRI-based training sessions were included in this analysis.

No adverse events were reported in over 90% of scanning and non-scanning sessions during the course of these studies for those participants completing at least one rtfMRI scanning session ($N=88$). Participants reported an average of 3.9 ± 0.4 adverse events during non-scanning baseline sessions, 4.2 ± 0.4 adverse events during fMRI scanning, and 2.7 ± 0.3 adverse events during rtfMRI-based training sessions out of a total possible 37 adverse events (Fig. 2). There was no significant increase in the number of reported adverse events following fMRI scanning compared with the baseline non-scanning condition. There was also no significant increase in the number of reported adverse events following rtfMRI-based training compared with the baseline non-scanning condition. In fact, there was an overall significant effect of visit type (Friedman test, $\chi^2(2)=9.03$, $N=88$, $p=0.01$), with post-hoc tests indicating that the number of adverse events was significantly lower for rtfMRI sessions compared with baseline (Wilcoxon signed-ranks test, $Z=-3.3$, $p=0.001$) and fMRI sessions (Wilcoxon signed-ranks test, $Z=-4.5$, $p<0.001$). For the limited number of adverse events that were reported, most were characterized by the participants as mild or moderate in severity (Fig. 3a–c).

An analysis of the reported adverse events associated with rtfMRI-based training using four distinct feedback ROIs indicated that there were no significant increases in the number of reported adverse events comparing baseline with rtfMRI scan sessions for patients receiving feedback from any of the training ROIs (Fig. 4). There were no significant differences between the number of adverse events reported at baseline and rtfMRI session in patients receiving feedback from the dACC (Wilcoxon signed-ranks test, $N=20$, $Z=-1.31$, $p=0.191$)

and RINS (Wilcoxon signed-ranks test, $N=16$, $Z=-0.94$, $p=0.345$). The number of adverse events decreased from baseline to rtfMRI scanning for patients receiving feedback from the rACC (Wilcoxon signed-ranks test, $N=23$, $Z=-2.25$, $p=0.024$) and LINS (Wilcoxon signed-ranks test, $N=28$, $Z=-2.08$, $p=0.038$).

To assess the long-term safety profile of repeated fMRI scanning and rtfMRI-based training, adverse events reported by participants that completed the entire course of rtfMRI-based training were evaluated further. There was no increase in adverse events observed following up to four fMRI scans or up to six rtfMRI scans in participants completing the rtfMRI-based training paradigm. Comparison of the total number of adverse events reported at baseline, fMRI, rtfMRI session 1, and the last rtfMRI session (session 5 or 6 depending upon the protocol) revealed an overall significant decrease in adverse events across visits (Friedman test, $\chi^2(3)=23.3$, $N=69$, $p<0.001$; Fig. 5a). Similarly, comparison of the number of mild adverse events reported at baseline, fMRI, rtfMRI session 1, and rtfMRI session 5/6 revealed an overall significant decrease across visits (Friedman test, $\chi^2(3)=21.4$, $N=69$, $p<0.001$; Fig. 5b). There were no significant differences in the reported number of moderate or severe adverse across visit days (Friedman tests, moderate: $\chi^2(3)=4.2$, $N=69$, $p=0.24$; severe: $\chi^2(3)=4.2$, $N=69$, $p=0.24$). Post-hoc tests indicated that there were fewer total and mild adverse events for the first and last rtfMRI sessions than both baseline and fMRI scan sessions, and the last rtfMRI session had fewer events than the first rtfMRI session (Wilcoxon signed-rank tests, all $p<0.05$).

The only individual adverse event types that significantly increased in incidence during the scan sessions compared to the baseline non-scanning session were ringing in the ears (Wilcoxon signed-ranks tests, $N=69$, baseline vs fMRI, $Z=-3.01$, $p=0.003$; baseline vs rtfMRI, $Z=-2.95$, $p=0.003$) and stuffiness in ears (Wilcoxon signed-ranks tests, $N=69$, baseline vs rtfMRI, $Z=-2.01$, $p=0.044$; Table 2). No individual adverse event was reported with higher incidence in rtfMRI scan compared to fMRI scan sessions (Wilcoxon signed-ranks tests, all $p>0.05$). Somnolence and increased pain were the most frequently reported adverse events during all three types of visits. The next most frequently reported adverse events were muscle twitching and a feeling of heat or burning for baseline sessions, muscle twitching and backache for fMRI scans, and backache and headache for rtfMRI scans.

Participants who withdrew from study participation during fMRI and rtfMRI scanning did not show greater changes in the number of adverse events from baseline compared to participants who did not withdraw from study participation (Fig. 6). There were no significant changes in the number of reported adverse events from baseline for participants who withdrew from the study during fMRI scanning (Mann–Whitney $U=1,057.5$, $p=0.604$) or during rtfMRI training (Mann–Whitney $U=575.5$, $p=0.417$) compared to those who did not withdraw from the study. Examination of the small incidence ($<1\%$) of events rated as severe by the participants (Fig. 3) revealed that sleepiness and increased pain were reported as two of the three most frequent events at all three visit types. Whereas muscle twitching was reported at baseline sessions, headache was reported during scanning sessions among the three most frequently reported adverse events rated as severe.

To identify the reasons why participants withdrew from the study that may not have been captured by the adverse event questionnaire, all participants who withdrew were questioned for the reason for their withdrawal. For the 26 participants that withdrew during fMRI scanning, 23 withdrew for reasons unrelated to adverse events (such as time commitment required by the study), one felt nausea and dizziness, one developed a headache, and one found the scanner noise uncomfortable. For the 19 that withdrew during rtfMRI scanning, one withdrew because of scanner noise and 18 withdrew for reasons unrelated to adverse events. No seizures, deaths, events requiring emergency medical attention, or events assessed as medically concerning by the research team were reported for any visits.

Discussion

The present study represents the most comprehensive and largest reported experience to date regarding the safety and tolerability of rtfMRI-based training paradigms involving repeated fMRI scanning, repetitive cognitive task performance, and neurofeedback targeting one of four distinct brain regions. The principal finding of this study is that repeated fMRI scanning sessions and repeated rtfMRI-based training sessions can be administered with no increase in the incidence or severity of adverse events compared with a baseline session that does not involve MRI scanning. Given this extensive dataset and consistent adverse event profile derived from participants with a broad range of chronic pain states and different target brain regions, these findings serve as an important indicator of the safety and tolerability of repeated fMRI and rtfMRI-based training procedures.

The incidence of reported adverse events was similar in the baseline non-scanning session and in fMRI scanning sessions and rtfMRI-based training sessions. This finding suggests that use of rtfMRI-based training using cognitive strategies to control the level of activation of brain regions contributing to the perception and maintenance of chronic pain did not produce observable untoward consequences in this population. In fact, the total number and the number of mild adverse events reported decreased for rtfMRI scan sessions compared to baseline or fMRI sessions for chronic pain patients completing the rtfMRI training paradigm. This observed decrease may have resulted from the participants becoming more accustomed to the scan procedures on successive occasions.

The safety of cognitive modulation of brain regional activation level appears to be a general phenomenon, as the adverse event incidence was similar for rtfMRI-based training using four distinct brain regions of interest serving a broad range of functions and involving several brain networks. In all four brain regions (dACC, rACC, RINS, and LINS), there was no significant increase in the number of adverse events reported in rtfMRI scans compared to non-scanning baseline sessions.

There were no adverse events reported following the great majority of sessions, and those adverse events that were reported were almost exclusively mild to moderate in severity. It should be noted that the adverse events were reported by the participants themselves on a questionnaire, so they involve the participant's own judgments of severity. Adverse events reported as severe were similar in baseline, fMRI scan, and rtfMRI scan sessions. The few adverse events rated by the participants as severe, in less than 1% of sessions, were not

increased in scanning sessions relative to the non-scanning baseline session, never required medical attention, and were not obviously related to scanning or study participation. Notably, no participant who reported an adverse event as severe withdrew from the study because of an adverse event or any other reason. In addition to the adverse event questionnaire which was analyzed in this report, all participants who withdrew were questioned for the reason for their withdrawal. Of the 114 participants included in this study, four withdrew for reasons that might be related to scanning, including nausea and dizziness, headache, and scanner noise, whereas the majority of withdrawn participants were removed from participation in the study at the investigator's discretion due to poor study compliance, for example not attending scheduled visits. There was no difference between the number of moderate or severe adverse events reported at fMRI or rtfMRI scanning sessions relative to non-scanning baseline sessions for study completers.

Somnolence and increased pain were the most frequently reported adverse events during baseline non-scanning sessions and both fMRI and rtfMRI scan sessions for chronic pain patients completing the rtfMRI training paradigm. The high incidence of somnolence is probably related to reclining posture during the baseline session and long periods (up to 1 h or more) spent in the scanner during scanning sessions. As the self-report of somnolence was made immediately after the baseline or scan session, no assessment can be made regarding the duration of the drowsiness following the end of the visit. The pain-related complaints are not unexpected for chronic refractory pain patients, who were asked to employ cognitive strategies to decrease as well as increase their pain. Additionally, lying flat in the scanner for an hour or more is generally tolerable but can cause significant discomfort in pain patients. Ringing and congestion in the ears were the only individual adverse events that increased in incidence during the scan sessions (both fMRI and rtfMRI scans) relative to baseline sessions. Although all reasonable precautions were taken (including double ear plugs in each ear), the ringing and the sensation of congestion in the ears was likely due to scanner acoustic noise. No individual adverse event was reported with higher incidence during rtfMRI relative to fMRI sessions, again suggesting that rtfMRI-based training sessions in which participants exert cognitive control over the level of brain activation poses no additional risk over routine fMRI scans.

Since it was possible that selective attrition of participants with an elevated level of adverse events could have biased the results, a detailed analysis of the adverse events in withdrawn participants was conducted. A total of 45 of 114 participants included in this report (39%) withdrew prior to completion of the rtfMRI training paradigm. This withdrawal rate is not surprising in comparison with typical clinical trial completion rates considering the level of commitment required by participants to attend eight to 10 visits, including six to nine scanning sessions, depending on the study protocol. An analysis of participants who withdrew during the fMRI and rtfMRI scanning portions of the training paradigm indicates that there was no change in number of adverse events from baseline to fMRI or rtfMRI scanning session for these participants compared to those participants who did not withdraw. This finding suggests that the results of this study were not biased by selective attrition of participants.

There are limitations of the conclusions that can be drawn from this dataset. These results may not generalize to all potential fMRI scanning parameters, particularly in cases where non-FDA-approved MRI pulse sequences are being used, or where experimental scanning parameters do not follow FDA guidelines. Although these results suggest that repetitive fMRI scanning and rtfMRI-based training are generally safe, they may not apply to training procedures targeting other brain regions or using different behavioral strategies. In addition, this study does not assess the potential for very-long-term adverse consequences of repeated fMRI or rtfMRI scanning, although participants completing the rtfMRI training paradigm were followed over a period of 6.4 ± 0.5 months. It is important that investigators performing rtfMRI studies continue to exercise appropriate caution and concern for participant safety.

All of the authors are current or former employees of Omneuron, Inc., a National Institutes of Health-funded company developing and testing neuroimaging-based approaches for diagnosing and treating neurologic and psychiatric diseases, including rtfMRI-based training. As in any study of this kind, it is theoretically possible that errors made in the conduct or analysis of the study could have biased the overall result that repetitive fMRI scanning was not associated with an increase in adverse event number or severity. In principle, it is possible that a bias affecting this overall result was introduced by: (1) differential instructions or coaching of participants in their completion of the adverse events questionnaire; (2) selection of subjects for inclusion in the analysis; (3) selective capture of questionnaire data; (4) errors made in the flow of data from the questionnaire form itself to the tables and graphs included in this report at any step, including data entry, software manipulations, or calculations; (5) biased statistical comparisons; and (6) the potential for subjects with elevated adverse events to withdraw from the study leading to selective inclusion of data from participants with low adverse events. Moreover, as Omneuron has a financial interest in demonstrating the safety of repetitive fMRI scanning and rtfMRI-based training, the theoretical potential exists for intentional bias to be introduced into this study at any of these levels. Regarding potential biases 1–5, each author of this study hereby attests that he/she has no knowledge of any error, intentional or unintentional, that exists in the dataset, analysis, or presentation. Regarding potential bias 6, we conclude from detailed analyses discussed above that no bias was introduced by selective attrition of participants.

Conclusion

Repeated fMRI scanning and rtfMRI-based training, employing repeated fMRI scanning, cognitive task performance, and real-time neurofeedback, are associated with a low incidence of self-reported adverse events that were almost exclusively mild to moderate in severity, and were not increased in scanning sessions relative to non-scanning baseline sessions. This low incidence of self-reported adverse events was observed in participants receiving neurofeedback from four distinct brain regions. Participants completing up to nine scan sessions, including up to six rtfMRI training sessions, did not report an increased incidence or severity of adverse events during either rtfMRI scanning or fMRI scanning compared to a non-scanning baseline session. These findings underscore the safety of repetitive fMRI scanning and the rtfMRI-based training paradigms used in these studies.

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Fig. 1.

Participant progression through the chronic pain rtfMRI-based training paradigm. Patients ($N=114$) were enrolled in one of three protocols following the baseline session: (1) one fMRI scan followed by five rtfMRI scans ($N=49$), (2) three fMRI scans followed by six rtfMRI scans ($N=55$), and (3) four fMRI scans followed by five rtfMRI scans ($N=10$). The number of participants that withdrew during the fMRI and rtfMRI portions of the paradigm is indicated

Fig. 2.

Comparison of adverse event incidence in non-scanning baseline, fMRI scanning, and rtfMRI-based training sessions for chronic pain patients completing at least one rtfMRI scan. Reported number of adverse events per participant (mean $\pm$ SEM) out of a total possible 37 adverse events. Includes a total of 88 participants completing rtfMRI scan 1. Data from 88 non-scanning baseline, 178 fMRI scan, and 406 rtfMRI scan sessions. Reported adverse events from multiple sessions were averaged for each participant

Fig. 3. Overall adverse event profile in rtfMRI-based training studies for chronic pain patients completing at least one rtfMRI scan. **a** Non-scanning baseline (88 sessions). **b** fMRI scans (178 sessions). **c** rtfMRI scans (406 sessions). Includes a total of 88 participants completing rtfMRI scan 1

Fig. 4.

Comparison of adverse event incidence for chronic pain patients in rtfMRI training receiving neurofeedback from four ROIs. Reported number of adverse events per participant per session (mean±SEM) out of a total possible of 37 adverse events in participants receiving real-time feedback from one of four distinct training ROIs. Includes a total of 88 participants completing rtfMRI scan 1. Data from 88 baseline and 406 rtfMRI scan sessions. The number of rtfMRI scans for the dACC, rACC, LINS, and RINS ROIs were 80 ($N=19$), 103 ($N=24$), 145 ($N=29$), and 78 ($N=16$), respectively, where N is the number of participants. Reported adverse events from multiple sessions were averaged for each participant

Fig. 5.

Adverse event incidence and severity in chronic pain patients completing the rtfMRI-based training paradigm ($N=69$). a Reported number of adverse events per participant per session (mean $\pm$ SEM) out of a total possible of 37 adverse events. b Percentage of adverse events reported as mild, moderate, or severe across treatment days. Following the baseline session, participants completed one fMRI scan followed by five rtfMRI scans ($N=37$), three fMRI scans followed by six rtfMRI scans ($N=25$), or four fMRI scans followed by five rtfMRI scans ($N=7$). Data included from one baseline session, initial fMRI scan, initial rtfMRI, and final rtfMRI scan for each participant

Fig. 6.

Adverse events in chronic pain patients withdrawn prior to completion of fMRI or rtfMRI scanning compared to participants completing these portions of the rtfMRI training paradigm. For the participants included in the study ($N=114$), 88 completed fMRI scanning and 26 withdrew prior to completion of fMRI scanning. Of these 88 participants entering rtfMRI training, 69 completed rtfMRI scanning and 19 withdrew prior to the completion of rtfMRI scanning. Data are expressed as the change in the mean number of reported adverse events reported for each type of scan session from baseline. See Fig. 1 for participant flow

Table 1

Talariach coordinates of rtfMRI-based training regions of interest (ROIs)

Training ROI	TAL (x, y, z)
dACC	-4, -2, -37
rACC	2, 15, 33
LINS	-37, 5, -4
RINS	36, 5, -4

dACC bilateral dorsal anterior cingulate cortex, *rACC* bilateral rostral anterior cingulate cortex, *LINS* left anterior insula, *RINS* right anterior insula, *TAL* Talariach coordinates

Table 2
Incidence of adverse events for chronic pain patients completing the rtfMRI-based training paradigm

Class	Adverse event	Baseline		fMRI scan		rtfMRI scan	
		%	#	%	#	%	#
Physical sensations	Muscle twitching	28	19	29	41	17	61
	Heat/burning	32	22	15	21	9	33
	Headache	23	16	23	32	25	90
	Increased pain	36	25	38	54	32	113
	Neck strain	26	18	16	23	21	74
	Backache	25	17	27	39	28	101
	Numbness	19	13	18	26	7	26
Digestive effects	General weakness	19	13	11	15	7	25
	Nausea	6	4	7	10	3	12
	Hunger/cravings	7	5	9	13	2	8
	Constipation	1	1	1	1	1	2
	Diarrhea	0	0	1	1	0	0
	Vomiting	0	0	1	1	0	0
	Dry mouth	9	6	20	28	8	28
	Loss of appetite	0	0	2	3	1	3
	Unusual taste	3	2	6	8	2	8
	Blurred vision	9	6	15	21	9	31
Sensory effects	Ringing in ears	3	2	18**	25	14**	51
	Stiffness in ears	3	2	8	12	7*	25
	Sleepiness	38	26	38	54	26	92
Nervous system	Dizziness	9	6	6	8	7	24
	Tingling/buzzing sensation	19	13	11	15	8	29
	Lightheadedness	17	12	14	20	13	45
	Memory loss	6	4	0	0	0	0
	Slurred speech	0	0	1	1	1	3
	Insomnia	1	1	1	2	0	1
	Tremor	3	2	2	3	1	2

Class	Adverse event	Baseline		fMRI scan		rtfMRI scan	
		%	#	%	#	%	#
Emotions/moods	Hallucinations	1	1	0	0	0	0
	Convulsions/seizure	0	0	1	1	0	0
	Nervousness/anxiety	25	17	17	24	10	37
	Crying	13	9	3	4	3	9
	Euphoria	6	4	1	2	1	2
	Agitation/irritability	13	9	9	13	9	31
	Mood swings	6	4	2	3	3	9
	Suicidal thoughts	0	0	0	0	1	2
	Rage	0	0	1	1	1	5
	Depression	6	4	5	7	3	9

Incidence of each individual adverse event for study participants completing rtfMRI-based training across non-scanning baseline, fMRI scanning, and rtfMRI-based training sessions. Values in the “%” column indicate the percent of sessions in which participants reported each individual adverse event for each type of session, where the total number of sessions was 69, 142, and 358 for baseline, fMRI scan, and rtfMRI scan, respectively. Values in the “#” column indicate the number of sessions in which participants reported each individual adverse event for each type of visit. Data is from a total of 69 participants who completed all rtfMRI scans (five or six depending on the protocol described in “Methods”). Significant differences between scan sessions compared to baseline session are indicated (Wilcoxon signed-ranks test, * $p < 0.05$, ** $p < 0.01$)