USE OF NEUROFEEDBACK TO ENHANCE RESPONSE TO HYPNOTIC ANALGESIA IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

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Abstract: This proof of principle study examined the potential benefits of EEG neurofeedback for increasing responsiveness to self-hypnosis training for chronic pain management. The study comprised 20 individuals with multiple sclerosis (MS) who received 5 sessions of self-hypnosis training—one face-to-face session and 4 pre-recorded sessions. Participants were randomly assigned to have the prerecorded sessions preceded by either (a) EEG biofeedback (neurofeedback) training to increase left anterior theta power (NF-HYP) or (b) a relaxation control condition (RLX-HYP). Eighteen participants completed all treatment sessions and assessments. NF-HYP participants reported greater reductions in pain than RLX-HYP participants. The findings provide support for the potential treatment-enhancing effects of neurofeedback on hypnotic analgesia and also suggest that effective hypnosis treatment can be provided very efficiently.

Chronic pain is a significant problem worldwide that places substantial emotional and physical burdens on the individuals living with the problem as well as a considerable financial burden on society due to pain-related health-care costs and lost productivity (Institute of Medicine, 2011; van Hecke, Torrance, & Smith, 2013). Multiple sclerosis (MS) is one of many neurologic conditions associated with high rates...
of chronic pain, affecting as many as 50% of people with this condition (Ehde, Osborne, Hanley, Jensen, & Kraft, 2006; O’Connor, Schwid, Herrmann, Markman, & Dworkin, 2008). Moreover, among individuals with MS, chronic pain has been shown to be associated with an increased risk for depression (Alschuler, Ehde, & Jensen, 2013) and poorer health-related quality of life (Brochet et al., 2009; Newland, Naismith, & Ullione, 2009). Unfortunately, chronic pain in MS generally remains refractory to the available biomedical and psychosocial treatments. New and more effective chronic pain treatments are urgently needed for MS-related chronic pain.

Self-hypnosis training has shown significant potential as an intervention that can reduce the severity and negative impact of chronic pain (Jensen & Patterson, 2014), including chronic pain in MS (Jensen et al., 2009). Given its demonstrated efficacy and excellent side-effect profile (e.g., Jensen et al., 2006), we are now recommending self-hypnosis training as a first-line treatment for chronic pain (Jensen, Day, & Miro, 2014).

However, not everyone reports clinically meaningful improvements in pain and other outcome domains with self-hypnosis training (Jensen, Barber, Romano, Hanley, et al., 2009; Jensen, Barber, Romano, Molton, et al., 2009). Moreover, a standard hypnosis treatment usually consists of at least four, and often many more, face-to-face sessions with highly trained clinicians. Given the high prevalence of chronic pain problems and the general lack of clinicians trained in the use of hypnosis, very few of the many individuals who might benefit from hypnosis actually receive it. Thus, procedures and practices that may increase the efficiency, availability, and efficacy of hypnosis treatment are needed.

We have previously noted (Jensen, Sherlin, et al., 2014), as have others (Batty, Bonnington, Tang, Hawken, & Gruzelier, 2006; Engstrom, London, & Hart, 1970) that responsivity to hypnosis treatment could potentially be enhanced by preparing patients for improved responsivity with the use of electroencephalogram (EEG) biofeedback, also known as neurofeedback. This idea is based in part on the finding that individuals with more EEG-assessed theta brain-wave oscillations tend to score higher on measures of hypnotizability than do individuals with less theta brain activity (Galbraith, London, Leibovitz, Cooper, & Hart, 1970; Kirenskaya, Novototsky-Vlasov, & Zvonikov, 2011; Sabourin, Cutcomb, Crawford, & Pribram, 1990; Tebecis, Provins, Farnbach, & Pentony, 1975). Also, the relative magnitude of different brain oscillations, including theta oscillations, can be altered with the use of neurofeedback (Gruzelier, 2014). In fact, slower wave (alpha and theta) oscillations appear to be particularly responsive to neurofeedback training (Jensen et al., 2013). As a group, these findings suggest that neurofeedback training that results in increased theta activity, if provided prior to self-hypnosis training, could potentially improve the beneficial effects of the hypnosis treatment.
The primary purpose of the current study was to examine the potential of using neurofeedback to make individuals more responsive to self-hypnosis training for chronic pain management. Given that this study was designed as a proof of principle study, we did not power the study to detect a statistically significant effect for neurofeedback training relative to the control condition. Instead, our goal was to enroll enough participants to be able to compute the effect sizes associated with the neurofeedback intervention and to determine from these effect sizes if future work in this area is warranted. We hypothesized that the participants assigned to the neurofeedback condition would report larger pain reductions with hypnosis than participants assigned to the relaxation control condition. We also aimed to explore the potential treatment-enhancing effects of the neurofeedback training on three additional (secondary) outcome variables: worst pain intensity, fatigue, and pain interference. This second aim was to help evaluate the specificity of any treatment-enhancing effects of neurofeedback; that is, if the effects are specific only to the primary treatment target (average pain intensity) or if they also generalize to either/or an outcome closely related to the primary treatment target (worst pain intensity) and two additional outcome domains that are conceptually and statistically more distinct from the primary treatment target (pain interference and fatigue). A third and final aim of this study was to evaluate the potential efficacy of a highly efficient method of providing hypnotic chronic pain treatment.

Method

Participants

Given that 3- to 10-subject per treatment conditions are commonly used in pilot studies (e.g., Brown, Bostick, Bellmore, & Kumanayaka, 2014; Jansen-Kosterink et al., 2013; Jastrowski Mano et al., 2013; Miller, Westrick, Diebal, Marks, & Gerber, 2013), we chose to recruit 10 participants per condition for the current proof-of-principle study. These participants were recruited from a variety of sources including former participants of an ongoing MS symptom self-management study (that did not, however, include neurofeedback or hypnosis training), patients seen at the University of Washington Medical Center (UWMC) Multiple Sclerosis Clinic, Harborview and/or UWMC Rehabilitation Clinic, and self-referrals from study brochures and flyers. Participants needed to be 18 years or older, be at least 6 months post-MS diagnosis, and otherwise healthy (i.e., no other secondary medical complications that could impact pain scores). In addition, to be eligible for the study, potential participants had (a) to report having daily pain related to their MS that has been present for at least 6 months, (b) to report an average MS pain intensity over the past week of at least 4 on a 0–10 numerical rating
scale, and (c) to read, write, and understand English. Potential subjects were excluded if they had a history of a seizure disorder, significant psychological or psychiatric disturbance, intermittent pain, hospitalization for psychiatric reasons in the past 6 months, or failure to pass a cognitive screening test. If a potential subject was experiencing an MS exacerbation (i.e., neurological symptoms occurring over a minimum of 24 hours in the absence of fever or infection; Frohman, Eagar, Monson, Stuve, & Karandikar, 2008; Ontaneda & Rae-Grant, 2009), at the time of screening, they would be required to wait until all new or increased symptoms resolved before the first study visit. If an exacerbation occurred during the study the subject was allowed to continue, but a description and duration of exacerbation would be noted.

Of the 20 participants who were enrolled into the study and randomized to the two treatment conditions (10 participants per condition), 18 completed all treatment sessions and provided data at all assessment points. One subject—who had been assigned to the neurofeedback condition—discontinued treatment after the second treatment session due to the cost of transportation but completed all assessments. We were unable to contact the other subject who dropped out of the study (who had been assigned to the relaxation control condition) completely after the second treatment session due to a disconnected telephone and no response to mailings. Thus, data from 19 participants were included in the analyses.

Demographic and MS history information for the 19 study participants for whom we have complete data are presented in Table 1. As can be seen, the average age of the study participants was about 50 years, and the majority (63%) were women and described themselves as white (90%). The plurality (42%) were college graduates, consistent with the high level of education reported by the population of individuals with MS who participate in our research studies (Ehde et al., 2006; Osborne, Ehde, Jensen, & Kraft, 2006). The majority (63%) of the sample reported that they had relapsing-remitting MS.

Measures

Demographic and MS-related descriptive variables. All participants were asked to provide basic demographic information, including their age, sex, race/ethnicity, education level, and type of MS. Participants were asked to indicate their type of MS (relapsing-remitting, secondary progressive, primary progressive, progressive-relapsing, and “don’t know”) after they were read a two-to three-sentence description of each MS type.\footnote{All four descriptions read to the study participants are available from the first author E-mail: (mjensen@uw.edu).} For example, the following description was read to them for
relapsing-remitting: “You have clear-cut relapses or flare-ups of symptoms that are followed by either complete or partial recovery. Between relapses, your MS is stable, and there is no worsening of your symptoms or your ability to perform your usual activities.”

**Primary outcome variable: Average pain intensity.** The primary study outcome domain was average pain intensity, measured using a composite score made up of four 0–10 numerical rating scales (NRS; Jensen & Karoly, 2011). With the 0–10 rating, participants are asked to select one number that best represents their pain intensity from 0 (no pain sensation) to 10 (most intense pain sensation imaginable). The 0–10 NRS has been recommended as the most appropriate measure of pain intensity in pain clinical trials because (a) it has strong evidence for its reliability and validity as a measure of pain intensity, (b) it is more understandable and easier to use by more individuals than other pain intensity measures, and (c) it can be administered using a variety of procedures (e.g., paper and pencil, interview, electronic diary), which enhances standardization and comparison across studies (Dworkin et al., 2005; Jensen & Karoly, 2011). In the current study and at each assessment point (pretreatment,
posttreatment, and 1-month follow-up), participants were contacted via
telephone on four different days (within a 7-day window) by a research
staff person. During the interviews, participants were asked to rate their
average pain intensity over the past 24 hours. The four ratings were then
averaged into a composite score. The use of composite scores has been
recommended as a way to increase measured reliability in pain clini-
cal trials, such as the current study, that have limited power due to low
sample sizes (Jensen, Turner, Romano, & Fisher, 1999).

Secondary outcome variables: Worst pain intensity, fatigue, and pain inter-
fERENCE. Worst pain intensity was measured using the same 0–10 NRS
used to assess pain intensity, except that participants were asked to rate
their worst pain during the past 24 hours during each interview. The
four worst intensity ratings from each assessment point were averaged
into a composite score of worst pain intensity.

Fatigue was assessed using the Fatigue Severity Scale (FSS; Krupp,
LaRocca, Muir-Nash, & Steinberg, 1989). The FSS is a nine-item mea-
sure that asks respondents to rate their level of agreement to nine
statements regarding how easily they are fatigued (e.g., “I am eas-
ily fatigued”) and the impact of fatigue on function (e.g., “Fatigue
interferes with my physical functioning”) on 7-point numerical scales
(1 = completely disagree; 7 = completely agree). The FSS is among the most
commonly used measures of fatigue in disability research and has a
great deal of evidence supporting its reliability and validity, including
among individuals with MS (Amtmann et al., 2012; Hagell et al., 2006;
Hjollund, Andersen, & Bech, 2007; Krupp et al., 1989). The fatigue items
were administered via telephone interview once before and once after
treatment.

Pain interference was assessed using a slightly modified version of
the seven-item Pain Interference Scale of the Brief Pain Inventory (BPI;
Cleeland & Ryan, 1994; Daut, Cleeland, & Flanery, 1983). The BPI asks
respondents to indicate the extent to which pain interferes with daily
activities (e.g., sleep, general activity, mood) on 0–10 numerical scales
where 0 = does not interfere and 10 = completely interferes. The slight mod-
ification was to change the interference with “walking ability” to read
“Mobility, that is, your ability to get around” to be more appropriate for
an MS population, some of whom are not ambulatory. This modified
BPI Pain Interference scale has demonstrated high levels of both reliabil-
ity and validity in individuals with MS (Osborne et al., 2006). The
seven pain interference items were assessed via telephone interview
once before and once again after treatment.

Procedures

Brief summary of the study design. This randomized controlled proof-
of-principle study was designed to help determine if a larger program
of research studying the potential of neurofeedback training for enhancing response to hypnotic treatment is warranted. All participants were first seen in a single face-to-face session by one of two clinicians experienced in self-hypnosis training for chronic pain management (MPJ or DME). They were then randomly assigned (using a computer-generated table of random numbers) to one of two treatment conditions: (a) four additional hypnosis sessions immediately preceded by 20 minutes of neurofeedback treatment designed to increase left anterior theta power (NF-HYP) or (b) four hypnosis sessions immediately preceded by 20 minutes of a relaxation control condition (RLX-HYP). Thus, participants in the two treatment conditions had an equal chance of receiving the hypnosis treatment from either of the two study clinicians. The outcome measures were administered via telephone interview by a research assistant before treatment, immediately after treatment, and at 1-month follow-up.

Hypnosis intervention. The hypnosis intervention was modelled after the hypnosis interventions we have successfully used in previous research studies (Jensen, Barber, Romano, Hanley, et al., 2009; Jensen, Barber, Romano, Molton, et al., 2009; Jensen et al., 2011, 2005). Consistent with our model arguing that the hypnotic suggestions in chronic pain treatment should address multiple factors related to pain (e.g., sleep, fatigue, the meaning of pain) and not only pain reduction, each session included suggestions that targeted different positive outcomes.

As the procedures for the current study were designed, we chose to provide four of the five planned hypnosis sessions via audio recording, rather than in face-to-face sessions, to help ensure that any beliefs that the study clinicians had regarding the effects of the neurofeedback training were not inadvertently communicated to the study participants and could therefore bias the results. Thus, randomization occurred after the first and only face-to-face hypnosis session with one of the two study clinicians. The remaining four hypnosis sessions were pre-recorded and administered by a research study assistant (AG or HG) by playing the audio-recorded sessions in headphones just after the neurofeedback or relaxation conditions. One of the benefits of this design feature is that the hypnosis treatment ended up requiring minimal time (just one 1-hour session) of a clinician trained in the use of hypnosis for chronic pain management. Given that we have data from previous studies regarding the efficacy of a similar treatment provided in 10 face-to-face sessions in the same population (Jensen, Barber,

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2The scripts used for the five hypnosis sessions are available from the first author (E-mail: mjensen@uw.edu).
Romano, Molton, et al., 2009), this design feature allows us to compare the relative efficacy of the two approaches (10 in-person sessions of treatment vs. a single in-person session followed by four audio-recorded sessions) using a quasi-experimental design. Thus, the findings would also provide a preliminary evaluation of the efficacy of a highly efficient hypnosis treatment approach relative to a treatment approach involving substantially more clinician involvement.

All of the hypnosis sessions were approximately 20 minutes long and began with an approximately 10-minute induction inviting the participant to experience levels of relaxation, comfort, and dissociation. All of the hypnosis sessions also ended with posthypnotic suggestions that (a) the cue of taking a deep breath will be followed with being able to experience a hypnotic state and comfort, as well as with an ability to experience the benefits of hypnosis treatment, and (b) the more the subject practices self-hypnosis, the more the benefits will become automatic.

In addition to the suggestions for relaxation and comfort embedded in the induction and posthypnotic suggestions, the first (face-to-face) session provided suggestions for ego strengthening (e.g., “you are going to feel physically stronger . . . emotionally much calmer . . . more settled . . . develop more confidence in yourself . . . personal well-being . . . more content”). The study clinician also made a live audio recording of the first session, and this recording was given to the participants as an audio file or on a CD. The participants were asked to listen to the recording at least once every day until the next session and to also practice brief (2–5 minute) self-hypnosis sessions throughout the day.

Each of the subsequent four hypnosis sessions used prerecorded audio files delivered by headphones and overseen by a research assistant who remained present for the duration of the session. Session 2 focused on physical relaxation (e.g., “allow your whole body to relax . . . more and more relaxed . . . and heavy”) and pain diminution (e.g., “you can enjoy discovering that the uncomfortable feelings just seem somehow to change . . . less and less strong . . . or smaller and smaller . . . so easy to ignore”). Session 3 included suggestions for hypnoanesthesia (e.g., “imagine the areas that are sometime uncomfortable being engulfed, induced, and completely surrounded by a psychological anesthesia”) and age progression to experience adaptive feelings and thoughts (e.g., “focus on taking a special trip to the future . . . you can see yourself feeling so good . . . yourself as confident . . . and as you come back, bring with you all of these positive experiences of joy, comfort, delight, accomplishments . . . and skills”). Session 4 included suggestions for decreased pain unpleasantness (“being somewhat interested, but also interestingly detached . . . to have a calm, warm, comfortable, acceptance of our sensations”) and fatigue management (“you can wake up and feel rested and energized . . . sometimes relaxed . . .“).
sometimes energized . . . as you and your body need”). The fifth and final sessions included suggestions for comfort (“an increased ability to notice comfortable sensations that can overwhelm other sessions . . . noticing feelings that you find most comfortable . . . and noticing how they can grow and grow . . . possible to be more aware of pleasant sensations”) and improved sleep quality (“The 3–2-1 technique . . . as the mind is experiencing what it hears, feels, and sees . . . it will drift to sleep . . . the sleep you achieve will be restful and comfortable . . . allow you to feel so very rested when you wake up”). As indicated previously, prerecorded audio files or CDs of the sessions (in the voice of the clinician who saw the participants in the first hypnosis sessions) were provided to the participants after each session, and they were asked to practice by listening to the recordings at least once every day. They were also encouraged to practice self-hypnosis without the recordings briefly several times each day. The study clinicians, who were unaware of whether participants received neurofeedback or relaxation control condition, called participants about a week after each session to encourage ongoing practice of the hypnosis and to problem solve any barriers to practice. These calls lasted approximately 5 minutes each, on average.

**Neurofeedback apparatus and procedures.** To help identify which oscillation bandwidth(s) to reinforce in the current study, we considered the EEG-assessed brain-activity patterns associated with response to a single session of prerecorded hypnotic analgesia (Jensen, Sherlin, et al., 2014). We found that higher levels of baseline theta activity—especially theta activity measured from left anterior electrodes—predicted response to hypnotic analgesia suggestions. Interestingly, both theory (Gruzelier, 1998) and recent research using repeated transcranial magnetic stimulation to reduce activity in the left anterior cortex prior to hypnosis (Dienes & Hutton, 2013) implicates the potential importance of decreased activity in the left frontal cortex as influencing hypnotic responding. These findings are also consistent with greater left anterior theta predicting response to hypnosis, because neurons that fire in theta bandwidths tend to be inhibitory—that is, they tend to decrease or suppress activity in the recipient neurons (Buzsáki, 2006).

Thus, we identified the left anterior scalp location as a potentially useful training site and the theta bandwidth as a potentially useful oscillation bandwidth for increasing response to hypnotic analgesia treatment. However, we were also aware of the research that suggests that more slow wave activity might have negative effects; for example, it has been associated with attention deficit disorder (Fonseca, Tedrus, Bianchini, & Silva, 2013; Rodrak & Wongsawat, 2013; Tye, Rijndijk, & McLoughlin, 2014). Moreover, more left versus right slow wave activity has been linked to negative mood (Davidson, 2004). Thus, we decided that it might not be ideal to only train individuals to increase left anterior
theta activity but to also reverse any enhanced left anterior theta activity obtained via neurofeedback training administered prior to hypnosis treatment with posthypnosis neurofeedback training to increase left anterior faster wave (i.e., beta oscillation) activity. An additional potential benefit of this approach is that it might teach and encourage the participants to be better able to alter brain oscillations as most appropriate to the situation (i.e., to increase theta or beta power, as needed), rather than to simply increase theta.

An important decision we needed to make when designing the current study was the “dose” (number of sessions) of neurofeedback training to use. When considering this issue, we were aware that the number of sessions of neurofeedback training varies widely in research in this area, from as few as one (e.g., Escolano, Olivan, Lopez-del-Hoyo, Garcia-Campayo, & Minguez, 2012; Peeters, Ronner, Bodar, van Os, & Lousberg, 2013; Reiner, Rozengurt, & Barnea, 2013) to as many as 40 or even more sessions (e.g., Caro & Winter, 2011; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013; Stokes & Lappin, 2010; Surmeli & Ertem, 2010). The risk of using too few a number of sessions, which could potentially result in an inadequately small effect on theta power, had to be weighed against the risk of too many sessions, which could result in an unacceptably high number of study dropouts. We elected for this proof-of-principle study to provide four sessions of neurofeedback, as this number of sessions has been shown to impact baseline oscillation power (Cho et al., 2008) and seemed more practical for ultimate clinical adoption if an effect was found. We also reasoned that if we obtained at least a weak effect for four neurofeedback sessions on response to hypnotic analgesia, this would support continued research in this area, which could then begin to identify the best dose of neurofeedback for research and clinical work.

A NeXus-4 amplifier was used to measure and amplify the EEG signals, and BioTrace+ software was used for signal process and providing feedback to the study participants. Participants who were assigned to the NF-HYP condition were administered a 20-minute neurofeedback session with electrodes placed at FP1 and F3, during which slow wave activity (5–9 Hz and 8–11 Hz) was reinforced. Immediately following the neurofeedback session, subjects listened to a 20-minute hypnosis recording by the study clinician from their initial study visit. Headphones were provided to block possible distractions. The recording provided a hypnotic induction, followed by different suggestions for pain management. Following the hypnosis session, participants were given an additional session of 10 minutes of neurofeedback at CZ, with reinforcement of a low beta band (12–15 Hz) activity and activity in the gamma (45–60 Hz), hi-beta (22–30 Hz), and theta (3–7 Hz) bandwidths inhibited.
Relaxation control condition procedures. Participants assigned to the RLX-HYP condition were asked to relax and listen to sounds of gentle ocean waves with headphones for 20 minutes. They then listened via headphones to a hypnosis recording from their initial study visit clinician. The clinician’s recording provided a hypnotic induction, followed by different suggestions for pain management. In order to control for therapist attention and time in treatment, given that the NF-HYP participants also received additional NF training after hypnosis, the RLX-HYP participants were invited to select a video that they found relaxing and to watch it for 10 minutes following the hypnosis session.

Data Analysis

To evaluate the effects of treatment condition on the primary (average pain intensity) and secondary (worst pain intensity, pain interference, fatigue severity) outcome variables, we performed four two-way repeated-measures analyses of variance with time (pretreatment, posttreatment, and 1-month follow-up) and treatment condition (neurofeedback, relaxation control) as the independent variables. One analysis was performed for each of the outcome variables. Although we planned to compute and report the $F$ values (and associated significance levels) for both the time main effect (addressing the question, “Was there a statistically significant change in outcome over time in participants in both treatment conditions?”) and the Time × Condition interaction (addressing the question “Was there a statistically significant difference between the two treatment conditions in the pattern of change in outcome over time?”), as indicated in the beginning of this article, we did not power the study to detect statistically significant effects. Instead, the primary statistic of interest from these analyses is the effect size ($\eta^2$) reflecting the time and interaction effects. If neurofeedback training resulted in a larger treatment response than the relaxation condition, we anticipated at least a small ($\eta^2 = 0.0100$; Cohen, 1988) effect size, with larger pre- to posttreatment and/or pre- to posttreatment improvements in the participants assigned to the neurofeedback treatment condition than the relaxation treatment condition. Medium ($\eta^2 = 0.0588$) or large ($\eta^2 = 0.1379$) effect sizes would suggest that the effects of neurofeedback were more substantial. To further describe any between-group differences that emerged—and only in the event that we found at least a small effect size for the Time × Condition interaction effect—we also planned to compute Cohen’s $d$ effect size estimates (small, $d = 0.20$; medium, $d = 0.50$; large, $d = 0.80$; Cohen, 1988) for the pre- to posttreatment and pretreatment to follow-up changes in outcome, separately for the participants in the neurofeedback and relaxation treatment conditions.
Results

Primary Outcome: Average Pain Intensity

Table 2 presents the means and standard deviations of the pretreatment, posttreatment, and 1-month follow-up average pain-intensity scores, as well as the $F$ and $\eta^2$ values associated with the time main effect and Time $\times$ Treatment Condition interactions. As can be seen, a large ($\eta^2 = .60$) time effect and a medium ($\eta^2 = .07$) interaction effect emerged. The time effect can be explained by the pre- to posttreatment and pretreatment to follow-up decreases in average pain intensity for participants in both conditions. The effect sizes (Cohen’s $d$) for these improvements were 0.47 and 0.47 for the relaxation group (pre- to posttreatment and pretreatment to follow-up, respectively; both medium effects) and 0.70 and 1.04 for the neurofeedback group (the first a medium/large effect and the second a large effect). The pre- to posttreatment and pretreatment to follow-up effect sizes for the neurofeedback group are similar to those found in a study of a 10-session face-to-face self-hypnosis training program for individuals with MS; that is, 1.02 (pre- to posttreatment) and 0.79 (pretreatment to 3-month follow-up) in the other study (Jensen, Barber, Romano, Molton, et al., 2009). The medium interaction effect that emerged in the current analyses, although not statistically significant, can be explained by the larger pre- to posttreatment and pretreatment to 1-month follow-up decreases in average pain intensity that occurred in those participants who received neurofeedback, relative to those who participated in the relaxation control condition.

Secondary Outcomes: Worst Pain Intensity, Pain Interference, and Fatigue Severity

Table 2 also presents the means and standard deviations of the pretreatment, posttreatment, and 1-month follow-up scores on the measures of worst pain intensity (0–10 NRS), pain interference (modified BPI Pain Interference Scale), and fatigue severity (FSS). Significant time main effects were found for all three measures; these effect sizes were large ($\eta^2$’s range .34 to .57). For worst pain intensity and fatigue severity, the time main effects are explained by the improvements in the measures of these domains over time, with the largest improvements in these outcomes occurring from pre- to posttreatment (Cohen’s $d$s for the pre- to post-treatment improvements in worst pain and fatigue severity were weak to moderate [0.47 and 0.35] for both treatment conditions for worst pain intensity, and moderate to large [0.77 and 0.70] for both treatment conditions for fatigue severity). The significant time effect for pain interference is also reflected by the large pre- to posttreatment improvements in pain interference in participants in both treatment conditions (Cohen’s $d$s, 0.70 and 0.84).
Table 2

Means and Standard Deviations of Primary and Secondary Outcome Measures

<table>
<thead>
<tr>
<th>Outcome domain (measure)</th>
<th>N</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>1-Month Follow-Up</th>
<th>$f$ for time effect ($\eta^2$)</th>
<th>$F$ for time $\times$ condition interaction ($\eta^2$)</th>
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<tbody>
<tr>
<td><strong>Average Pain Intensity</strong></td>
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<tr>
<td>Relaxation, mean (SD)</td>
<td>9</td>
<td>5.24 (1.96)</td>
<td>4.32 (1.90)</td>
<td>4.31 (1.96)</td>
<td>11.91*** (0.60)</td>
<td>0.64 (0.07)</td>
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<td>Neurofeedback, mean (SD)</td>
<td>10</td>
<td>5.30 (1.27)</td>
<td>4.41 (0.71)</td>
<td>3.98 (0.86)</td>
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<td><strong>Worst Pain Intensity</strong></td>
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<tr>
<td>Relaxation, mean (SD)</td>
<td>9</td>
<td>6.38 (1.89)</td>
<td>5.49 (2.18)</td>
<td>5.35 (2.19)</td>
<td>10.02** (0.56)</td>
<td>0.57 (0.07)</td>
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<tr>
<td>Neurofeedback, mean (SD)</td>
<td>10</td>
<td>6.68 (1.49)</td>
<td>5.90 (1.20)</td>
<td>5.18 (1.36)</td>
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<td><strong>Pain Interference (BPI)</strong></td>
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<tr>
<td>Relaxation, mean (SD)</td>
<td>9</td>
<td>5.40 (1.68)</td>
<td>4.22 (1.59)</td>
<td>4.17 (1.46)</td>
<td>10.76*** (0.57)</td>
<td>0.51 (0.08)</td>
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<tr>
<td>Neurofeedback, mean (SD)</td>
<td>10</td>
<td>4.99 (1.41)</td>
<td>3.81 (1.90)</td>
<td>4.82 (2.24)</td>
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<td><strong>Fatigue Severity (FSS)</strong></td>
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<tr>
<td>Relaxation, mean (SD)</td>
<td>9</td>
<td>49.87 (6.74)</td>
<td>44.71 (11.76)</td>
<td>44.46 (8.66)</td>
<td>4.18* (0.34)</td>
<td>0.21 (0.01)</td>
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<tr>
<td>Neurofeedback, mean (SD)</td>
<td>10</td>
<td>46.60 (8.77)</td>
<td>40.50 (13.96)</td>
<td>42.85 (14.78)</td>
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Notes. Means with different subscripts are significantly ($p < .05$) different from one another. Interpretation of $\eta^2$ values: small = .0100, medium = .0588, and large = .1379 (Cohen, 1988).

*p < .05. **p < .01. ***p < .001.
The effect sizes for the Time × Condition interaction effects for the secondary outcomes varied. They were medium ($\eta^2 = .07$ and .08) for worst pain intensity and pain interference, and weak ($\eta^2 = .01$) for fatigue severity. The interaction effect for worst pain intensity is reflected by the larger effect of NF-HYP on this variable (i.e., pretreatment to follow-up effect size, $d = 1.10$), relative to RLX-HYP (pretreatment to follow-up effect size, $d = 0.54$). The interaction effect for pain interference is explained mostly by the larger posttreatment to follow-up increase in pain interference among participants in the NF-HYP condition, relative to the RLX-HYP condition (pretreatment to follow-up Cohen’s $d$s = 0.73 and 0.12 for RLX-HYP and NF-HYP, respectively). The weak Time × Condition interaction effect for fatigue severity is consistent with the participants in both treatment conditions showing very similar improvements in fatigue severity over time (see Table 2).

**Discussion**

The study findings provide preliminary support for the primary study hypothesis. Study participants assigned to the neurofeedback training condition that reinforced left anterior theta brain oscillations immediately before hypnosis treatment reported larger pre- to posttreatment and pretreatment to 1-month follow-up decreases in average pain intensity than did participants assigned to the relaxation control condition. The effect size of this outcome-enhancing impact, relative to hypnosis training preceded by the relaxation control experience, was moderate. Although the hypnosis-treatment-enhancing effects of neurofeedback on average pain intensity (i.e., interaction effects) were not statistically significant, as a proof-of-concept study, the experiment was not powered to detect statistically significant effects. The treatment-enhancing effects of neurofeedback were mirrored in the secondary outcome domain of worst pain intensity. However, they were not observed in the measures of pain interference or fatigue. An important additional finding is that the relatively brief (five session) and highly efficient (only one face-to-face session with a trained clinician) self-hypnosis training program not only resulted in significant pre- to posttreatment decreases in pain intensity that were maintained for at least one month but for the group that received neurofeedback training, the treatment was about as effective as this same treatment when provided as 10 face-to-face treatment sessions.

The medium effect size that emerged for the outcome-enhancing effects of neurofeedback on average pain intensity indicates that further research to study these effects is warranted. If the findings are
replicated in an adequately powered clinical trial, they could have significant implications for understanding and enhancing hypnosis treatment. Importantly, by encouraging clinicians to include a simple theta-enhancing strategy prior to hypnosis treatment, they could potentially increase the number of individuals who could benefit from self-hypnosis training for chronic pain management, thereby giving even more individuals with MS an opportunity to gain control over their pain experience.

In designing a larger trial to examine this question further, a critical question concerns the dose (number of sessions) of neurofeedback that should be used in such a trial. While the ideal dose response trial would randomly assign study participants to a variety of numbers of neurofeedback sessions (e.g., 2, 4, 10, 20, 40), including a number of different dose groups in a single trial would come at a high cost, both in terms of the total number of subjects that would be required for the study (in order to maintain an adequate level of power) as well as in terms of substantially reduced the ability to detect significant effects (i.e., reduced power), if the total number of available subjects is limited. At this point, two reasonable options to address this issue would include either (a) conducting a full trial testing the effects of four sessions of neurofeedback as was used in this study and power the study based on the current findings of a medium effect or (b) conducting another feasibility study comparing the effects of 4 versus 10 or more neurofeedback sessions to determine if adding additional neurofeedback sessions leads to higher dropout rates and/or a larger treatment-enhancing effect prior to conducting a full trial.

The fact that the neurofeedback training sessions appeared to enhance the benefits of hypnosis on worst pain intensity in addition to average pain intensity is not surprising, given that (a) there is a close conceptual and statistical association between average and worst pain and (b) the neurofeedback training target (increased theta power) and training site (anterior left hemisphere) were based on pilot research examining the correlates of pain-intensity reduction following hypnotic analgesia. The lack of any apparent treatment-enhancing benefits of neurofeedback on the two other secondary outcomes assessing pain interference and fatigue is perhaps not surprising, for the same reasons; that is, (a) pain interference and fatigue are more distinct from average pain intensity than worst pain intensity is and (b) the target oscillation (theta power) and training site (left anterior) of the neurofeedback training protocol used in this study have not been shown to prospectively predict improvements with either of these outcome domains with hypnosis treatment.

In the current study, there was not even a small trend for improved outcomes in either of these secondary outcome domains in the neurofeedback group, relative to the relaxation control condition group.
In fact, had the study had sufficient power (e.g., many more subjects) and if the estimates of the effects of neurofeedback on the measures of these two additional domains are accurate, the neurofeedback group would evidence worse (treatment-detracting) effects on these latter secondary outcome domains relative to the relaxation group. It is not possible to say at this point if these potential treatment-outcome-detracting effects of neurofeedback training on pain interference and fatigue are reliable or represent random effects, although it is interesting to note that a worsening in fatigue was found in a previous study of neurofeedback training in individuals with spinal cord injury (Jensen et al., 2013). The need to address these questions provides additional support for proceeding to a full clinical trial of the effects of neurofeedback on hypnosis outcome. The findings also provide additional empirical support for measuring a variety of secondary outcome domains in pain clinical trials and to not limit outcome assessment to a single primary (i.e., pain intensity) outcome domain only (Turk et al., 2003).

Although the experiment was designed primarily as a proof-of-principle study to determine if additional research examining the potential of neurofeedback to enhance response to hypnotic analgesia was warranted, one of the benefits of the study design was that we could also evaluate if a very efficient way of providing hypnotic treatment— one that required very little time from a clinician trained in the use of hypnosis—would be of benefit. Our finding that the treatment resulted in significant and substantial reductions in pain intensity similar to those we have found in previous research in the same population suggests the possibility that high resource-intensive hypnosis interventions may not be needed to obtain positive effects (see also Tan et al., 2015). The development of innovative strategies for providing highly efficient and effective hypnosis treatment could therefore improve the reach of this intervention; that is, substantially increase the number of individuals who could benefit from this treatment. This possibility should be examined further, given the difficulties people with MS often have accessing psychosocial treatments (Ehde, Kratz, Robinson, & Jensen, 2013) and the fact that there are substantially more individuals with chronic pain who could benefit from self-hypnosis training than could possibly be seen by the clinicians who are currently trained in the use of hypnotic approaches for pain management. Related to this, other perhaps even more efficient strategies for providing hypnosis treatment should be explored, including (but not limited to) group treatment (Spiegel & Bloom, 1983) and treatment by professional disciplines other than just psychologists and physicians (e.g., nurses, physical therapists, and occupational therapists). The evidence that hypnosis is effective for chronic pain management is increasing. We think that it is time to seriously consider methods for ensuring that more individuals with MS as
well as those with other painful conditions who could benefit from this treatment receive it.

The most significant limitation of this study is that it is a proof-of-principle study and was therefore not powered to detect statistically significant effects. Also, because the research staff that collected outcome data were not blind to treatment condition, research staff bias could potentially have influenced the results. Thus, at best we can only conclude that the findings suggest that neurofeedback training (focusing on increasing anterior left hemisphere theta power) may enhance the beneficial effects of self-hypnosis training for reducing the intensity of chronic pain in people with MS. Research is needed to determine if this finding is reliable and to provide a more definitive estimate of the effect size of the intervention. In addition, we did not assess treatment expectations regarding the two interventions. It is possible that the neurofeedback treatment provided generated more positive outcome expectations than the relaxation control condition did, and these possible differences in outcome expectancies may explain the treatment-enhancing effects of neurofeedback. Future research should include measures of outcome expectancies in the treatment conditions to make it possible to evaluate this possible explanation of the findings. An additional study limitation is that the type of chronic pain experienced by the study population—individuals with MS and chronic pain—may or may not be representative of the chronic pain experience by individuals with other conditions, such as individuals with spinal cord injury, low-back pain, fibromyalgia, and headache, among many others. Thus, even if the current findings were replicated in a larger sample of individuals with MS, they would also need to be replicated in individuals with other chronic pain conditions to help determine their generalizability. In addition, it is important to remember that the neurofeedback intervention had two components: (a) a theta- and alpha-enhancing component provided prior to the hypnosis sessions and (b) a low beta- (12–15 Hz) enhancing component provided just after the hypnosis sessions. Low beta neurofeedback training has itself been shown to be effective for reducing pain in one study using individuals with fibromyalgia (Kayiran, Dursun, Dursun, Ermutlu, & Karamursel, 2010). It is possible that this component of the neurofeedback protocol had direct positive effects and therefore contributed to the benefits observed in participants who received neurofeedback. Future researchers should assess actual changes in brain oscillation patterns that occur with treatment to help determine which brain activity patterns are most closely linked to the benefits found.

Although our results are promising in suggesting that minimal (one session + brief follow-up phone calls) therapist contact in a self-hypnosis training intervention may be efficacious in decreasing chronic pain, the audio-recorded sessions occurred in the presence of
a research assistant and the neurofeedback or relaxation procedure. Further refinement and testing of self-hypnosis training delivered via audio-recordings and minimal therapist contact are needed. A final important limitation related to the dose of neurofeedback used has already been discussed. It is possible that had more neurofeedback sessions been provided before the hypnosis treatment, an even larger treatment-enhancing effect on reducing pain intensity (or, perhaps, on interfering with the beneficial effects of hypnosis on fatigue) might have been observed. Future research should examine these potential dose effects.

Despite the study’s limitations, we were very encouraged by the effect size for the treatment-enhancing effects of neurofeedback found. While such a finding from a proof-of-principle study does not provide the evidence needed to recommend that clinicians who use hypnosis should immediately start providing neurofeedback training for their clients prior to hypnosis treatment, it does suggest that neurofeedback has the potential for increasing the number of individuals who could benefit from hypnosis treatment. The results also suggest that minimal contact self-hypnosis interventions have potential efficacy, which may lead to better reach of this intervention. Given the serious problems associated with chronic pain, including in people with MS, this is promising news indeed.

References


Die Anwendung von Neurofeedback, um die Antwort auf hypnotische Analgesie bei Patienten mit Multipler Sklerose zu verstärken

Mark P. Jensen, Ann Gianas, Holly R. George, Leslie H. Sherlin, George H. Kraft und Dawn M. Ehde


Stephanie Reigel, MD

L’utilisation de la neurothérapie (neurofeedback) pour améliorer la réponse à l’analgésie hypnotique chez les personnes atteintes de sclérose en plaques

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Résumé: Cette étude de démonstration de principe a permis d’examiner les avantages potentiels de la neurothérapie électroencéphalographique (EEG) dans la formation à l’augmentation de la réactivité à l’auto-hypnose pour gérer la douleur chronique. L’étude portait sur 20 personnes atteintes de sclérose en plaques (SP) ayant reçu 5 séances de formation en auto-hypnose : 1 séance en face à face et 4 séances préenregistrées. Les participants ont été sélectionnés au hasard, soit comme candidats aux séances préenregistrées précédées soit par 1) une formation à la rétroaction biologique (biofeedback) EEG (neurothérapie) afin d’augmenter la puissance du coefficient thêta
antérieur gauche (NF-HYP), soit 2) par un état de relaxation (RLX-HYP) en tant que témoins. Dix-huit participants ont assisté à toutes les séances de traitement et à l'évaluation. Les participants NF-HYP ont signalé une réduction plus importante de la douleur comparativement aux participants RLX-HYP. Ces résultats appuient les effets potentiellement avantageux du traitement avec neurothérapie sur l'analgésie hypnotique et indiquent également qu'un traitement hypnotique efficace peut être fourni avec beaucoup d'efficience.

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El uso del neurofeedback para mejorar la respuesta a la analgesia hipnótica en individuos con Esclerosis Múltiple

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Resumen: Este ensayo de prueba de concepto examinó los beneficios potenciales del neurofeedback EEG para incrementar la respuesta al entrenamiento autohipnótico en el manejo del dolor crónico. El estudio incluyó a 20 individuos con esclerosis múltiple (EM) que recibieron 5 sesiones de entrenamiento en autohipnosis −1 sesión frente a frente y 4 sesiones grabadas. Los participantes fueron asignados aleatoriamente para tener las 4 sesiones grabadas precedidas por (1) entrenamiento con biofeedback EEG (neurofeedback) para incrementar el poder theta anterior izquierdo (NF-HYP) o (2) una condición control de relajación (RLX-HYP). Dieciocho participantes completaron todas las sesiones y evaluaciones. Los participantes del grupo NF-HYP reportaron mayor reducción de dolor que los participantes RLX-HYP. Los resultados sustentan los efectos potenciales del tratamiento de neurofeedback para incrementar la analgesia hipnótica y también sugieren que el tratamiento hipnótico efectivo puede proveerse muy eficientemente.

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