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Robert T. Thibault
McGill University

Amanda MacPherson
McGill University

Michael Lifshitz
McGill University

Raquel R. Roth
McGill University

Amir Raz
Chapman University, raz@chapman.edu

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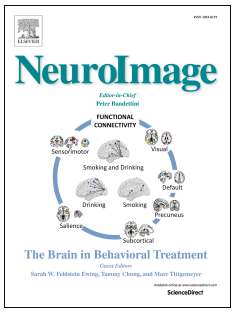

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Neurofeedback with fMRI:

A critical systematic review

Robert T. Thibault [a,b], Amanda MacPherson[a], Michael Lifshitz [a,b], Raquel R. Roth [a], Amir Raz* [a,b,c,d]

[a] McGill University, 3775 University Street, Montreal, QC, H3A 2B4, Canada

[b] Institute for Interdisciplinary Behavioral and Brain Sciences, Chapman University, Irvine, CA, 92618, USA

[c] Institute for Community and Family Psychiatry, 4333 Cote Ste. Catherine, Montreal, QC, H3T 1E4, Canada

[d] The Lady Davis Institute for Medical Research at the Jewish General Hospital, 3755 Cote Ste. Catherine, Montreal, QC, H3T 1E2, Canada

*Please address correspondence to:

Professor Amir Raz, 4333 Cote Ste. Catherine, Montreal, QC, H3T 1E4, Canada

amir.raz@mcgill.ca

Tel: 1-514-340-8210; Fax: 1-514-340-8124

ABSTRACT

Neurofeedback relying on functional magnetic resonance imaging (fMRI-nf) heralds new prospects for self-regulating brain and behavior. Here we provide the first comprehensive review of the fMRI-nf literature and the first systematic database of fMRI-nf findings. We synthesize information from 99 fMRI-nf experiments—the bulk of currently available data. The vast majority of fMRI-nf findings suggest that self-regulation of specific brain signatures seems viable; however, replication of concomitant behavioral outcomes remains sparse. To disentangle placebo influences and establish the specific effects of neurofeedback, we highlight the need for double-blind placebo-controlled studies alongside rigorous and standardized statistical analyses. Before fMRI-nf can join the clinical armamentarium, research must first confirm the sustainability, transferability, and feasibility of fMRI-nf in patients as well as in healthy individuals. Whereas modulating specific brain activity promises to mold cognition, emotion, thought, and action, reducing complex mental health issues to circumscribed brain regions may represent a tenuous goal. We can certainly change brain activity with fMRI-nf. However, it remains unclear whether such changes translate into meaningful behavioral improvements in the clinical domain.

Keywords: fMRI, neurofeedback, real-time fMRI, psychiatry, self-regulation, systematic review

MAIN TEXT

1. INTRODUCTION

In recent years, neurofeedback using fMRI (fMRI-nf) has increasingly captured the interest of scientists, clinical researchers, practitioners, and the general public. This technique provides individuals with near real-time feedback from their ongoing brain activity (Figure 1). FMRI-nf offers many advantages over traditional, albeit increasingly challenged, forms of neurofeedback aiming to entrain and control electroencephalographic signals (EEG-nf; Birbaumer, Ruiz, & Sitaram, 2013). Unlike EEG-nf, fMRI-nf provides millimetric spatial resolution and consistently guides participants to successfully regulate their brain activity indexed by the blood-oxygen-level dependent (BOLD) signal (Thibault, Lifshitz, Birbaumer, & Raz, 2015). In addition, research on fMRI-nf improves on many key methodological shortcomings that plague typical EEG-nf experiments (e.g., Arnold et al., 2013; Thibault & Raz, 2016)—employing more rigorous control conditions (e.g., sham neurofeedback from an unrelated brain signal) and measuring both learned regulation of the BOLD signal as well as behavioral response. Here we offer a critical systematic review of the fast growing literature on fMRI-nf, with an eye to examining the underlying mechanisms, observable outcomes, and potential therapeutic benefits.

INSERT FIGURE 1 AROUND HERE

The present review gathers findings from nearly all available primary experiments involving fMRI-nf, which aim to train neural regulation or modify behavior (we exclude case studies and other experiments that present only individual level analyses). We opt for a systematic review rather than a meta-analysis due to the wide variety of experimental designs

and statistical methods used in fMRI-nf. Whereas meta-analyses generally focus on a specific treatment and outcome measure, the spectrum of fMRI-nf studies hardly renders itself to this meta-analytic approach—the studies train distinct brain regions, employ a variety of controls, use different time points as their baseline, measure diverse behaviors, and vary in the length of training and instructions provided. While we encourage meta-analyses for more specific questions concerning fMRI-nf (e.g., Emmert et al., 2016), a comprehensive meta-analysis would risk misrepresenting the heterogeneity of the field by assigning a single valuation to the technique as a whole (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009; S. G. Thompson, 1994).

After outlining the parameters of our literature search, we present the distribution of control conditions and experimental designs throughout the field. We then examine the effectiveness of fMRI-nf protocols in (1) training self-regulation of the BOLD signal and (2) modifying behavior. Some scholars speciously conflate these two distinct outcome categories, assuming that altered BOLD patterns will inevitably or necessarily drive observable changes in behavior; however, this assumption hardly holds true. After considering the observable outcomes, we evaluate the status of fMRI-nf as it begins to edge towards clinical acceptance. We conclude that fMRI-nf presents a reliable tool for modulating brain activity, but that current experimental protocols vary too widely to reify therapeutic efficacy and endorse practical guidelines at this time.

INSERT BOX 1 AROUND HERE

2. REVIEW PROTOCOL

We searched the *Topic*: *(neurofeedback) AND (fMRI OR "functional magnetic resonance imag*" OR "functional MRI")* across *All Databases* and all years in Web of Science on August 25th, 2017 (see Figure 1 for a flow chart of study inclusion). Of the 434 published articles written in English that were returned, we omitted 114 not directly related to fMRI-nf (e.g., performed neurofeedback with a different imaging modality or used fMRI as a means of analysis only), 72 conference proceedings or abstracts, and 9 duplicates. On Nov 8th, 2017 we re-conducted our original search and found three additional primary fMRI-nf studies. We then performed the additional search query: *rtfMRI* OR *("real-time"* OR *"real time") AND (fMRI OR "functional magnetic resonance imag*" OR "functional MRI")* across *All Databases* and all years in Web of Science to capture any experiments our primary search may have missed. Of the 938 additional records retrieved, 15 met our inclusion criteria.

Of the remaining 257 articles, we identified 133 primary research experiments, 76 review papers, and 48 methods articles (see Figure 2 for a graph depicting publication trends). Primary research included experiments where participants observed real-time fMRI data (i.e., neurofeedback) and attempted to modulate the feedback signal. Reviews discussed fMRI-nf (e.g., summarized findings, proposed new directions, or revisited previous data) but contained no original data. Methodological articles presented software, experimental procedures, or data analysis techniques relevant to fMRI-nf. Although, the number of published reviews nears the number of primary research articles, we present the first formal systematic review of fMRI-nf. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), where applicable to this exploratory field, to guide our systematic review (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

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We excluded 16 of the 133 primary research articles from our analysis. Two of these studies asked participants to actively move their hand to induce motor cortex activation (Neyedli et al., 2017; Yoo & Jolesz, 2002). While combining movement and neurofeedback may help rehabilitate stroke patients, this methodology differs substantially from the fMRI-nf experiments we examine here and would thus require a distinct evaluation. The other 14 studies we excluded reported data at the individual level only, as a series of case studies with no group-level analysis. (Buyukturkoglu et al., 2013, 2015; Cohen et al., 2014; Dyck et al., 2016; Gerin et al., 2016; Krause et al., 2017; Lee, Ryu, Jolesz, Cho, & Yoo, 2009; Liew et al., 2016; Mathiak et al., 2010; Sitaram et al., 2014, 2012; Weiskopf et al., 2003, 2004; Yoo et al., 2004). To avoid reviewing the same dataset twice, on 16 occasions we collapsed two publications, which analyze the same dataset, into one (i.e., Caria et al., 2007 and Lee et al., 2011; Rota et al., 2009, 2011; Emmert et al., 2014 and Emmert, Breimhorst, et al., 2017; Scharnowski et al., 2014 and Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012; Paret et al., 2014, 2016; Haller et al., 2013 and Van De Ville et al., 2012; Hui, Zhang, Ge, Yao, & Long, 2014 and Xie, Xu, Long, Yao, & Wu, 2015; Yoo et al., 2007 and Lee, Kim, & Yoo, 2012; Sherwood, Kane, Weisend, & Parker, 2016 and Sherwood, Weisend, Kane, & Parker, 2016; Cortese et al., 2016, 2017; Li, Tong, Guan, et al., 2016 and Li, Tong, Wang, et al. 2016; Radua et al., 2016 and Scheinost et al., 2013; Robineau, Meskaldji, et al., 2017 and Robineau et al. 2014; Young, Misaki, et al., 2017 and Young, Siegle, et al., 2017; Ihssen et al., 2017 and Sokunbi et al., 2014; Zhang, Yao, & Zhao, 2016 and Zhang, Yao, Zhang, Long, & Zhao, 2013) and on one occasion combined three publications due to overlapping data (Young et al., 2014; Yuan et al., 2014; Zotev et al., 2016).

In total, therefore, we report findings from 99 primary research experiments. From each publication we extracted information regarding experimental design (e.g., control group, participant population, brain region(s) of interest, mental strategy, respiration correction) and findings (e.g., BOLD regulation, behavioral regulation, and follow-up measurements).

This contribution expands on our previous work (Thibault, Lifshitz, & Raz, 2016) by providing a more in-depth, comprehensive, and up-to-date review. It builds off of landmark reviews in the field which highlighted the need for rigorous standards and offered a prospective stance about the future of fMRI-nf (Stoeckel et al., 2014; Sulzer et al., 2013). Extending these previous accounts, here we systematically amalgamate data on the vast majority of fMRI-nf studies to answer whether fMRI-nf can help individuals to control their brain activity and modify their behavior. To answer these questions we explore data concerning four themes: control measures, brain regulation, behavioral outcomes, and clinical relevance. We present all the collected data in Table 1 and depict them in Figures 3-6. We include Table 1 as a downloadable spreadsheet so that researchers can efficiently explore and analyze the field of fMRI-nf. For a discussion on the history of neurofeedback, theories of neurofeedback learning, relevant animal experiments, or how EEG-nf studies helped shape the field of fMRI-nf, please refer to other reviews (e.g., Sitaram et al., 2017; Stoeckel et al., 2014). We now begin with a discussion on the theme of control measures.

INSERT FIGURE 2 AROUND HERE

3. EXPERIMENTAL DESIGN IN fMRI-nf

How does the fMRI-nf literature stack up to the gold standard of experimental science across most clinical research domains: placebo-controlled and double-blind? Ideally, control groups receive a highly comparable treatment that omits the active ingredient or mechanism of action purported to drive improvement, and neither participants nor experimenters can identify who receives veritable versus placebo treatment. Increasingly, fMRI-nf experiments are rising to this standard and employing a variety of placebo-nf methods (see Table 1). With appropriate controls, we can disentangle brain-based versus psychosocial mechanisms driving treatment outcomes.

INSERT FIGURE 3 AROUND HERE

While fMRI-nf experiments vary in terms of control groups, targeted brain regions, and outcome measures, a general procedure remains consistent across most studies. Researchers explain the procedure to participants, administer consent forms, and usually provide an overarching strategy to modulate the BOLD signal of interest (e.g., imagine tapping your finger, recall emotional memories). Participants lie supine (horizontally) in an MRI scanner and generally look upwards at a display device. After an anatomical brain scan, which takes a few minutes, researchers identify voxels from which they will provide feedback (i.e., the target region of interest (ROI)). Participants then undergo a few neurofeedback runs wherein they view a simplified representation of brain activity originating from the ROI (e.g., a thermometer style bar graph). These runs generally last between 5-10 minutes and alternate between approximately 20-60 second blocks of “REGULATE”, when participants actively attempt to modulate the visual feedback, and “REST”, when participants refrain from attempting to modify the BOLD

signal. Participants must hold still and maintain their head position throughout. Control groups generally receive placebo-nf (e.g., from an unrelated brain region or previously recorded participant) or attempt to modulate their brain activity using mental techniques in the absence of neurofeedback. The median experiment recruits 18 participants (mean: 20.8 ± 12.1). Researchers may measure behavior before and after neurofeedback training, as well as in-between runs. An average experiment lasts for about one to two hours, but increasingly training occurs over multiple days.

As the field develops, fMRI-nf studies are taking on new and diverse forms. For example, as experimental evidence in both animals and humans (e.g., Alegria et al., 2017; Fetz, 1969) shows that providing a strategy is unnecessary, or even counterproductive (Sepulveda et al., 2016), for learning neural control, a number of recent experiments have begun to avoid suggesting a specific strategy. Furthermore, some studies now leverage within-subjects design where they identify two distinct multi-voxel activation patterns in each participant (e.g., for seeing red versus green, or observing one conditioned stimulus versus another). Researchers then train participants to activate only one of these patterns and employ the other as a control—often demonstrating behavioral effects for the trained pattern only (Amano, Shibata, Kawato, Sasaki, & Watanabe, 2016; Koizumi et al., 2016; Shibata, Watanabe, Sasaki, & Kawato, 2011). Target neurofeedback signals are no longer restricted to single brain regions and can now reflect the strength of functional connections between regions or individualized machine-learned brain maps associated with a particular behavior. In addition, experimenters increasingly employ randomized controlled trials (e.g., Alegria et al., 2017) and began testing the long term sustainability of learned brain regulation (e.g., Robineau et al., 2017).

3.1 Control groups in fMRI-nf: blinding, mental rehearsal, and placebo-neurofeedback

Of the 99 experiments we investigated, 38 used no control group, 19 used only a control condition that likely differed in terms of expectation and motivation (e.g., mental rehearsal without neurofeedback or no treatment controls), and 39 employed placebo-nf (refer to Figure 3A to see how we grouped control types). Of the 39 studies that leveraged placebo-nf—thus, holding the potential for a double-blind—only six reported blinding both participants and experimenters (Guan et al., 2015; Hamilton et al., 2016; Paret et al., 2014/Paret, Kluetsch, et al., 2016; Yao et al., 2016; Young et al., 2014/Yuan et al., 2014/Zotev et al., 2016; Young, Misaki, et al., 2017/Young, Siegle, et al., 2017). In single-blind studies, experimenters may unintentionally transmit their hypotheses and expectations to participants, and thus inflate demand characteristics in experimental participants more than in controls. Demand characteristics can increase effort and motivation leading to downstream differences in behavior (Kihlstrom, 2002; Nichols & Maner, 2008; Orne, 1962) and likely brain activity (e.g., Raz, Fan, & Posner, 2005). These potential differences in motivation are particularly important in fMRI-nf because participants must effortfully engage to achieve neural and behavioral self-regulation. Accordingly, double-blind fMRI-nf experiments are feasible and go a long way toward demonstrating the specific brain-derived benefits of neurofeedback; unfortunately, such studies are rare.

Control groups employing mental strategies in the absence of neurofeedback receive fewer psychosocial and motivational influences compared to neurofeedback participants. Some examples include healthy participants instructed to recall emotional memories to increase insular activity (Caria et al., 2007) or patients asked to mentally imagine movement to heighten motor cortex activity (Subramanian et al., 2011). These mental rehearsal control participants also

experience placebo effects, but probably less so than experimental subjects. They interface with less flashy cutting-edge technology (Ali, Lifshitz, & Raz, 2014), receive a less intense (Kaptchuk et al., 2006) and perceivably less expensive treatment (Waber, Shiv, Carmon, & Ariely, 2008), lack a contingent visual aid to help them maintain concentration on the task (Greer, Trujillo, Glover, & Knutson, 2014), and they encounter fewer demand characteristics in the majority of cases where the experimenters expect a superior performance under neurofeedback (Nichols & Maner, 2008). These parameters alter psychosocial treatment mechanisms and present confounding factors that require balancing between experimental and control groups.

Placebo effects are more comparable between genuine and placebo neurofeedback groups. Various types of placebo-nf (e.g., from a large background region of one's own brain versus from the ROI of another participant's brain) come with distinct advantages in terms of motivation level, positive feedback quantity, and reward contingency (see Stoeckel et al., 2014; Sulzer et al., 2013; Thibault et al., 2016 for a more in-depth discussion on the intracacies of control groups in neurofeedback). Collecting data regarding believed group assignment and motivation levels can help bolster the reliability of control groups (e.g., Zilverstand, Sorger, Sarkheil, & Goebel, 2015). Crucially, one report showed that simply attempting to modulate the fMRI-nf signal, even when provided with sham-neurofeedback, up-regulates widespread neural activity compared to passively viewing the same signal (Ninaus et al., 2013). In this study, neural activity increased in the insula, anterior cingulate cortex (ACC), motor cortex, and prefrontal regions—the four most commonly trained cortices in fMRI-nf (see Figure 3C). Because sham-neurofeedback can drive changes in BOLD self-regulation, placebo-nf control groups (used in just 39% of fMRI-nf studies) would be crucial to distinguish the benefits of genuine fMRI-nf over and above psychosocial influences.

3.2 Respiration influences the BOLD signal

FMRI-nf carries a number of unique, and often overlooked, confounding variables. Whereas this technique aims to train self-regulation of neural activity, the feedback originates from the blood-oxygen-level dependent (BOLD) signal, an indirect index of neural activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Crucially, the BOLD signal stems from hemodynamic processes that are sensitive to physiological variables, including respiration volume (Di, Kannurpatti, Rypma, & Biswal, 2013) and heart rate variability (Shmueli et al., 2007). During MRI scans, for example, holding the breath can drive a 3-6% change in the BOLD signal (Abbott, Opdam, Briellmann, & Jackson, 2005; Kastrup, Krüger, Glover, & Moseley, 1999; Thomason, Burrows, Gabrieli, & Glover, 2005). On the other hand, fMRI-nf training seldom propels BOLD fluctuations beyond 1%. Moreover, subtle variations in breathing rate and depth, which occur naturally during rest, can also substantially sway the BOLD signal (Birn, Diamond, Smith, & Bandettini, 2006; Birn, Smith, Jones, & Bandettini, 2008). Thus, neurofeedback participants could change their breathing patterns, possibly without explicit awareness, to modulate the BOLD signal. This possibility poses a glaring caveat across many fMRI-nf experiments. Unlike experimental participants, few control groups receive feedback contingent on their own respiration. For example, sham-feedback from the brain of a previously recorded participant contains no information concerning the cardiopulmonary measures of the participant receiving the sham-feedback. In this sense, experimental participants, but not most controls, receive a surreptitious form of “respiration-biofeedback” that may help guide them toward BOLD regulation.

Fortunately, fMRI-nf experiments increasingly account for respiration artifacts in a variety of ways (see Figure 3B). Of the 37 fMRI-nf studies that explicitly report accounting for respiration, seven statistically compare heart rate and breathing rate between REST and REGULATE blocks, 19 subtract BOLD activity from a large background ROI, and nine regress out physiological noise using additional recording instruments (Figure 3B). MRI experts suggest that researchers regress out physiological variables in any experiment that involves conditions or groups wherein participants may breathe differently (e.g., meditators vs controls or REST vs REGULATE blocks in fMRI-nf) (Biswal, Kannurpatti, & Rypma, 2007; Handwerker, Gazzaley, Inglis, & D'Esposito, 2007; Kannurpatti, Motes, Rypma, & Biswal, 2011; Weinberger & Radulescu, 2016).

Establishing statistically non-significant differences between heart rates or breathing rates between conditions or groups (i.e., $p > .05$) cannot fully eliminate cardiovascular confounds—"absence of evidence is not evidence of absence" (Altman & Bland, 1994). Moreover, at least two fMRI-nf experiments find statistically significant differences in cardiorespiratory measures between REST and REGULATE blocks (Marxen et al., 2016; Sorger, Kamp, Weiskopf, Peters, & Goebel, 2016).

A more common method—subtracting ongoing BOLD fluctuations in a large background region from activity in the ROI—overlooks the fact that respiration influences the BOLD signal in some neural regions more than in others (Di et al., 2013; Kastrup, Krüger, Glover, & Moseley, 1999). Notably, fMRI-nf targets many of the regions most susceptible to respiration (e.g., cingulate gyrus, insula, frontal, sensorimotor, and visual cortices: see Figure 3C).

Of the remaining 62 experiments that do not explicitly report accounting for respiration, few mention the involvement of ulterior cardiorespiratory variables in the BOLD signal. A number of studies ask participants to breathe normally, but refrain from further dealing with respiration. And yet, this request can prompt undue stress and irregular breathing patterns (Schenk, 2008), and holds the potential to subtly suggest at least one way to modulate the BOLD signal. In some fMRI-nf experiments, participants explicitly report focusing on their breath as a strategy to alter the BOLD signal (e.g., Alegria et al., 2017; Garrison et al., 2013; Harmelech, Preminger, Wertman, & Malach, 2013). Of the available approaches, only systematically regressing out physiological artifacts can ensure that BOLD regulation reflects neural modulation.

3.3 Muscle activity influences the BOLD signal

Just as seeing alters the BOLD signal in the visual cortex, muscle engagement alters the BOLD signal in sensorimotor regions. In fMRI-nf experiments targeting sensorimotor regions, researchers typically instruct participants to perform motor imagery without recruiting muscle activity. Evoking a movement, however, increases cortical activity much more than imagining the same movement (Berman, Horovitz, Venkataraman, & Hallett, 2011; Lotze et al., 1999; Yuan et al., 2010). Thus, participants could potentially flex their muscles, perhaps unintentionally or covertly, to increase BOLD activity. One seminal fMRI-nf experiment demonstrated the power of this general approach by asking participants to move their fingers to successfully modulate the BOLD signal (Yoo & Jolesz, 2002). Another fMRI-nf study reported correlations between EMG measures and BOLD changes in many participants, even though

participants were instructed to refrain from moving (Berman et al., 2011). Furthermore, muscle tension reflects mental load, which presumably increases during REGULATE blocks compared to REST blocks (Iwanaga, Saito, Shimomura, Harada, & Katsuura, 2000). To account for such potential muscle effects, the most rigorous fMRI-nf studies targeting sensorimotor regions measure EMG activity (e.g., Chiew et al., 2012; DeCharms et al., 2004; Subramanian et al., 2011) or arm movement (e.g., Auer, Schweizer, & Frahm, 2015; Marins et al., 2015).

Typical placebo-nf protocols seldom fully control for muscle-driven modulation of the BOLD signal. Whereas experimental participants receiving feedback from motor areas could implicitly learn to tense muscles to regulate the BOLD signal, most placebo participants receive feedback unrelated to their muscle tension. Thus, even in the presence of placebo-nf controls—oftentimes considered the gold standard in the field—fMRI-nf studies that target sensorimotor cortices must also account for muscle tension before identifying neural modulation as the driver of BOLD regulation. Even though cardiorespiratory and motion artifacts are broadly recognized issues in the field of fMRI, they are particularly relevant to neurofeedback because participants can inadvertently learn to modify the BOLD signal via artifacts. Still, many fMRI-nf experiments neglect to control for these measures (Figure 3). The solution to adopting stronger control groups and control measures lies more in enforcing the standards of clinical and fMRI research than in developing new techniques.

4. BOLD SELF-REGULATION

The question at the heart of fMRI-nf research is whether individuals can learn to volitionally modulate neural activity in circumscribed brain regions. The cumulative evidence

suggests that participants can indeed successfully modulate the BOLD signal from a wide variety of brain regions (Fig 4A). While this overarching finding may spark enthusiasm, we would do well to remember that participants in thousands of imaging studies before the advent of neurofeedback had already regulated their own BOLD activity. Whenever we perform specific cognitive tasks or assume distinct mental states we influence the BOLD signal. For example, an early meta-analysis of 55 fMRI and PET experiments showed that recalling emotional memories increases activity in the ACC and insula (Phan, Wager, Taylor, & Liberzon, 2002). The vast majority of fMRI-nf studies (79%) provide participants with at least a general mental strategy to help modulate the BOLD signal (see Table 1). Thus, it would be strange if we did not see BOLD signal differences between REST and REGULATE trials. The potential breakthrough of fMRI-nf, instead, rests on whether participants can outperform appropriate control groups that account for mental rehearsal and placebo factors.

4.1 How we measure learned BOLD regulation

Based on the 99 experiments surveyed and different methodological approaches, we divided learned regulation into four distinct categories, each with specific implications for neurofeedback:

(1) *Comparing endpoints to baseline measures* (taken before neurofeedback or during REST blocks). This measure holds particular relevance in studies that report greater improvements for experimental participants over control participants. Improving compared to a control group can stem from a decreased performance in control participants rather than an

356 improvement in experimental participants (e.g., Zhang et al., 2013). Comparing endpoints to
357 baseline measures confirms that neurofeedback benefits experimental participants.

358 (2) *Comparing endpoints to the first neurofeedback trial* and (3) *identifying a linear trend.*
359 These approaches reveal whether participants continue to improve their self-regulation beyond
360 the first session. If participants improve BOLD regulation compared to baseline but improve
361 neither beyond the first neurofeedback run nor in a linear fashion, then the benefits of fMRI-nf
362 may quickly plateau. In this case, the improvement in neural regulation could rely on any
363 variable that changed between the baseline test and the first neurofeedback trial (e.g. the mere act
364 of attempting to modulate the BOLD signal).

365 (4) *Comparing experimental and control participants.* This approach remains standard
366 clinical research practice and allows experimenters to tease apart the specific benefits of a
367 particular fMRI-nf paradigm from more general psychosocial factors.

368 Leveraging a combination of these four tests paints a more detailed picture of
369 neurofeedback that can better inform researchers about psychosocial influences, the importance
370 of mental strategies, and ideal training regimens. The number of studies where neurofeedback
371 participants successfully modulate the BOLD signal—compared to baseline, compared to the
372 first feedback trial, compared to controls, or in a linear fashion—far outnumber the experiments
373 where participants were unsuccessful (Fig 4). Thus, fMRI-nf appears to provide participants with
374 the ability to self-regulate the BOLD signal originating from various brain regions.

375

376 ***INSERT FIGURE 4 AROUND HERE***

377

4.2 Are positive results overrepresented?

Figure 4 presents convincing evidence that fMRI-nf drives BOLD regulation. Nonetheless, as in many fields of research, veiled factors such as publication bias, selective reporting, variable research designs, and methodological nuances may sway the cumulative evidence in favor of positive findings (Button, 2016; Goldacre et al., 2016; Ioannidis, 2005).

A number of experiments report promising findings and adopt a positive tenor despite finding few significant results. For example, some studies find significance in only a few runs out of many: for instance, run 7 and 8 out of eleven total runs (Yoo et al., 2006), run 2 of 4 (Berman, Horovitz, & Hallett, 2013), the difference between run 3 and run 4 (Hui et al., 2014), or the difference between run 2 and 3 (Zilverstand et al., 2017) . A few experiments stop neurofeedback training once participants achieve a predefined level of BOLD regulation or once statistical tests reach significance (e.g., Lee, Kim, & Yoo, 2012; Scharnowski et al., 2015). This uncommon experimental design inflates positive results because training continues until statistical significance surfaces. Other analyses divide participants into “learners” and “non-learners” (i.e., those successful and unsuccessful at achieving neural self-regulation), and in turn generate positive findings for the “learners” group (e.g., Bray, Shimojo, & O’Doherty, 2007; Chiew et al., 2012; Marxen et al., 2016; Ramot, Grossman, Friedman, & Malach, 2016; Robineau et al., 2014; Scharnowski et al., 2012). Many studies run multiple statistical tests but neglect to discuss how they accounted for multiple comparisons. For someone perusing the literature, the aggregate of the above fMRI-nf studies might give the impression of a robust base of converging findings in support of fMRI-nf, whereas in fact, positive findings remain scattered across select runs and chosen participants.

Statistical nuances can further frame the available evidence with an overly positive spin. Of the 62% of experiments that include a control group, over a quarter forego reporting statistics that directly compare experimental and control participants in terms of BOLD regulation. Some of these studies demonstrate an improvement in the experimental group and no significant difference in the control group but refrain from directly comparing the two groups (e.g., Caria et al., 2007; Rota et al., 2009; Subramanian et al., 2011). These findings might project the image that veritable feedback outperforms placebo-nf. But with these measures alone, we cannot confirm the superiority of veritable neurofeedback (Nieuwenhuis, Forstmann, & Wagenmakers, 2011). Moreover, 31% of the control procedures used in fMRI-nf experiments diverge substantially from the experimental procedures in terms of motivational factors and training parameters (e.g., mental rehearsal without neurofeedback; see Figure 3A). Taking these factors into account, the value of fMRI-nf findings are not all equal; some studies provide relatively weak evidence compared to others.

4.3 BOLD regulation in summary

The evidence for fMRI-nf-driven self-regulation of the BOLD signal remains promising yet underdetermined. While the previous sections highlighted how several publications appear to oversell their findings, very few experiments find an absence of learning, and a number of robust studies document learned BOLD regulation. To bolster evidence in this domain, researchers stand to benefit from directly comparing veritable and placebo-nf groups, measuring muscle activity and breathing patterns, and pre-specifying and reporting all planned measures and statistical tests.

5. BEHAVIORAL SELF-REGULATION

The promise of fMRI-nf stems from the potential to regulate brain processes and, in turn, to improve well-being. Nonetheless, we remain far from establishing causal links between circumscribed patterns of brain activity and complex human behaviors. Whereas neuroscientists have successfully mapped discrete stimuli onto the sensory cortices (e.g., primary motor, sensory, or visual areas), the neural correlates of psychiatric conditions and multifaceted mental processes appear to rely on the synthesis of information from a variety of brain regions (Akil et al., 2010). To provoke meaningful behavioral change, fMRI-nf will likely need to influence broader neural circuitry. Increasingly, neurofeedback studies probe and largely confirm that fMRI-nf rearranges functional connectivity between brain regions (see Table 1). And yet, research has yet to establish whether changing brain activity as recorded by fMRI is sufficient or necessary to improve mental health conditions.

5.1 fMRI-nf modifies behavior

Of the experiments we reviewed, 59 statistically compare behavior from before to after neurofeedback (a number of additional studies measure behavior at one time point and test whether behavior and neural measures correlate, but not whether neurofeedback alters behavior—e.g., Marxen et al., 2016; Zotev et al., 2011). In 69% (41/59) of these behavioral studies, participants improve compared to baseline measures taken either before neurofeedback training, during the first trial of training, or during rest blocks (Fig 4B). Of the behavioral studies that include a control group, 59% (24/41) report a greater behavioral improvement in the

444 experimental group compared to the control group. Because demand characteristics can alter
445 behavior, and repeating a test can improve performance scores, experiments without control
446 groups—or with control conditions that carry fewer motivational factors (e.g., mental
447 rehearsal)—provide insufficient evidence to confidently attribute improvement to veritable
448 neurofeedback, rather than to ulterior factors. The cumulative behavioral findings stand less
449 robust than the consistent results supporting BOLD regulation. Nonetheless, the combination of
450 neurofeedback-specific effects plus psychosocial influences may produce an effective behavioral
451 intervention.

452 We must ponder, moreover, whether observed behavioral improvements are clinically—
453 not just statistically—significant. Clinical significance implies that, statistical significance aside,
454 patients manifest improvements of ample magnitude to increase well-being (Jacobson & Truax,
455 1991; B. Thompson, 2002). The threshold for clinical significance varies depending on the
456 research question and patient population. Whereas some scientists define clinical significance as
457 the minimum improvement a practitioner can observe (e.g., Leucht et al., 2013), others refer to
458 the smallest positive difference a patient can subjectively notice (e.g., B. C. Johnston et al.,
459 2010). Researchers have devised various methods for calculating clinical significance and often
460 referring to the term minimally important clinical difference (MICD) (Wright, Hannon, Hegedus,
461 & Kavchak, 2012). For some common measurements, researchers prefer calculating the
462 minimum change on more objective scales that corresponds to an observable subjective
463 improvement (e.g., a reduction of 3-7 points on the Hamilton Rating Scale for Depression:
464 Leucht et al., 2013). More often, however, researchers must set their own definition for clinical
465 significance. This definition should be determined a priori in order to tease apart whether a
466 statistically significant result (e.g., improved face recognition in people with schizophrenia: Ruiz

et al., 2013) translates into a meaningful improvement in the condition of a patient. Research on fMRI-nf employs diverse methodologies and measurements—a standardized implementation has yet to emerge and each application comes with varying degrees of evidence. The following more scrutinous examination explores whether behavioral findings in fMRI-nf research reach clinical significance.

INSERT FIGURE 5 AROUND HERE

5.2 Dissecting the behavioral effects of fMRI-nf

In our review, we assumed a liberal approach to labeling behavioral change as successful. We included experiments where at least one behavioral variable differed between endpoints and baseline or between experimental and control groups. Some experiments, however, measure many behavioral variables, make no mention of accounting for multiple comparisons, and emphasize only significant findings. Below we outline the current state of evidence for the three potential clinical applications of fMRI-nf that have been investigated in at least five studies: affect, nicotine addiction, and pain.

Eleven fMRI-nf experiments have examined changes in affect using the positive and negative affect schedule (PANAS). Across these studies, we observe few findings that overlap reliably. Rather, we see the following collection of distinct outcomes: no difference in PANAS scores (S. J. Johnston et al., 2011; Z. Li et al., 2016; Sarkheil et al., 2015); global PANAS scores remain consistent, but both positive and negative subscales decreased, no controls used (Gröne et al., 2015); positive and negative subscales decrease, no global measure and no control group

(Mathiak et al., 2015); no differences in PANAS score, but changes in the ability to recognize facial expressions (Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2013); higher mood disturbance reported, but no relevant statistical tests included (S. J. Johnston, Boehm, Healy, Goebel, & Linden, 2009); lower negative affect in experimental participants across sessions, but no main effect of session or interaction of group by session (Linden et al., 2012); no correlation between PANAS scores and BOLD regulation (Cordes et al., 2015); PANAS mentioned in methods section, but not included in results section (Rota et al., 2009); and affect tested only post-training (Hamilton et al., 2016). Although the target ROIs of these experiments vary from the ACC, to the prefrontal cortex, to individually identified areas involved in emotion, the results hardly follow a pattern based on the ROI targeted. Notably, a number of these experiments may mask the clinical utility of fMRI-nf because they investigated healthy participants who may experience ceiling effects more quickly than patients. Nonetheless, a coherent story scarcely emerges from the multiple experiments using the PANAS. The presence of multiple studies that report at least one positive finding and include a number of matching behavioral variables may prompt a misleading image of replicability; upon closer inspection, however, specific results vary substantially.

In the case of nicotine dependence, three studies report a decreased desire to smoke after fMRI-nf, but do not include control participants (Canterberry et al., 2013; Hanlon et al., 2013; X. Li et al., 2012), one experiment shows a decreased desire to smoke in terms of positive anticipation of a cigarette, but not in terms of the expected relief of cravings (Hartwell et al., 2016), and another reveals an absence of changes in cigarette craving (Kim et al., 2015); all of these studies target the ACC and all but one also target the prefrontal cortex. While these results

suggest a promising application, only one experiment uses a control group (Hartwell et al., 2016), and none actually test whether participants smoke less after training.

As for fMRI-nf and pain perception, experiments report the following—somewhat more promising—spectrum of findings: decreased pain ratings during neurofeedback and a correlation between BOLD regulation and pain ratings, no control group (Emmert et al., 2014/Emmert, Breimhorst, et al., 2017); decreased pain after veritable fMRI-nf compared to both baseline measures and placebo-nf participants, but no correlation between BOLD regulation and pain ratings (Guan et al., 2015); decreased pain ratings compared to both baseline measures and controls participants, pain ratings correlated with BOLD regulation (deCharms et al., 2005); and, no effect of neurofeedback on pain (Rance, Ruttorf, Nees, Schad, & Flor, 2014; Rance, Ruttorf, Nees, Schad, Flor, et al., 2014). All five of these studies target the ACC, four of them hone in on the rostral ACC specifically and three also target the left insula. Compared to affective experience and nicotine dependence, fMRI-nf seems to exert a more reliable positive effect on pain ratings. And yet, while current evidence indicates that fMRI-nf may lead to pain reduction, the link between successful BOLD regulation and pain perception remains tenuous. Taken together, the scarcity of robust and converging evidence surrounding many interventions—perhaps with the exception of pain management—calls for further studies before applying fMRI-nf behaviorally.

5.3 Behavioral effects of fMRI-nf in clinical populations

Beyond the clinically relevant behaviors outlined above, researcher have tested fMRI-nf directly on a number of clinical populations, including patients with major depressive disorder,

Parkinson's disease, schizophrenia, anxiety, tinnitus, obesity, alcohol abuse, and ADHD. Here we discuss every clinical condition where at least two experiments have been conducted.

For depression, two strong experiments account for respiration artifacts, employ robust control groups, and leverage a double-blind design to show that genuine-nf, compared to placebo-nf, allows depressed patients to regulate their amygdala and improve their mood (Young et al., 2014, 2017). Other experiments show that depressed patients can modulate individually identified ROIs that respond to emotion and that they improve on scales measuring mood; however, BOLD regulation and behavior hardly correlated (Hamilton et al., 2016; Linden et al., 2012).

Patients with Parkinson's disease can learn to regulate their SMA and improve their finger tapping speed compared to a mental rehearsal control group (Subramanian et al., 2011). In a further studies, however, patient improved on only one of five subscales of motor performance and this change was comparable to a control group (Subramanian et al., 2016). Studies with a healthy population similarly find that genuine-nf leads to better regulation of the PMC and increased finger tapping frequency compared to placebo-nf (Hui et al., 2014; Zhao et al., 2013). However, another study shows that healthy participants could neither regulate primary motor cortex nor improve motor performance (Blefari, Sulzer, Hepp-Reymond, Kollias, & Gassert, 2015). An important next step would be to examine whether improved finger tapping speed and better scores on scales of emotion translate into meaningful improvements in the lives of patients.

While the findings with depressed and Parkinsonian patients hold some promise, the results from other clinical populations are less clear. Patients with schizophrenia, for example, learned

555 to regulate their ACC and anterior insula in two studies (Cordes et al., 2015; Ruiz et al.,
556 2013)(Cordes et al., 2015; Ruiz et al., 2013). However, one of these studies found no correlation
557 between brain activity and changes in either affect or mental imagery (Cordes et al., 2015) while
558 the other observed an increased ability to detect disgust faces, but no change in affect (Ruiz et
559 al., 2013). Moreover, both studies lacked control groups. As for anxiety, whereas one study
560 found an increased ability to control orbitofrontal activity alongside a reduction in anxiety
561 (Scheinost et al., 2013), another experiment showed increased insular control alongside a
562 marginal increase in anxiety (Zilverstand et al., 2015). Individuals with tinnitus learned to
563 downregulate their auditory cortex in two studies. However, in one experiment they only
564 improved on one out of eight tinnitus subscales (Emmert, Kopel, et al., 2017) and the other study
565 found that two of six patients reported improvements in their condition (Haller, Birbaumer, &
566 Veit, 2010); both studies lacked control groups. Obese participants and healthy individuals both
567 learned to control hunger-related ROIs that were individually identified in each participant. In
568 one study, participants reported a decrease in hunger but no change to satiety (Ihssen, Sokunbi,
569 Lawrence, Lawrence, & Linden, 2017). In another study, learned brain regulation drove no
570 change in hunger, fullness, satiety, or appetite, while causing a marginal worsening of snacking
571 behavior but improvement toward selecting lower calorie foods (Spetter et al., 2017). In a third
572 study, obese participants learned to regulate their anterior insula, but this had no effect on mood
573 and changes in hunger were not reported (Frank et al., 2012). These three studies on eating
574 behavior lacked control groups. Other studies found that heavy drinkers could regulate
575 individualized brain regions associated with craving (Karch et al., 2015) or the ventral striatum
576 (Kirsch, Gruber, Ruf, Kiefer, & Kirsch, 2016) resulting in either a marginal reduction in craving
577 or no effect on craving, respectively. Both studies included placebo-nf conditions. For ADHD,

adults showed no difference in BOLD regulation or behavior between genuine and placebo-nf groups (Zilverstand et al., 2017). Alternatively, children receiving genuine-nf better regulated BOLD activity than a placebo-nf group, but behavioral improvement was comparable between the groups (Alegria et al., 2017). These ADHD studies stand out as some of the first registered fMRI-nf trials. For many clinical applications, we would need further controlled experiments to more clearly establish the benefits of fMRI-nf.

5.4 Behavioral effects of fMRI-nf in healthy populations

Beyond the direct clinical applications, researchers have investigated whether fMRI-nf can alter perceived valence, working memory, reaction time, and visual performance. In this section, we review all behavioral applications of fMRI that appear in at least two studies and that we have yet to discuss.

Five studies have investigated whether fMRI-nf can alter how participants subjectively rate stimulus valence. These studies report a variety of results: no ability to modulate the amygdala and no effect on valence (Paret et al., 2014); an ability to regulate the amygdala and mention of valence rating in the methods, but not in the results section (Paret, Kluetsch, et al., 2016); an ability to upregulate insular activity and a correlated change in rating aversive pictures as more negative (Caria, Sitaram, Veit, Begliomini, & Birbaumer, 2010); a capacity to upregulate the insula, but no effect on valence ratings (Lawrence et al., 2014); and learned regulation of functional connectivity between the dmPFC and the amygdala, alongside increases in positive valence ratings (Koush et al., 2017).

As for working memory, whereas genuine neurofeedback led to increased DLPFC regulation and increased performance on five working memory tasks, placebo-nf reduced DLPFC regulation, yet drove a comparable increase in performance on four of the five tasks (Zhang, Yao, Zhang, Long, & Zhao, 2013). Another study demonstrated that neurofeedback participants could regulate the DLPFC and improve working memory performance compared to a mental rehearsal control (Sherwood, Kane, et al., 2016). In a more recent study, participants failed to regulate their parahippocampal gyrus, but improved on 3 of 14 memory tests (Hohenfeld et al., 2017); however, the researchers make no mention of accounting for multiple comparison and they used an underpowered placebo-nf group with four participants, compared to the 16 receiving genuine-nf.

Five fMRI-nf studies primarily investigate reaction time and have mixed findings. Two studies selected post-hoc for participants who learned to regulate motor cortex activity and found that they decreased their reaction time in one experiment (Bray et al., 2007) but not in the other (Chiew et al., 2012). Other studies demonstrated increased ACC regulation and faster reaction times, but included no control group (Mathiak et al., 2015), and found no difference between experimental participants and a mental rehearsal control (Sherwood, Kane, et al., 2016). A more recent study leveraged an inverse design where one group trained to upregulate functional connectivity between the motor and parietal cortex while the other group trained to down-regulate the same connectivity pattern (Yamashita, Hayasaka, Kawato, & Imamizu, 2017). The groups successfully learned to regulate connectivity in opposing directions, but the behavioral findings fail to form a cohesive story. One group increased reaction time on a vigilance task, the other increased reaction time on a flanker task, and both groups decreased reaction times on a

Stroop test. Altogether, the findings concerning valence, memory, and reaction time are hardly conclusive and demand replication efforts.

Some scientist investigating neuroplasticity are also interested in whether fMRI-nf can modulate low level cortical areas such as early visual cortices. The more robust studies demonstrate either that neurofeedback can alter early visual cortex activity and in turn bias perception towards certain line orientations (Shibata et al., 2011) and alter color perception (Amano et al., 2016). Other studies report a variety of results: successful regulation of the ratio of activity between the parahippocampal and fusiform face area, but no effect on perception (Habes et al., 2016); an increased ability to lateralize visual cortex activity and subsequent reductions in the severity of hemi-neglect patients (Robineau, Saj, et al., 2017); and improved regulation of primary visual areas alongside either improved visual discrimination (Scharnowski et al., 2012) or unaffected visual extinction (Robineau et al., 2014). However, these latter two studies identified *post-hoc* participants who learned to regulate their BOLD signal and analyzed those participants separately. The ability to regulate low-level cortical areas holds important implication for neuroplasticity research; the implications for behavioral or clinical outcomes remain less clear.

5.5 Behavioral self-regulation in summary

FMRI-nf affects behavior; yet, the various findings come together as a mosaic of disparate results rather than a clear unified picture. The disparity between findings may stem from the uniqueness of each study and the all-too-common insufficient sample size in fMRI-nf

experiments. Small samples can lead to an increase in false-negatives (i.e., masked interesting results) as well as an increase in false-positives (Button et al., 2013).

Crucially, disentangling the relative contribution of genuine feedback versus psychosocial influences requires further investigation. To help establish the specific behavioral effectiveness of fMRI-nf, relevant experiments could benefit from testing behavioral improvements compared to both baseline measures and control groups, while also examining correlations between behavior and BOLD regulation. Moreover, probing whether BOLD regulation negatively impacts any behavioral measure would provide a more complete understanding of this technique. For example, whereas fMRI-nf experiments for pain regulation aim to down-regulate the rostral ACC, affect research often calls for up-regulation of this same region. While behavioral improvements may manifest for some measures, impairments could develop for others.

6. SUSTAINABILITY, TRANSFERABILITY, AND PRACTICALITY OF fMRI-nf

While positive findings abound in fMRI-nf research, the clinical feasibility and value of this technique remains unconfirmed. A few years ago, several prominent neurofeedback researchers stated in an authoritative review that the “real usefulness [of fMRI-nf] in clinical routine is far from being demonstrated” (Sulzer et al., 2013). The present review suggests that their statement remains valid: to date, few studies have tested clinical significance, examined patient populations, or investigated follow-up measures.

6.1 Sustainability

663 The dominant view of fMRI-nf posits that participants learn to modulate brain activity
664 during neurofeedback training and then maintain this ability throughout daily life—regulating
665 neural function when required (deCharms, 2008). An alternative theory (discussed in Sulzer et
666 al., 2013 in relation to deCharms et al.'s unpublished experiments) suggests that neural
667 regulation may not be necessary to achieve positive behavioral outcomes. Rather, this theory
668 posits that the value of fMRI-nf may lie more in developing effective mental strategies. Once the
669 researchers know what mental strategies work, they can teach these strategies to new participants
670 who can obtain most of the benefits of fMRI-nf without ever undergoing fMRI-nf themselves.
671 Moreover, participants may experience behavioral benefits even though they lack the ability to
672 regulate the specific brain region of interest. This second theory offers an alternative to the
673 theoretical foundation of neurofeedback, arguing that learned regulation of a specific ROI may
674 not be the primary determinant of positive behavioral outcomes in fMRI-nf interventions.
675 Another theory that garners some empirical support suggests that providing mental strategies
676 may hamper learning and that operant conditioning is sufficient to drive neurofeedback learning
677 (e.g., Dworkin, 1988; Sepulveda et al., 2016; see Sitaram et al., 2017 for a more detailed
678 discussion). Notably, 79% of fMRI-nf experiments provide participants with at least a general
679 mental strategy to modulate the BOLD signal (see Table 1).

680 To support the prevailing mechanistic theory of neurofeedback, researchers must
681 demonstrate that participants can continue to modulate the BOLD signal in the absence of
682 neurofeedback (i.e., during a "transfer run"). Of the 34 studies that measure this ability, 23
683 suggest that participants can transfer their neural regulation to runs without neurofeedback, while
684 11 suggest they cannot (Fig 6A). Of these 34 studies with transfer runs, nine include patients, of
685 which six document that patients maintain BOLD regulation capacity in the absence of feedback

(see Table 1). These few studies hint at a promising trend. Future experiments using transfer runs would help to establish the supposed neurobiological basis of neurofeedback treatment outcomes.

Follow-up measures of behavior, functional connectivity, and BOLD regulation (i.e., transfer runs conducted beyond the day of neurofeedback training)—taken days, weeks, or months after training—could also help document the sustainability of neurofeedback (Fig 6B). Of the 99 experiments analyzed, four conduct follow-up analyses on BOLD regulation (all successful), six analyze follow-up functional connectivity (five successful), and 11 examine follow-up behavior (nine successful; see Table 1). Notably, on a number of these follow-up measures, experimental and control groups showed similar improvements (e.g., Chiew et al., 2012; Yuan et al., 2014; Zilverstand, Sorger, Sarkheil, & Goebel, 2015). At the moment, the sparsity of follow-up measurements across fMRI-nf experiments precludes claims that a single training session may impart long-term benefits (see Figure 7 for a conceptual diagram overviewing the theory and actualities of fMRI-nf).

INSERT FIGURE 6 AROUND HERE

INSERT FIGURE 7 AROUND HERE

6.2 Transferability

To promote fMRI-nf as a medical tool, researchers will need to document clinically significant benefits in the populations they intend to treat. Currently, the majority of fMRI-nf

participants are healthy, in their twenties (see supplementary table), and presumably—as in most psychology and neuroimaging experiments (Chiao & Cheon, 2010; Henrich, Heine, & Norenzayan, 2010)—undergraduate university students. Compared to this young and well-educated sample, patient populations might find it more difficult to modulate brain activity.

Testing fMRI-nf on patients provides the most direct way to document clinical utility. Twenty-eight experiments we reviewed study patient samples (Fig 5c). Of these patient samples, five suffer from nicotine addiction, four from depression, and two from each of chronic pain, schizophrenia, Parkinson's disease, ADHD, tinnitus, and obesity, as well as seven from other conditions. Fifteen of these studies include control groups. Notably, a number of pilot fMRI-nf studies, which include only individual level statistics, also test patient samples (Buyukturkoglu et al., 2013: Parkinson's disease, Buyukturkoglu et al., 2015: obsessive compulsive disorder; Dyck et al., 2016: schizophrenia; Gerin et al., 2016: posttraumatic stress disorder; Liew et al., 2016: stroke; Sitaram et al., 2014: criminal psychopaths). Participants in four of the 99 studies had an average age over 50 years and suffered from Parkinson's disease, hemi-neglect, or Alzheimer's disease (see supplementary table). Their learning and behavioral improvement appears comparable to younger participants. Experiments with patient samples often find statistical significance yet lack the measures necessary to argue for clinical significance. For example, neurofeedback can decrease cravings for cigarettes, but does this change translate to fewer cigarettes smoked? Are the magnitudes of changes in pain ratings, subjective scales of mood and affect, or the perceived valence of images large enough to impart a meaningful benefit for patients? Do observed effects persist beyond the day of neurofeedback training? To elucidate such questions researchers must measure clinically relevant behaviors and gather follow-up

information (e.g., Robineau et al., 2017; Scheinost et al., 2013; Subramanian et al., 2011; Zilverstand et al., 2015).

6.3 Practicality

Even if fMRI-nf triumphs as a medical treatment, the sparse availability and high price of MRI scanners may remain a barrier to accessible treatment. The 3-Tesla MRI scanners typically used in fMRI-nf research are currently available only in advanced medical facilities and research centers. Such facilities exist mostly in medium to large size cities within rich countries. A 3-Tesla MRI facility costs a few million USD to install and requires ongoing maintenance and specialized technicians. An average medical MRI scan costs over 2,600 USD in the United States (Center for Medicade and Medicare Services, 2014). These medical scans, moreover, usually measure anatomy alone and require much less scan-time than a typical fMRI-nf session would demand. A less expensive option could involve booking an MRI scanner in a non-hospital environment (500-1,000 USD per hour) and hiring an independent fMRI-nf practitioner. Nonetheless, if fMRI-nf parallels EEG-nf, which can take 20-40 sessions to actualize substantial benefits, the scanning costs could quickly become prohibitively expensive. Alternatively, if only a few fMRI-nf sessions can drive meaningful clinical outcomes, this technique could benefit patients in industrialized nations with geographic and financial access to an MRI scanner. However, before coming to premature conclusions about the practicality of fMRI-nf, one would need to also consider a cost-benefit analysis. For example, if fMRI-nf could successfully treat refractory depression, then the defrayed costs of ongoing medical treatment and reduced worker efficiency could dwarf the cost of neurofeedback treatment. Thus, scientists could benefit from

evaluating the practicality of fMRI-nf not in isolation, but in relation to the price, availability, and efficacy of other treatment options.

INSERT BOX 1 AROUND HERE

7. IMPLICATIONS

7.1 *Steps forward in neurofeedback protocols*

Since the inception of fMRI-nf in 2003, research on neurofeedback has progressed significantly. For one, fMRI-nf makes several important advances over more traditional, EEG-based, approaches to neurofeedback. EEG-nf experiments generally involve dozens of training sessions and often neglect to directly measure whether participants learn to modulate neural activity. In contrast, fMRI-nf requires only a few runs to impart BOLD modulation, and relevant experiments almost always measure neural regulation capacities. As evidence continues to mount suggesting that individuals can easily regulate the BOLD signal, fMRI-nf may one day surpass the clinical utility of EEG-nf (which notably derives most of its powerful healing effects from psychosocial influences: Schabus et al., 2017; Schönenberg et al., 2017; Thibault & Raz, 2016)

Regulating brain signals via fMRI-nf may be more effective due to the superior localization specificity of the BOLD signal compared to the EEG signal. Whereas the BOLD signal reflects spatially precise cardiovascular processes, the EGG signal arises from the interaction of diverse electrical signals, which scatter as they pass through the electro-conductive fluids and tissues that surround the brain. Empirical research on the difference between learning

773 in fMRI- and EEG-nf, however, remains absent from the literature. For the time being, therefore,
774 such comparisons remain speculative.

775 In an attempt to advance fMRI-nf, some scientists argue that greater magnetic fields (e.g.,
776 7-Tesla or higher) will allow researchers to target sub-millimetric neural regions and improve the
777 effectiveness of fMRI-nf (Goebel, 2014). To date, however, researchers have yet to localize sub-
778 millimetric clusters of brain activity responsible for most conditions that fMRI-nf aims to treat.
779 Furthermore, tiny head movements can offset the potential increase in precision that 7-Tesla
780 scanners offer. An empirical effort even demonstrated a counter-intuitive benefit of 3-Tesla over
781 7-Tesla scanners for fMRI-nf (Gröne et al., 2015): researchers found a lower signal-to-noise ratio
782 at 7-Tesla and suggested that including physiological noise parameters could help overcome this
783 issue.

784 In recent years, researchers have begun to employ a new fMRI-nf approach targeting
785 functional connections between regions rather than activity in single ROIs. All of the six
786 experiments using this technique demonstrate that individuals can learn to regulate functional
787 connectivity patterns (Kim et al., 2015; Koush et al., 2013, 2017; Megumi et al., 2015; Spetter et
788 al., 2017; Yamashita et al., 2017). Three of these experiments employ placebo-nf controls and
789 show better neural regulation in the genuine-nf group (Koush et al., 2017; Megumi et al., 2015;
790 Yamashita et al., 2017). These functional connectivity studies also report positive behavioral
791 effects for valence ratings (Koush et al., 2017), hunger (Spetter et al., 2017), and reaction time
792 (Yamashita et al., 2017), but not for cigarette craving (Kim et al., 2015). Notably, many fMRI-nf
793 studies that train individuals to modulate singles ROIs also demonstrate changes in functional
794 connectivity (see Table 1). Comparative studies would be needed to establish whether functional
795 connectivity neurofeedback outperforms more traditional single-ROI approaches.

A third type of fMRI-nf uses feedback derived from multi-voxel pattern analysis (MVPA) in a process entitled decoded neurofeedback, or DecNef (see Watanabe, Sasaki, Shibata, & Kawato, 2017 for a more detailed review on this topic). This method analyses brain activity from each participant to create an individualized brain signature associated with a specific perception. For example, training a brain signature in early visual areas that reflects a particular line orientation can bias individuals to perceive lines of that orientation in obscured Gabor patches (Shibata et al., 2011). Similarly, training the MVPA associated with the color red can drive individuals to observe red more often than green in achromatic images (Amano et al., 2016). Moreover, using DecNef to train opposite activity in the cingulate cortex between two groups of participants, researchers increased facial preferences in one group and decrease facial preference in the other (Shibata, Watanabe, Kawato, & Sasaki, 2016). Researchers also reduced fear responses by encouraging a fearful brain state and then reconditioning it with a monetary reward (Koizumi et al., 2016). Another experiment trained opposing brain patterns within single subjects and demonstrated bi-directional confidence judgements depending on which brain pattern they activate (Cortese, Amano, Koizumi, Lau, & Kawato, 2017). In contrast with common fMRI-nf protocols, DecNef researchers neither provide a strategy to participants nor inform them regarding what the feedback represents. While these behavioral findings stand out amongst fMRI-nf studies, in a number of these experiments participants remain statistically unsuccessful at modulating the brain signal of interest (Cortese et al., 2017; Shibata et al., 2016). Instead of imposing an overarching correlation between a brain region and behavior, DecNef is personalized and data-driven; it could quickly become a prevailing fMRI-nf method.

7.2 The future of behavioral fMRI-nf

This systematic review synthesizes an eclectic assortment of experimental protocols. The reviewed studies target an array of brain regions and associated behaviors using a wide range of instructions, mental techniques, reward mechanisms, and lengths of training. The available evidence suggests that fMRI-nf can help participants modulate BOLD activity from almost any cortical region while also modifying diverse behaviors. To promote fMRI-nf as a clinical tool, however, researchers must hone in on specific applications and assess therapeutic measures, underlying mechanisms, and replicability.

In this quest, we must consider that demonstrating statistical significance alone falls short of implying clinical significance. For example, a statistically significant reduction in cigarette craving does not necessarily translate to a meaningful decrease in smoking behavior. Similarly, a statistically significant change of a few points on scales of affect, mood, or pain may reflect only a negligible impact in terms of clinical outcome. Furthermore, it remains to be seen whether the effects of fMRI-nf endure in the long-term or dwindle shortly after training.

While the presence of 99 primary fMRI-nf experiments may paint a picture of reproducibility, few of these studies overlap sufficiently in their methods to be considered replications. In light of the replication crisis in psychology (Open Science Collaboration, 2015), and a hint at a similar trajectory for the neurosciences (Boekel et al., 2015; Button, 2016; Button et al., 2013), proponents of fMRI-nf would benefit greatly from pre-registering experiments and conducting confirmatory replication studies (i.e., with pre-specified outcome measures based on the results of previous experiments). Irreproducible results may stem from common publication bias (Easterbrook, Gopalan, Berlin, & Matthews, 1991), which can inflate the perceived effectiveness of any technique—fMRI-nf included. In clinical research about half of all trials go unpublished (Riveros et al., 2013) and many published studies bolster their findings by

withholding a selection of pre-specified measures or reporting additional post-hoc tests as if they were confirmatory results (Goldacre et al., 2016). Unlike in clinical trials, however, researchers seldom pre-register fMRI-nf studies. Thus, we cannot calculate how many studies have yet to reach publication or estimate the prevalence of questionable research practices such as optional stopping (e.g., when significance tests reach $p < .05$) and selective reporting (John, Loewenstein, & Prelec, 2012; Simmons, Nelson, & Simonsohn, 2011). Fortunately, fMRI-nf lacks the overbearing financial conflicts of interest that can offset the integrity of some medical research. Nonetheless, at least one of the largest fMRI-nf studies—which found comparable behavioral benefits between placebo and veritable feedback groups—remains unpublished (discussed in Sulzer et al., 2013). The combination of aforementioned issues has brought scientific research to a state where "most published research findings are false" (Ioannidis, 2005). While this statement rings more true for some fields than for others, the small sample sizes and flexible research designs common in fMRI-nf research increase the risk of false positives (Button et al., 2013; Ioannidis, 2005). We hope that the figures and table in this manuscript sufficiently highlight the heterogeneity among fMRI-nf methods and findings, and that our systematic appraisal prompts future replication efforts with robust controls. Pre-registered replication experiments may hold the key to advancing the science of fMRI-nf while distinguishing this domain from neighboring fields on the brink of crisis.

7.3 Other applications of fMRI-nf

Whereas this review focuses on fMRI-nf as a tool to modulate behavior, other applications have cropped up in recent years (Sitaram et al., 2017). For example, studies have employed fMRI-nf to help relate subjective experience and brain activity (Garrison et al., 2013), implicitly train brain activity to bias conscious perception (Amano et al., 2016; Shibata et al., 2016) and

confidence (Cortese, Amano, Koizumi, Kawato, & Lau, 2016), or act as an attentional crutch that alerts participants when neural signatures of vigilance begin to dwindle (DeBettencourt et al., 2015). In addition, many experiments investigate whether combining computer classification algorithms with fMRI-nf can allow individuals to control a brain-computer interface (BCI). This application holds particular potential for helping locked-in patients communicate decisions to their caregivers. Yet, whereas healthy participants can control such BCIs (e.g., Yoo et al., 2004), completely locked-in patients typically have less success (Monti et al., 2010). Moreover, as a bed-side communication device, portable imaging modalities such as EEG and functional near infrared spectroscopy prove more practical than fMRI (Naci et al., 2012). Nonetheless, fMRI-nf holds potential as both a research tool and communication device independent of its applications in the domain of clinical treatment.

8. CONCLUSION

The present comprehensive review suggests that fMRI-nf may develop into a powerful biobehavioral intervention. Experiments repeatedly demonstrate that real-time feedback allows individuals to modulate the BOLD signal from a plethora of cortical regions. And yet, BOLD self-regulation falls short of implying behavioral self-regulation. Our in-depth review reveals three important lacunae in the domain of fMRI-nf:

First, replications remain sparse. Of the 99 experiments we identified, few show overlap across multiple factors such as brain regions targeted, control conditions employed, behavioral outcomes measured, analyses conducted, and results obtained. Until research hones in on

886 standardized fMRI-nf protocols, we may attain only tenuous conclusions based on the results of
887 disparate experiments.

888 Second, findings are often overstated. While the majority of studies do obtain some
889 positive results, a cohesive narrative often fails to integrate all of the outcomes regarding brain
890 regulation, behavioral changes, and control groups.

891 Third, many fMRI-nf experiments lack the critical variables required to (i) identify
892 veritable neurofeedback as a necessary and sufficient mechanism for learning neural self-
893 regulation, and (ii) demonstrate the practical behavioral and clinical benefits of fMRI-nf. Only
894 robust and replicable experimental findings can thrust fMRI-nf beyond the proof-of-principle
895 stage toward inclusion in the clinical armamentarium as a praiseworthy intervention.

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CONTRIBUTORS

RTT, the guarantor of this article, led the systematic review, defined the search criteria, extracted data from the publications, and prepared the initial draft of the manuscript. AM and RRR helped review the publications and edit the manuscript. AR and ML provided comments throughout manuscript preparation and worked with RTT to produce the final draft.

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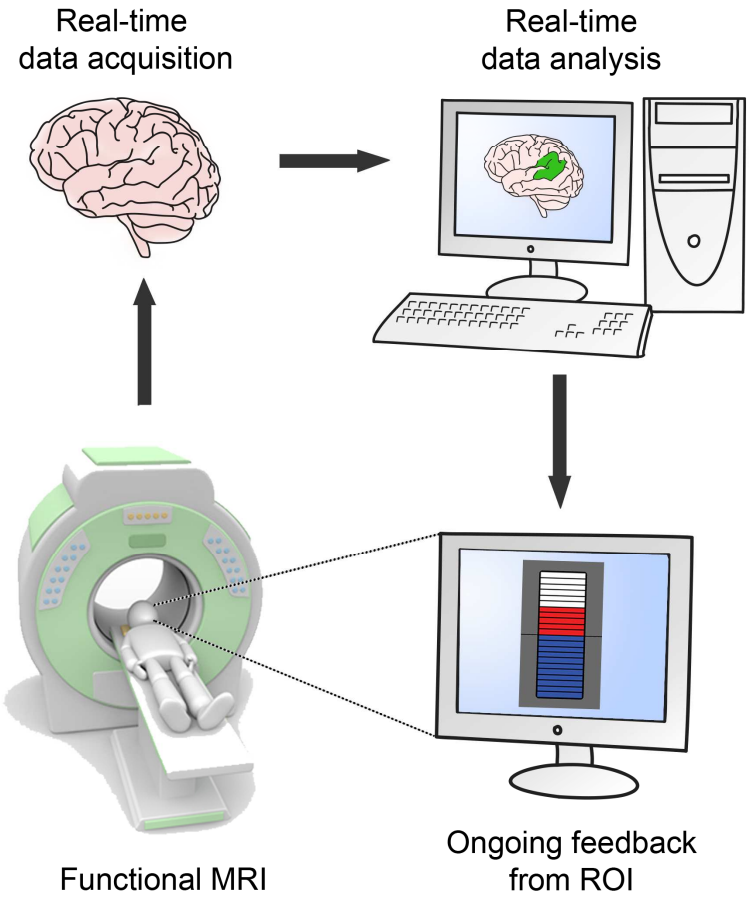
1504 **FIGURES**

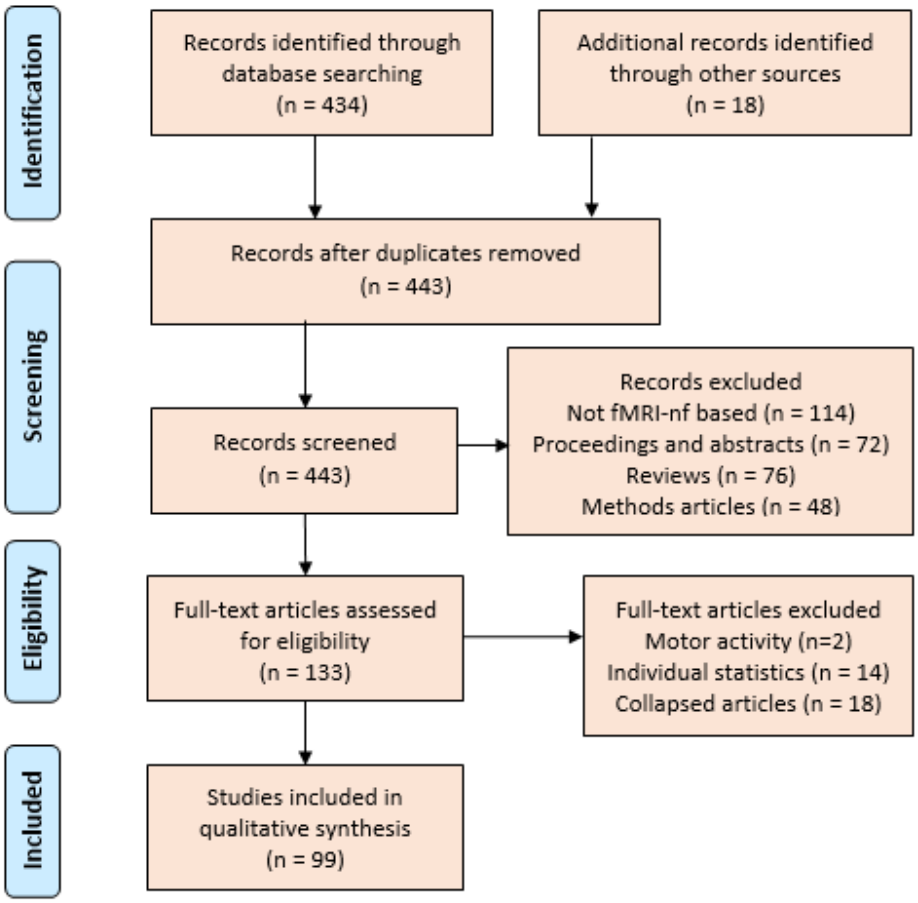


1505

1506 **Figure 1**. fMRI-nf with a standard thermometer feedback display (adapted from Thibault et al.,

1507 2016).

1508



Flowchart. Study inclusion as per the PRISMA Transparent Reporting of Systematic Reviews and Meta-Analyses Guidelines (Moher et al., 2009).

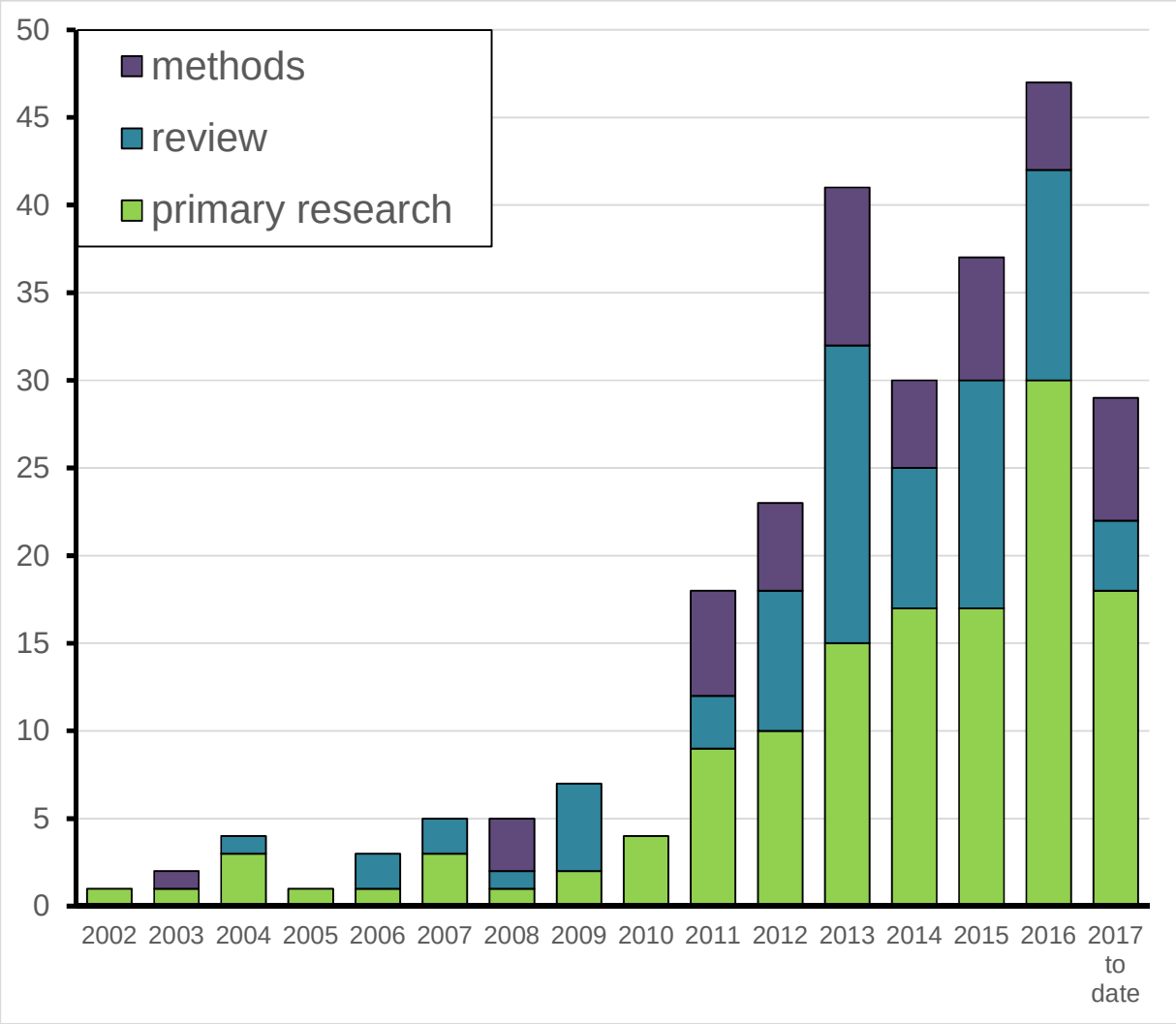


Figure 2. fMRI-nf research began surging in 2013; primary research continues to rise. This graph presents the composition of fMRI-nf publications found in our literature search.

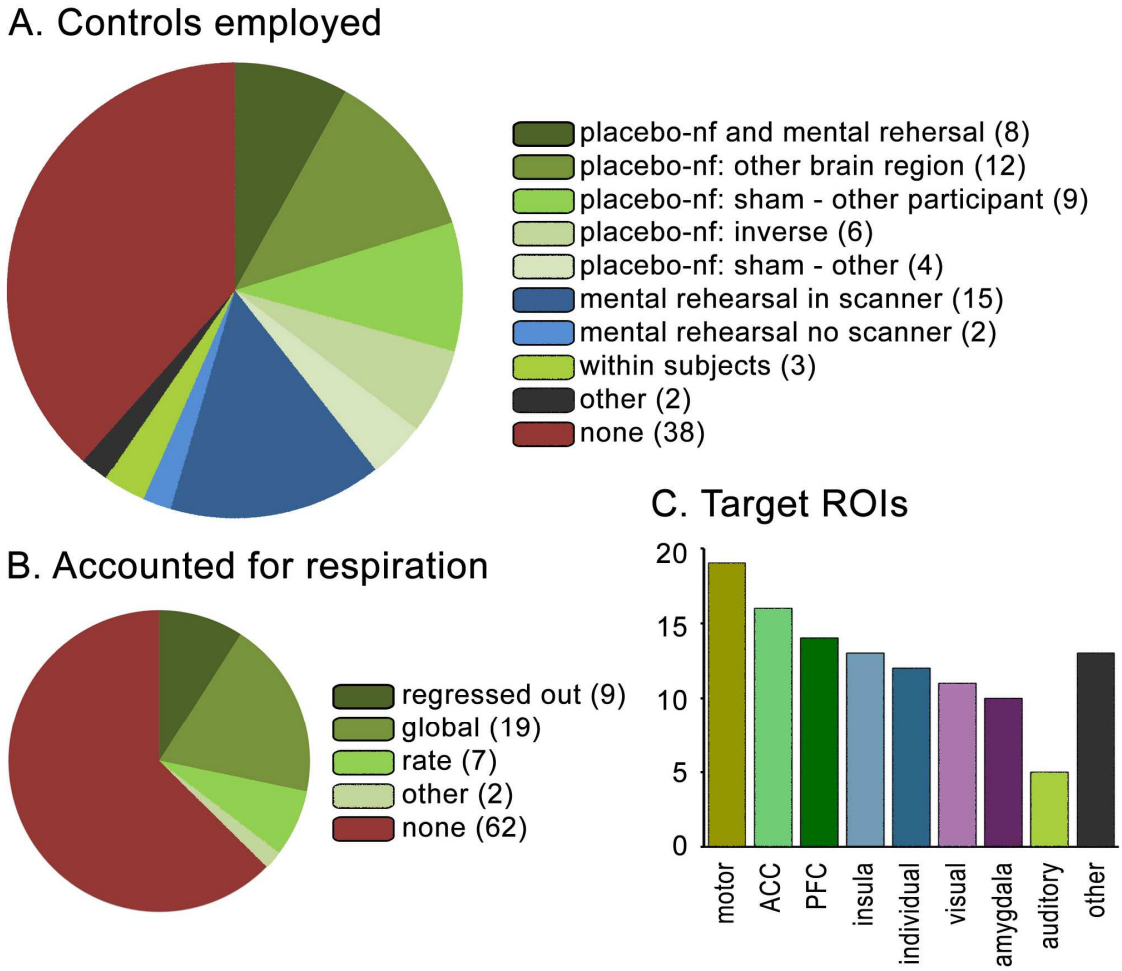


Figure 3. Experimental design and controls

(A) Distribution of controls used in fMRI-nf studies. Experiments employ no control (red), placebo-nf control (green), or non-neurofeedback control (blue). Placebo-nf encompasses any of the following: (1) brain activity from a previous participant who received veritable feedback, (2) activity from a neural region within the participant's brain but distinct from the region of interest (ROI)—often a large background area, (3) a scrambled or random signal, or (4) the inverse of the signal of interest. Although many researchers use the term sham-neurofeedback to describe any of the four conditions presented above, we opt for the term placebo-nf to avoid confusion

(feedback from a distinct neural region remains contingent on a participant's brain and therefore falls short of a true "sham"). We reserve the term sham-neurofeedback for non-contingent feedback control methods. Less common, substandard, controls include no treatment groups, where baseline and endpoints are measured in the absence of an intervention, and mental strategy rehearsal without neurofeedback, either inside or outside an MRI scanner. Some experiments leverage both placebo-nf and mental rehearsal control groups. Throughout the present review we define control groups as conditions wherein participants receive a treatment other than veritable neurofeedback from the target ROI. We consider controls absent if all participants receive genuine feedback—this includes studies that contrast healthy and patient populations, different reward mechanisms (e.g., social vs standard: Mathiak et al., 2015), distinct target ROIs (e.g., Rance, Ruttorf, Nees, Schad, & Flor, 2014), or other factors (e.g., 3T vs 7T MRI systems: Gröne et al., 2015). A few recent experiments use within-subject controls (see introduction of section 3 for a more detailed explanation).

(B) Distribution of respiratory artifact correction approaches. Some experiments effectively remove respiratory artifacts using additional instruments and algorithms (regressed out), others subtract the activity from a large background region to account for global changes in the BOLD signal (subtraction), and a few statistically analyze differences in respiration rates between conditions (rate). Accounting for respiration artifacts guards us from confounding cardiorespiratory influences with neural activity in regards to the BOLD signal.

(C) Target ROIs for self-regulation. This graph depicts the brain regions trained in fMRI-nf experiments (see Table 1 for the precise ROIs used in each study). If an experiment trained more than one ROI, we included both in this graph (thus, the total number of ROIs in this graph exceeds the 99 experiments analyzed). Some experiments identify ROIs specific to each

1549 participant based on individual BOLD responses to a particular paradigm. If these ROIs spanned
1550 multiple cortical regions across participants, we labeled them as “individual” in the graph. Six
1551 experiments present feedback based on measures of functional connectivity between ROIs (Kim
1552 et al., 2015; Koush et al., 2013, 2017; Megumi et al., 2015; Spetter et al., 2017; Yamashita et al.,
1553 2017); the graph includes all ROIs for these studies.

1554

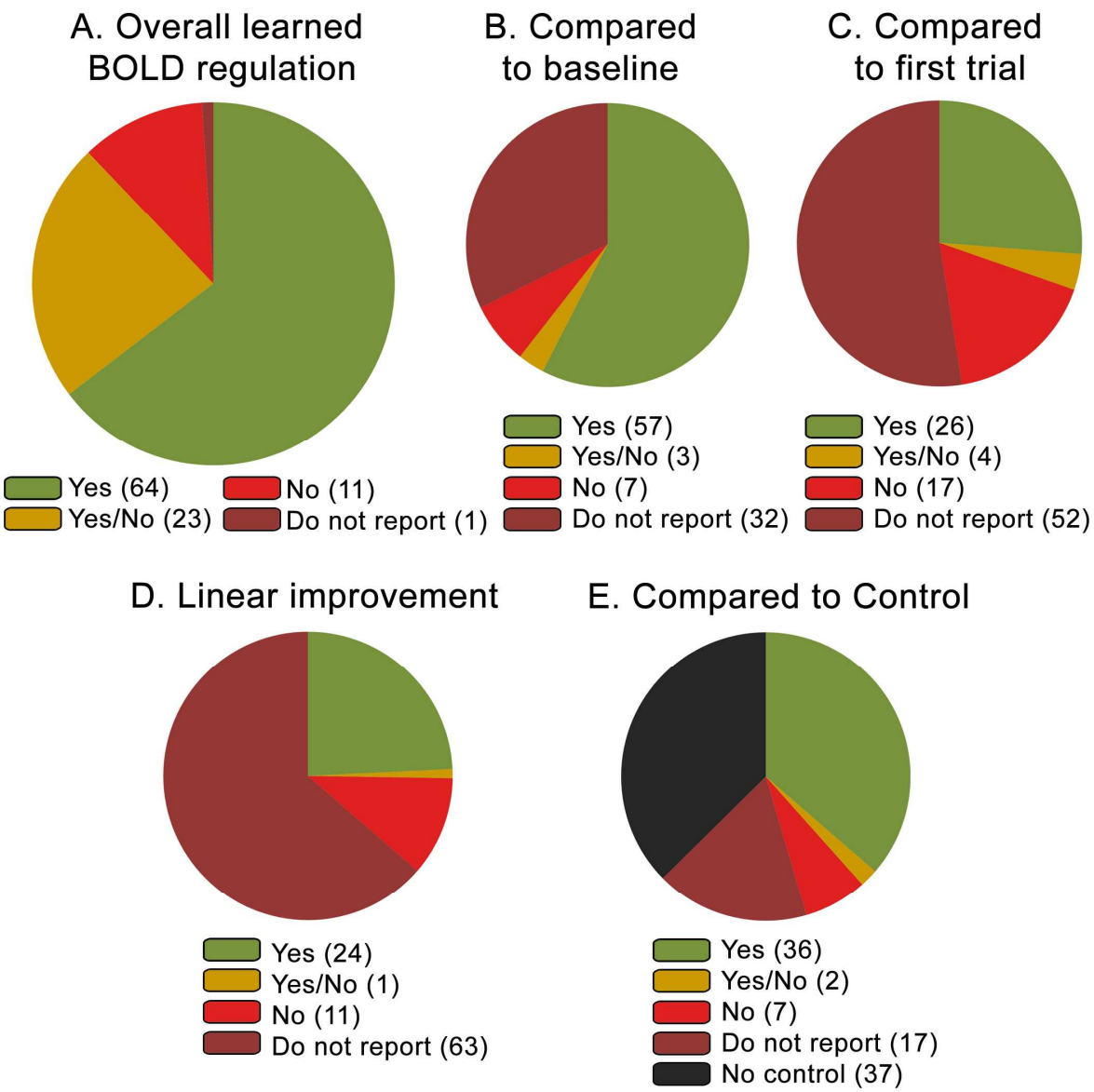


Figure 4. Methods of measuring BOLD regulation. In most experiments, participants learn to modulate the BOLD signal according to at least one statistical test (A). Graph A synthesizes the data from graphs B-E labeling *"Yes"* if one or more of the four measures (B-E) are positive and none negative; "No" if one or more of the four measures are negative and none positive; *"Yes/No"* if there are at least one negative and at least one positive result, or one or more

"Yes/No" results; and *"Do not report"* if the publication does not report on BOLD regulation of the target ROI. Graphs B-E employ the label *"Yes/No"* for experiments where the analysis divides participants into a group that learned regulation and one that did not. Graph E includes experiments with no control group. Notably, we labeled findings as non-significant if they were trending toward significance (e.g., Hamilton et al., 2016) or lost significance after accounting for multiple comparisons (e.g., Paret, Klütsch, et al., 2014). We also labeled neural regulation compared to controls as "Do not report" if statistical comparisons between experimental and control groups were absent (even if experimental participants improved and control participants did not). Of the 99 experiments we reviewed, none test all four of these measures, 26 test three, 45 test two, 27 test one, and 1 tests none. As for the analyses they perform, 67 of the experiments compare feedback trials to a baseline measure, 47 compare a later trial to the first neurofeedback trial, 36 measure if regulation improved linearly across trials, and 45 statistically compare results from control and experimental groups. Only ten studies compared neither to baseline nor first trial.

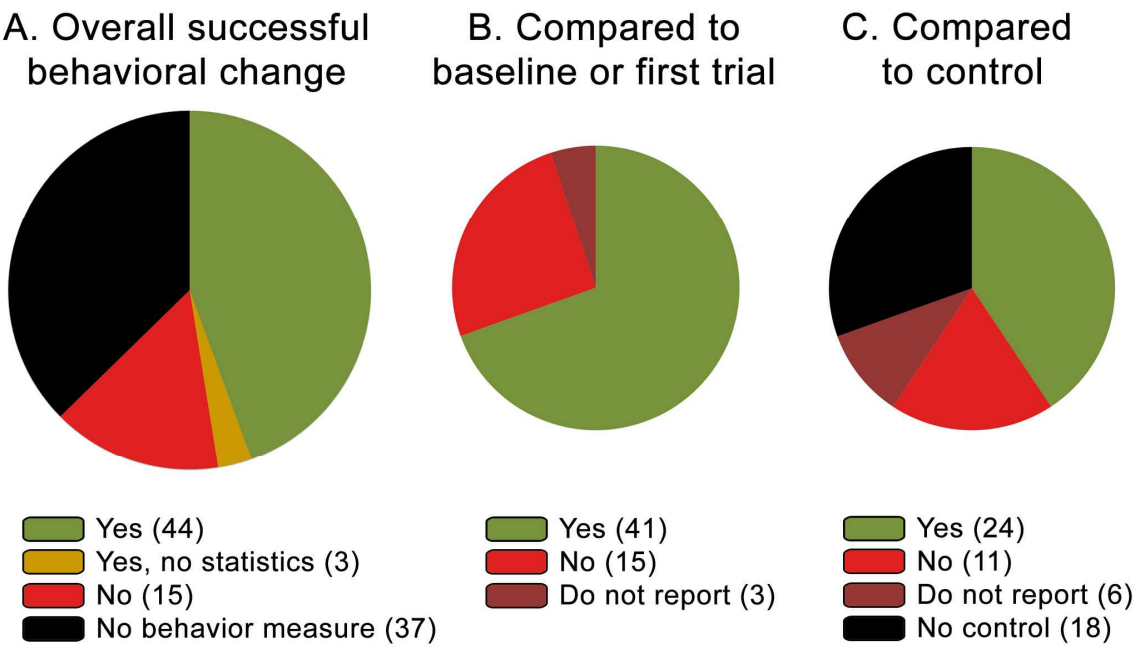
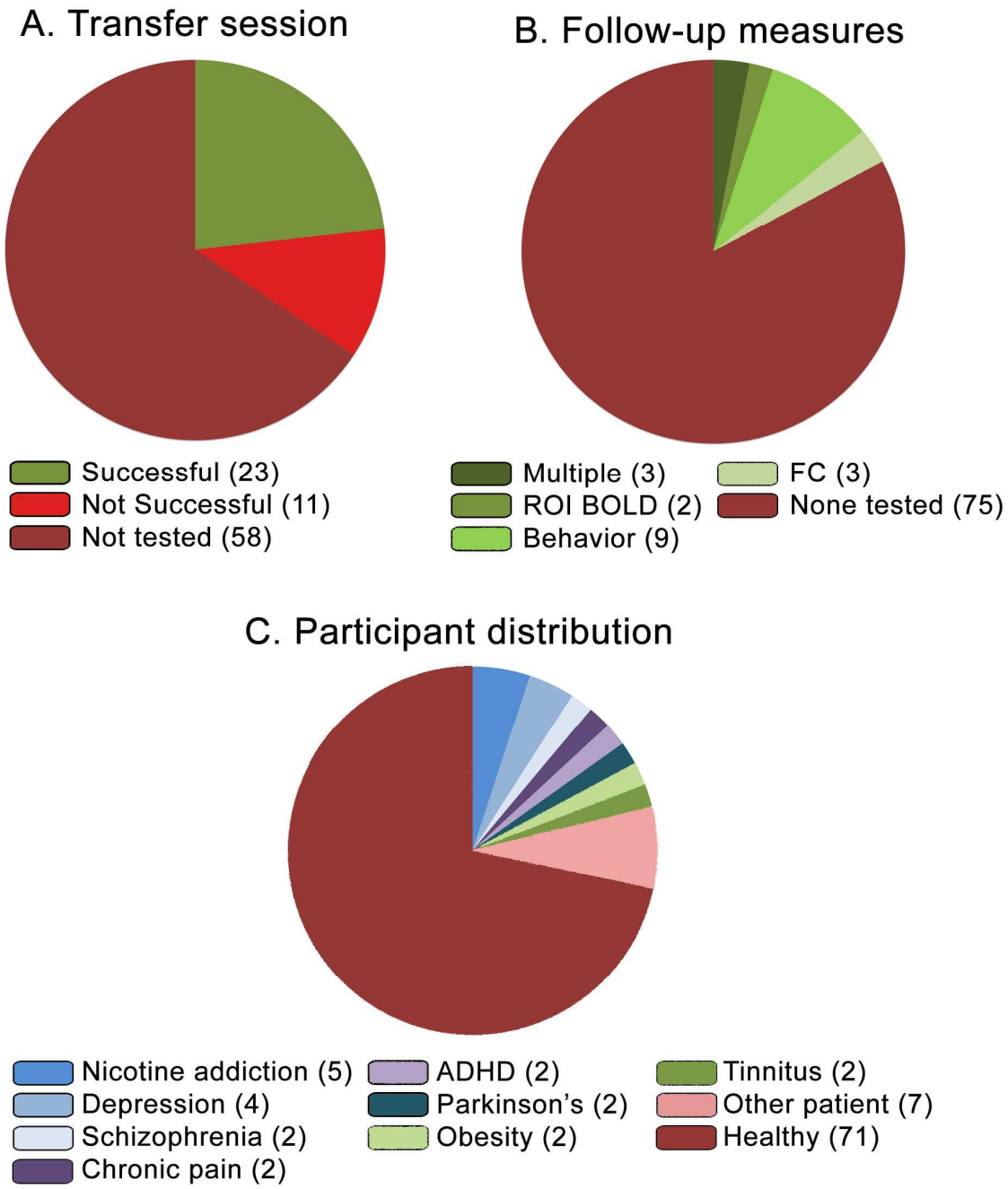


Figure 5. Behavioral modulation via fMRI. Of the 59 fMRI-nf experiments that take pre-post behavioral measures and use statistical analyses (A), some compare endpoints to measures taken at baseline, the first trial, or REST blocks (B), and some contrast experimental and control groups (C). We label studies as including a behavioral measure if they test changes in behavior between at least two time points. We label tests as positive if group level statistics reveal significance, but not if significance appears only in a subset of participants, such as "learners" (e.g., Robineau et al., 2014). In graph A only, we include publications that report a change in behavior without any supporting significance testing. Graph A includes all 99 studies; graphs B and C include the 59 studies that statistically test behavior. Of these 59 studies, 32 test post-treatment behavior compared to both controls and to a baseline or first trial while 27 test only one of these options.

1589



1590
1591 **Figure 6.** The clinical feasibility of fMRI-nf depends on whether participants can continue to
1592 modulate their brain activity in the absence of feedback (A), whether neural self-regulation,

behavioral impacts, and changes in brain networks persist beyond the day of training (B), and whether patient populations can benefit (C). These three graphs depict the portion of fMRI-nf experiments that test feasibility measures.

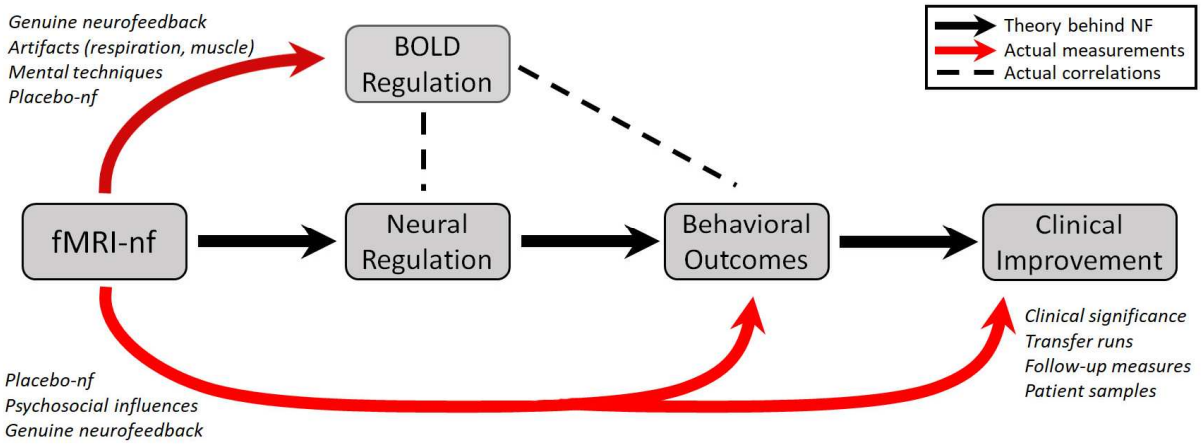


Figure 7. In theory, fMRI-nf trains neural regulation, which in turn, alters behavior and improves clinical conditions (black arrows). In practice, however, researchers measure a proxy for neural activity (the BOLD signal), which is susceptible to contamination from a number of artifacts including respiration and cardiovascular influences. Moreover, studies can only identify neural regulation as the driver of behavioral or clinical change if they account for various factors (listed in italics). These control measures can help establish the presupposed link between neural regulation and behavioral outcomes (see Box 1 for an example of an ideal fMRI-nf experiment).

Box 1. An exemplary fMRI-nf experiment

Here we describe a feasible hypothetical study that would help elucidate many of the questions that continue to linger in the field of fMRI-nf. This illustrative paradigm investigates the potential to down-regulate ACC activity to reduce smoking.

Control groups: To best disentangle the mechanisms underlying the benefits of fMRI-nf, an ideal experiment would employ several of the following control groups: (1) an *inverse* group receiving positive feedback for up-regulating the ACC, (2) a *non-contingent-sham* group presented with feedback from a previously recorded participant, (3) a *contingent-placebo* group receiving feedback from a brain region largely independent of the ACC, (4) a *mental rehearsal* group who, in the absence of feedback, perform cognitive techniques known to modulate ACC activity, and (5) a *no treatment* control group. We recognize that including all of these control conditions would be prohibitively expensive and time-consuming for many research groups. Thus, here we propose an experimental design using one of the strongest of these controls: *inverse*. According to the theoretical foundation of neurofeedback, if experimental and inverse groups successfully learn to control ACC activity in opposing directions, we would expect opposing behavioral results between groups. While an inverse condition raises ethical concerns, participants already train regulation in opposing directions across fMRI-nf experiments. The theory that negative outcomes will manifest, however, has yet to gain empirical footing (see Hawkinson et al., 2012; Thibault et al., 2016 for a detailed discussion). To further ensure no harm, researchers can test behavior throughout training, terminate the experiment if substantial negative effects emerge, and offer genuine-nf training to all participants after the experiment. As the case for all placebo-nf options, an inverse group also comes with drawbacks. This control cohort may end up worse off than a no-neurofeedback control group and thus provide an imperfect reference point. To account for physiological confounds, all participants would wear a respiration belt and researchers would regress out artifactual BOLD activations that parallel the time-course of respiratory volume. Only smokers would participate.

Variables and time-points: Our ideal experiment would measure BOLD activity (ACC activity during rest and regulation blocks), behavioral factors (cigarette craving, number of cigarettes smoked), and subjective placebo factors (participant motivation, faith in neurofeedback, belief that they received genuine feedback, and effort exerted). All measures would be collected at multiple time points (before neurofeedback, during training, immediately after training, and at a follow-up session a few months after training).

Analyses: The researchers would perform four main analytic tests, both within and between experimental and control groups: (1) Comparing ACC regulation across time-points; this analysis would reveal whether fMRI-nf improves BOLD regulation and how much participants retain this capacity. (2) Comparing cigarette cravings and number of cigarettes smoked across time-points; this analysis would probe whether neurofeedback alters attitudes and behaviors in a clinically meaningful way. (3) Testing the degree of correlation between ACC regulation and smoking behavior, as well as between placebo factors and smoking behavior; these analyses would help disentangle the relative

contributions of BOLD regulation and psychosocial influences in determining behavioral outcomes. (4) Comparing subjective attitudes and expectations between experimental and control groups: this analysis would test whether psychosocial influences were comparable under genuine and inverse conditions.

1609

Box 2. Best Practice Checklist for fMRI-nf		
Pre-registration	1.1	Pre-register the experiment and analyses on a platform such as www.osf.io, as an RCT (e.g., on clinicaltrials.gov), or by submitting a *registered report*.
	1.2	In a publication, report which analyses were pre-registered and which were exploratory.
Sample size	2.1	Justify with a power analysis based on an expected effect size or label the experiment as a pilot study.
Control measures	3.1	Record and regress cardiorespiratory artifacts out of the BOLD signal for each individual.
	3.2	Quantify and correct for head motion.
	3.3	If training sensorimotor cortices, measure muscle activity with an EMG.
	3.4	Report condition and group effects for control measures.
Control groups	4.1	Employ a placebo-nf control group. Alternatively, use a specialized design that largely controls for non-specific effects (e.g., a within-subjects control as in Koizumi et al., 2016).
	4.2	In clinical efficacy studies, employ a standard-of-care intervention group as a benchmark for improvement.
	4.3	When leveraging a placebo-nf control group, employ a double-blind design and test whether participants and experimenters remain blinded. When feasible, blind the statistician analyzing the data (i.e., a triple-blind design).
	4.4	Collect data on psychosocial factors (e.g., participant motivation, faith in neurofeedback, effort exerted, subjective sense of success).
BOLD data	5.1	Collect and report the feedback signal as displayed to the subject for: (i) a pre-training baseline, (ii) REST blocks, (iii) REGULATE blocks, (iv) a post-training transfer run without neurofeedback, and (v) follow-up, when feasible.
Behavioral data	6.1	Include measures of clinical significance, identified *a priori*, and describe whether they were reached.
Outcome measures	7.1	Report regulation success based on the feedback signal displayed to the subject.
	7.2	Run correlational analyses between regulation success and behavioral outcomes.

	7.3	Report p-values and effect sizes for all analyses performed. Include corrections for multiple comparisons.
Note, this checklist represents recommendations only. Future reports may benefit from following a number of these best practices and identifying and discussing which items they did and did not accommodate.		

1610

1611 **Table 1.** This spreadsheet contains the references for the 99 experiments reviewed as well as the
1612 information collected from each study used to produce the figures and numbers we reference
1613 throughout this article.

1614

1615 **Supplementary Table.** This spreadsheet contains demographic information including the age
1616 and gender of participants for all 99 experiments. For age, we include the mean and standard
1617 deviation, if provided. Many experiments report the age of the genuine-nf and control groups
1618 separately; in that case, we included the age of the genuine-nf group. Some articles only provide
1619 the age range of participants

	DATA FOR FIRGURE 3			DATA FOR FIGURE 4				DATA FOR FIGURE 5			DATA FOR FIGURE 6			ADDITIONAL DATA			Bibliography
Article	**Control group**	**Account for respiration**	**ROI to regulate**	**CTB**	**CTF**	**Linear**	**CTC**	**Behavioral measure**	**CTB or CTF**	**CTC**	**Transfer run**	**Follow-up**	**Participants**	**Strategy provided**	**# of subjects**	**Tested FC**	**Full Reference**
Alegria et al., (2017)	other brain region	DNR	PFC (right inferior gyrus)	Y	DNR	Y	Y	ADHD scales	Y	N	Y-S	Y-S (behavio	ADHD	N	31	N	Alegria, A. A., Wulff, M., Brinson, H
Amano et al., (2016)	within subjects	DNR	V1, V2 (classifier decoded sub-region)	DNR	DNR	DNR	DNR	color perception	Y	Y	N	Y-S (behavio	healthy	N	18	N	Amano, K., Shibata, K., Kawato, M.,
Auer et al., (2015)	no treatment	DNR	somatomotor cortices	Y	DNR	DNR	Y	N	-	-	Y-S	N	healthy	Y	33	N	Auer, T., Schweizer, R., & Frahm, J.
Banca et al., (2015)	none	DNR	visual (hMT+/V5)	Y	DNR	DNR	NA	N	-	-	N	N	healthy	Y	20	Y	Banca, P., Sousa, T., Catarina Duart
Berman et al., (2013)	none	global	insula (right anterior)	Y	DNR	DNR	NA	N	-	-	Y-US	N	healthy	Y	16	Y	Berman, B. D., Horovitz, S. G., & Ha
Berman et al., (2012)	none	global	M1 (left)	N	DNR	DNR	NA	N	-	-	Y-US	N	healthy	Y	15	N	Berman, B. D., Horovitz, S. G., Venk
Blefari et al., (2015)	none	DNR	M1 (contralateral)	N	N	DNR	NA	motor performanc e	N	NA	N	N	healthy	Y	13	N	Blefari, M. L., Sulzer, J., Hepp-Reym
Bray et al., (2007)	mental rehearsal scanner	other	somatomotor cortex (left)	DNR	Y/N	Y	Y	reaction time	Y	DNR	N	N	healthy	Y	22	N	Bray, S., Shimojo, S., & O'Doherty, J
Bruehl et al., (2014)	none	DNR	amygdala (right)	DNR	Y	Y	NA	N	-	-	N	N	healthy	Y	6	N	Bruehl, A. B., Scherpiet, S., Sulzer, J
Canterberry et al., (2013)	none	DNR	ACC	N	N	DNR	NA	cigarette craving	Y	NA	N	N	nicotine addiction	Y	9	N	Canterberry, M., Hanlon, C. a., Hart
Caria et al., (2010)	other brain region mental rehearsal scanner	global	insula (left anterior)	Y	Y	Y	Y	valence ratings, arousal ratings	Y	Y	N	N	healthy	Y	27	N	Caria, A., Sitaram, R., Veit, R., Beglie
Caria et al., (2007); Lee et al., (2011)	other brain region mental rehearsal scanner	global	insula (right anterior)	DNR	Y	Y	DNR	N	-	-	Y-US	N	healthy	Y	15	Y	Caria, A., Veit, R., Sitaram, R., Lotze
Chiew et al., (2012)	sham - other participant	DNR	M1 (laterality)	DNR	Y/N	Y	Y	reaction time	N	N	N	N	healthy	Y	18	N	Chiew, M., LaConte, S. M., & Graha
Cordes et al., (2015)	none	DNR	ACC	Y	DNR	DNR	NA	affect, mood	-	-	N	N	schizophreni a	Y	22	N	Cordes, J. S., Mathiak, K. A. K., Dyck
Cortese et al., (2016, 2017)	inverse	DNR	individualized (confidence)	DNR	N	N	DNR	confidence	Y	Y	N	Y-S (behavio	healthy	N	18	N	Cortese, A., Amano, K., Koizumi, A.,
Debettencourt et al., (2015)	sham - other participant mental rehearsal no scanner	DNR	individualized (face/scene attention)	DNR	DNR	DNR	Y	attention	Y	Y	N	N	healthy	N	80	N	DeBettencourt, M. T., Cohen, J. D.,
deCharms et al., (2004)	sham - other	global	somatomotor cortex (left)	Y	DNR	Y	Y	N	-	-	Y-S	N	healthy	Y	9	N	DeCharms, R. C., Christoff, K., Glove
deCharms et al., (2005)	sham - other participant other brain region mental rehearsal no scanner	global	ACC (rostral)	Y	Y	Y	DNR	pain ratings	Y	Y	N	N	chronic pain	Y	36	N	deCharms, R. C., Maeda, F., Glover,
Emmert et al., (2014, 2017a)	none	DNR	insula (left anterior), ACC	DNR	Y	DNR	NA	pain ratings	Y	NA	N	N	healthy	N	28	N	Emmert, K., Breimhorst, M., Bauern
Emmert et al. (2017b)	none	regressed out	auditory cortex	Y	N	N	NA	tinnitus scale	Y	NA	N	Y-US (behav	tinnitus	Y	14	Y	Emmert, K., Kopel, R., Koush, Y., Ma
Frank et al., 2012	none	DNR	insula (anterior)	Y	DNR	DNR	NA	mood	N	NA	N	N	obese	Y	21	N	Frank, S., Lee, S., Preissl, H., Schulte
Garrison et al., (2013)	none	DNR	posterior cingulate cortex	Y	DNR	DNR	NA	N	-	-	N	N	healthy	Y	44	N	Garrison, K. a., Scheinost, D., Worh
Greer et al., (2014)	mental rehearsal scanner	DNR	nucleus accumbens	Y	DNR	DNR	Y	affect	-	-	Y-US	N	healthy	Y	25	Y	Greer, S. M., Trujillo, A. J., Glover, G
Groene et al., (2015)	none	DNR	ACC (rostral)	Y	DNR	DNR	NA	affect	Y	NA	N	N	healthy	Y	24	N	Gröne, M., Dyck, M., Koush, Y., Ber
Guan et al., (2015)	other brain region	DNR	ACC (rostral)	Y	Y	DNR	Y	pain ratings	Y	Y	N	N	chronic pain	Y	14	N	Guan, M., Li, L., Tong, L., Zhang, Y.,
Habes et al., (2016)	mental rehearsal scanner	regressed out	PPA/FFA	Y	DNR	DNR	DNR	visual performanc e	N	N	N	N	healthy	Y	17	N	Habes, I., Rushton, S., Johnston, S.
Haller et al., (2010)	none	global	A1	DNR	Y	Y	NA	tinnitus	-	-	N	N	tinnitus	N	6	N	Haller, S., Birbaumer, N., & Veit, R.
Hamilton et al., (2016)	sham - other participant	regressed out	individualized (salience network)	Y	DNR	DNR	N	emotion	DNR	Y	N	N	depression	Y	20	Y	Hamilton, J. P., Glover, G. H., Bagar
Hamilton et al., (2011)	sham - other participant	global	ACC (subgenual)	Y	DNR	DNR	Y	N	-	-	Y-US	N	healthy	Y	17	Y	Hamilton, J. P., Glover, G. H., Hsu, J
Hampson et al., 2011	none	DNR	SMA	Y	N	DNR	NA	0	-	-	N	N	healthy	Y	8	Y	Hampson, M., Scheinost, D., Qiu, M
Hanlon et al., (2013)	none	DNR	ACC (ventral), PFC (dorsomedial)	Y	DNR	DNR	NA	cigarette craving	Y	NA	N	N	nicotine addiction	Y	21	N	Hanlon, C. a., Hartwell, K. J., Canter
Harmelech et al., (2015)	other brain region Mental rehearsal scanner	DNR	5 visual areas, inferior parietal lobule	Y	DNR	DNR	Y	N	-	-	N	N	healthy	Y	8	N	Harmelech, T., Friedman, D., & Mal
Harmelech et al., (2013)	none	DNR	ACC (dorsal)	Y	DNR	DNR	NA	N	-	-	N	Y-S (FC)	healthy	Y	20	Y	Harmelech, T., Preminger, S., Wert
Hartwell et al., (2016)	mental rehearsal scanner	DNR	ACC, PFC (individualized: craving)	DNR	DNR	DNR	Y	cigarette craving	DNR	Y	N	N	nicotine addiction	Y	44	N	Hartwell, K. J., Hanlon, C. a., Li, X., E
Hohenfeld et al., (2017)	other brain region	DNR	PHC	N	N	DNR	N	memory	Y	DNR	N	N	Alzeimer's	Y	30	Y	Hohenfeld, C., Nellessen, N., Dogan
Hui et al., (2014); Xie et al., (2015)	sham - other participant	global	PMC (right)	DNR	N	DNR	Y	motor performanc e	Y	Y	N	N	healthy	Y	28	Y	Hui, M., Zhang, H., Ge, R., Yao, L., &
Johnson et al., (2012)	sham - randomized	DNR	premotor cortex (left)	DNR	DNR	DNR	Y/N	N	-	-	N	N	healthy	Y	13	N	Johnson, K. a, Hartwell, K., Lematty
Johnston et al., (2009)	none	DNR	individualized (emotion)	Y	Y	DNR	NA	affect, mood	-	-	N	N	healthy	Y	13	N	Johnston, S. J., Boehm, S. G., Healy,
Johnston et al., (2011)	mental rehearsal scanner	DNR	individualized (emotion)	DNR	Y	DNR	Y	affect, mood	N	N	N	N	healthy	N	27	N	Johnston, S. J., Linden, D. E. J., Heal
Kadosh et al., (2015)	none	DNR	insula (right anterior)	Y	N	N	NA	N	-	-	N	N	healthy	Y	17	Y	Kadosh, K. C., Luo, Q., de Burca, C.,
Karch et al., (2015)	other brain region	DNR	individualized (craving)	Y	DNR	DNR	DNR	alcohol craving	Y	DNR	N	N	alcohol addiction	N	27	Y	Karch, S., Keeser, D., Hümmer, S., P
Kim et al., (2015)	none	other	ACC, PFC (medial, orbito), and FC to PCC and precuneus	DNR	Y	DNR	NA	cigarette craving	N	NA	N	N	nicotine addiction	N	14	Y	Kim, D.-Y., Yoo, S.-S., Tegethoff, M.,
Kirsch et al., (2016)	sham - other participant	DNR	ventral striatum	DNR	Y	DNR	Y	alcohol craving	N	Y	Y-S	N	heavy drinkers	N	33	N	Kirsch, M., Gruber, I., Ruf, M., Kiefe
Koizumi et al., (2016)	within subjects	DNR	individualized (fear response)	Y	Y	DNR	DNR	fear response	Y	Y	N	N	healthy	N	7	N	Koizumi, A., Amano, K., Cortese, A.,
Koush et al., (2017)	sham - other participant	rate	PFC (dorsomedial), amygdala (FC)	Y	DNR	Y	Y	valence ratings	Y	Y	Y-S	N	healthy	Y	15	Y	Koush, Y., Rosa, M. J., Robineau, F.,
Koush et al., (2013)	none	rate	visual, parietal (FC)	Y	DNR	N	NA	N	-	-	N	N	healthy	Y	17	Y	Koush, Y., Meskaldji, D.-E., Pichon,

LEGEND

CTB	Compared to baseline
CTF	Compared to first trial
CTC	Compared to control
Linear	A linear trend

Table data

Y	Yes
N	No
Y/N	Yes' for at least one measure AND 'No' for at least one measure; Or,
DNR	Do not report
Y-S	Yes, successful
Y-US	Yes, unsuccessful
NA	Not applicable
ROI	Region of interest
FC	Functional connectivity
rate	Respiration rate and/or heart rate are statistically tested between c
global	The percent BOLD change from a large background brain region is su
removed	Additional intruments and calclations are used to regress out respira
PCC	posterior cingulate cortex
PFC	perfrontal cortex
A1	primary auditory cortex
A2	secondary auditory cortex
V1	primary visual cortex
V2	primary visual cortex
M1	primary motor cortex
SMA	supplementary motor area
PMC	premotor cortex
VTA	ventral tegmental area
PPA	parahippocampal place area
FFA	fusiform face area
PHC	parahippocampal cortex

Lawrence et al., (2014)	other brain region	global	insula (right anterior)	DNR	DNR	Y	Y	valence ratings, arousal ratings	N	N	N	N	healthy	Y	24	N	Lawrence, E. J., Su, L., Barker, G. J.,
Li et al., (2012)	none	DNR	ACC, PFC (medial)	Y	DNR	DNR	NA	cigarette craving	Y	NA	N	N	nicotine addiction	Y	10	N	Li, X., Hartwell, K. J., Borckardt, J., F
Li et al., (2016a, 2016b)	mental rehearsal scanner	global	individualized (emotion)	DNR	Y	DNR	DNR	affect	N	N	N	N	healthy	Y	23	Y	Li, Z., Tong, L., Wang, L., Li, Y., He,
Linden et al., (2012)	mental rehearsal no scanner	DNR	individualized (emotion)	DNR	Y	Y	DNR	mood	Y	Y	N	N	depression	Y	16	N	Linden, D. E. J., Habes, I., Johnston,
MacInnes et al., (2016)	sham - randomized other brain region mental rehearsal scanner	regressed out	VTA	Y	DNR	DNR	Y	N	-	-	Y-S	N	healthy	Y	73	Y	MacInnes, J. J., Dickerson, K. C., Ch
Marins et al., (2015)	mental rehearsal scanner	DNR	premotor cortex (left)	DNR	Y	DNR	Y	N	-	-	N	N	healthy	Y	28	N	Marins, T., Rodrigues, E., Engel, A.,
Marxen et al., (2016)	none	rate	amygdala (bilateral)	N	DNR	DNR	NA	N	-	-	Y-S	N	healthy	N	32	N	Marxen, M., Jacob, M. J., Müller, D.
Mathiak et al., (2015)	none	DNR	ACC (dorsal)	Y	DNR	Y	NA	affect, reaction time	Y	NA	Y-S	N	healthy	Y	24	N	Mathiak, K. A., Alawi, E. M., Koush,
McCaig et al., 2011	sham - other participant mental rehearsal scanner	DNR	PFC (rostrolateral)	DNR	Y	DNR	Y	0	-	-	N	N	healthy	Y	30	N	McCaig, R. G., Dixon, M., Keramati
Megumi et al., (2015)	sham - other participant mental rehearsal scanner	DNR	M1 (left), lateral parietal cortex (left) (FC)	DNR	DNR	DNR	Y	N	-	-	N	Y-S (FC)	healthy	Y	33	Y	Megumi, F., Yamashita, a, Kawato,
Moll et al., (2014)	mental rehearsal scanner	DNR	individualized (tenderness/pride)	DNR	Y	DNR	Y	emotion	N	N	N	N	healthy	Y	25	N	Moll, J., Weingartner, J. H., Bado, P
Nicholson et al., (2017)	none	DNR	amygdala	Y	N	N	NA	N	-	-	Y-S	N	PTSD	N	10	Y	Nicholson, A. A., Rabellino, D., Den
Paret et al., (2014, 2016a)	other brain region	DNR	amygdala	N	DNR	N	N	valence ratings, arousal ratings	N	N	Y-US	N	healthy	Y	32	Y	Paret, C., Kluetsch, R., Ruf, M., Dem
Paret et al., (2016b)	none	DNR	amygdala	Y	N	N	NA	emotional awareness, valence ratings	Y	NA	Y-US	N	borderline personality disorder	N	8	Y	Paret, C., Kluetsch, R., Zaehringer, J
Perronnet et al., (2017)	none	DNR	M1 (left)	Y	N	DNR	NA	N	-	-	Y-US	N	healthy	Y	10	N	Perronnet, L., Lécuyer, A., Mano, M
Ramot et al., (2016)	inverse	DNR	PPA/FFA	Y/N	N	DNR	DNR	N	-	-	N	N	healthy	N	16	Y	Ramot, M., Grossman, S., Friedman
Rance et al., (2014a)	none	DNR	ACC (rostral) / insula (left posterior)	Y	Y	DNR	NA	pain ratings	N	NA	N	N	healthy	N	10	N	Rance, M., Ruttorf, M., Nees, F., Sch
Rance et al., (2014b)	none	DNR	ACC (rostral), insula (left posterior)	Y	Y	DNR	NA	pain ratings	N	NA	N	N	healthy	N	10	N	Rance, M., Ruttorf, M., Nees, F., Sch
Robineau et al., (2014, 2017a)	none	rate	visual (left/right)	Y/N	Y/N	Y/N	NA	visual extinction	N	NA	Y-S	N	healthy	Y	14	N	Robineau, F., Rieger, S. W., Mermo
Robineau et al., (2017b)	none	DNR	V1	Y	Y	DNR	NA	visual neglect tests	Y	NA	N	N	hemineglect	Y	9	N	Robineau, F., Saj, A., Neveu, R., Van
Rota et al., (2009, 2011)	other brain region	global	inferior frontal gyrus (right)	DNR	Y	Y	DNR	prosody identification	Y	DNR	N	N	healthy	Y	12	Y	Rota, G., Sitaram, R., Veit, R., Erb, M
Ruiz et al., (2013)	none	global	insula (bilateral anterior)	Y	Y	Y	NA	facial recognition	Y	NA	Y-US	N	schizophrenia	Y	9	Y	Ruiz, S., Buyukturkoglu, K., Rana, M
Sarkheil et al., (2015)	mental rehearsal scanner	DNR	PFC (left lateral)	DNR	DNR	DNR	N	affect	DNR	N	N	N	healthy	Y	14	Y	Sarkheil, P., Zilverstand, A., Kilian-H
Scharnowski et al., (2012, 2014)	other brain region	rate	retinotopic visual cortex	Y/N	DNR	DNR	Y/N	visual detection	Y	DNR	Y-S	N	healthy	Y	16	Y	Scharnowski, F., Hutton, C., Joseph
Scharnowski et al., (2015)	inverse	DNR	SMA/PHC	Y	DNR	Y	Y	N	-	-	Y-S	Y-S (ROI)	healthy	Y	7	Y	Scharnowski, F., Veit, R., Zopf, R., S
Scheinost et al., (2013); Radua et al., (2016)	sham - other participant	DNR	PFC (orbito)	Y	DNR	DNR	N	anxiety	Y	Y	Y-S	Y-S (behavio	anxiety	Y	10	Y	Scheinost, D., Stoica, T., Saksa, J., P
Sepulveda et al., (2016)	none	global	SMA	Y	Y/N	DNR	NA	N	-	-	Y-S	N	healthy	Y/N	20	Y	Sepulveda, P., Sitaram, R., Rana, M
Sherwood et al., (2016a, 2016b)	mental rehearsal no scanner	DNR	PFC (left dorsolateral)	Y	DNR	Y	DNR	working memory	Y	Y	N	N	healthy	Y	18	N	Sherwood, M. S., Kane, J. H., Weise
Shibata et al., (2016)	inverse no treatment	DNR	cingulate cortex	N	N	DNR	N	facial preference	Y	Y	N	N	healthy	N	33	N	Shibata, K., Watanabe, T., Kawato,
Shibata et al., (2011)	within subjects no treatment	DNR	V1, V2	Y	DNR	DNR	DNR	visual discrimination	Y	Y	N	N	healthy	N	16	N	Shibata, K., Watanabe, T., Sasaki, Y.
Sokunbi et al., (2014); Ihssen et al., (2017)	none	DNR	individualized (food craving)	Y	DNR	DNR	NA	hunger	Y	NA	N	N	healthy	Y	10	N	Sokunbi, M. O., Linden, D. E. J., Hab
Sorger et al., (2016)	mental rehearsal scanner	rate	individualized (mental task)	Y	DNR	DNR	Y	N	-	-	N	N		Y	10	N	Sorger, B., Kamp, T., Weiskopf, N.,
Sousa et al., (2016)	none	DNR	visual (hMT+/V5)	Y	DNR	DNR	NA	N	-	-	Y-S	N	healthy	Y	20	N	Sousa, T., Direito, B., Lima, J., Ferre
Spetter et al., (2017)	none	DNR	PFC (dorsolateral), PFC (ventromedial) (FC)	Y	Y	N	NA	hunger	Y	NA	N	N	obesity	Y	8	Y	Spetter, M. S., Malekshahi, R., Birba
Subramanian et al., (2011)	mental rehearsal scanner	DNR	SMA	Y	DNR	DNR	DNR	motor performance	Y	DNR	N	Y-S (behavio	Parkinson's disease	Y	10	N	Subramanian, L., Hindle, J. V., Johns
Subramanian et al., (2016)	motor therapy alone	regressed out	SMA	Y	DNR	N	DNR	motor performance	Y	N	Y-S	N	Parkinson's disease	Y	30	N	Subramanian, L., Morris, M. B., Bro
Sulzer et al., (2013)	inverse	regressed out	substantia nigra, VTA	Y	Y	DNR	Y	N	-	-	Y-US	N	healthy	Y	32	Y	Sulzer, J., Sitaram, R., Blefari, M. L.,
Van De Ville et al, (2012) Haller et al., (2013)	none	DNR	A1 (right)	DNR	DNR	Y	NA	N	-	-	N	Y-S (FC)	healthy	N	12	Y	Van De Ville, D., Jhooti, P., Haas, T.,
Veit et al., 2012	none	DNR	insula (anterior)	Y	N	Y	NA	0	-	-	N	N	healthy	Y	11	Y	Veit, R., Singh, V., Sitaram, R., Caria
Yamashita et al., (2017)	inverse	global	M1, lateral parietal coretx (FC)	Y	DNR	DNR	Y	reaction time	Y	Y	N	N	healthy	Y	30	Y	Yamashita, A., Hayasaka, S., Kawato
Yao et al., (2016)	other brain region	global	insula (left anterior)	DNR	Y	Y	Y	pain empathy	Y	Y	Y-S	Y-S (ROI), Y-	healthy	Y	37	Y	Yao, S., Becker, B., Geng, Y., Zhao, Z
Yoo et al., (2008)	sham - randomized	DNR	M1 (left)	Y	DNR	DNR	Y	N	-	-	Y-S	Y-S (ROI)	healthy	Y	24	N	Yoo, S.-S., Lee, J.-H., O'Leary, H., Pa
Yoo et al., (2006)	mental rehearsal scanner	DNR	A1 (left), A2 (left)	Y	DNR	DNR	DNR	N	-	-	N	N	healthy	Y	22	N	Yoo, S.-S., O'Leary, H. M., Fairneny,
Yoo et al., (2007), Lee et al., (2012)	sham - randomized	DNR	A1, A2	Y	DNR	DNR	Y	N	-	-	Y-S	Y-S (ROI, FC)	healthy	Y	24	Y	Yoo, S.-S., Lee, J.-H., O'Leary, H., Le

Young et al., (2017a, 2017b)	other brain region	global	amygdala	Y	DNR	DNR	Y	autobiographical memory vigilence	Y	Y	Y-S	Y-S (behavio	depression	Y	34	N	Young, K. D., Misaki, M., Harmer, C
Young et al., (2014), Yuan et al., (2014), Zotev et al., (2016)	other brain region	regressed out	amygdala (left)	Y	DNR	Y	Y	mood	Y	Y	Y-S	Y-S (FC, beha	depression	Y	21	Y	Young, K. D., Zotev, V., Phillips, R.,
Zhang et al., (2016, 2013)	sham - other participant	global	PFC (dorsolateral)	DNR	Y	Y	Y	working memory	Y	Y	N	N	healthy	Y	30	Y	Zhang, G., Yao, L. L., & Zhao, X. (20
Zhang et al., (2013)	mental rehearsal scanner	DNR	PCC	DNR	N	DNR	Y	N	-	-	N	N	healthy	Y	32	N	Zhang, G., Zhang, H., Li, X., Zhao, X.
Zhao et al., 2013	sham - other participant	global	PMC (dorsal, ipsilateral)	DNR	N	N	Y	finger tapping	Y	Y	N	N	healthy	Y	24	N	Zhao, X., Zhang, H., Song, S., Ye, Q.,
Zilverstand et al., (2015)	mental rehearsal scanner	rate	insula (right)	Y	DNR	Y	Y	anxiety	N	Y	N	Y-S (behavio	phobia	Y	18	N	Zilverstand, A., Sorger, B., Sarkheil,
Zilverstand et al., (2017)	mental rehearsal scanner	DNR	ACC	DNR	DNR	N	N	attentional tasks	Y	N	Y-US	Y-S (behavio	ADHD	Y	13	N	Zilverstand, A., Sorger, B., Slaats-W
Zotev et al., (2011)	other brain region	regressed out	amygdala (left)	DNR	DNR	Y	Y	identifying feelings	-	-	Y-S	N	healthy	Y	28	Y	Zotev, V., Krueger, F., Phillips, R., Al
Zotev et al., (2014)	none	regressed out	amygdala (left)	Y	N	DNR	NA	N	-	-	Y-S	N	healthy	Y	6	N	Zotev, V., Phillips, R., Yuan, H., Mis

'Yes' for "learners" and 'No' for "non-learners'

onditions

ubtracted from the percent BOLD change in the ROI

ation artifacts

Highlights

- We conducted a systematic review of 99 fMRI neurofeedback (fMRI-nf) experiments
- fMRI-nf successfully drives BOLD regulation and behavioral change
- BOLD regulation guarantees neither neural regulation nor clinical improvement
- Psychosocial factors may contribute to regulation of BOLD signal and behavior
- Efficacy remains undetermined because few studies test for clinical significance