NeuroImage 221 (2020) 117194

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Network-based fMRI-neurofeedback training of sustained attention

Gustavo S.P. Pamplona[a,b,c,*], Jennifer Heldner[c], Robert Langner[d,e], Yury Koush[f], Lars Michels[g], Silvio Ionta[a], Frank Scharnowski[c,h,i,j,1], Carlos E.G. Salmon[b,1]

[a] Sensory-Motor Laboratory (SeMoLa), Jules-Gonin Eye Hospital/Fondation Asile des Aveugles, Department of Ophthalmology/University of Lausanne, Lausanne, Switzerland
[b] InBrain Lab, Department of Physics, University of São Paulo, Ribeirão Preto, Brazil
[c] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Switzerland
[d] Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[e] Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany
[f] Department of Radiology and Biomedical Imaging, Yale School of Medicine, Yale University, New Haven, CT, USA
[g] Department of Neuroradiology, University Hospital Zurich, Zurich, Switzerland
[h] Neuroscience Center Zurich, University of Zurich and Swiss Federal Institute of Technology, Zurich, Switzerland
[i] Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland
[j] Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria

ARTICLE INFO

Keywords:
Sustained attention
Default mode network
Neurofeedback
Real-time fMRI
Anticorrelated networks
Behavioral changes

ABSTRACT

The brain regions supporting sustained attention (sustained attention network; SAN) and mind-wandering (default-mode network; DMN) have been extensively studied. Nevertheless, this knowledge has not yet been translated into advanced brain-based attention training protocols. Here, we used network-based real-time functional magnetic resonance imaging (fMRI) to provide healthy individuals with information about current activity levels in SAN and DMN. Specifically, 15 participants trained to control the difference between SAN and DMN hemodynamic activity and completed behavioral attention tests before and after neurofeedback training. Through training, participants improved controlling the differential SAN-DMN feedback signal, which was accomplished mainly through deactivating DMN. After training, participants were able to apply learned self-regulation of the differential feedback signal even when feedback was no longer available (i.e., during transfer runs). The neurofeedback group improved in sustained attention after training, although this improvement was temporally limited and rarely exceeded mere practice effects that were controlled by a test-retest behavioral control group. The learned self-regulation and the behavioral outcomes suggest that neurofeedback training of differential SAN and DMN activity has the potential to become a non-invasive and non-pharmacological tool to enhance attention and mitigate specific attention deficits.

1. Introduction

Attention please! This simple phrase refers to a complex cognitive process by which the brain selects relevant aspects of incoming information while ignoring irrelevant input. The continuous competition between different inputs and outputs can be biased top–down by expectations and goals as well as bottom–up by salient events. When such salient events are not relevant for the task at hand, they are usually called "distractors". Most of the time, attentional lapses due to distraction (i.e., shifts of the attentional focus) or the failure to keep up a sufficient intensity level of attention over time are harmless, but they can also take tragic turns, for example, when causing accidents (Robertson, 2003). While the long-term impact on attention due to modern multitasking distractive devices is still unclear (Wilmer et al., 2017), attentional deficits are common symptoms of psychiatric and neurological disorders, such as attention-deficit/hyperactivity disorder (Bellgrove et al., 2005), anxiety disorders (Eysenck et al., 2007), schizophrenia (Green, 1996), and dementias (O'Keeffe et al., 2007).

Attention is a multifaceted cognitive function, its core being the creation of a selective processing focus (Sood and Jones, 2013). The attentional function that enables the continuous focus on a particular task for longer periods is defined as sustained attention. This ability is not represented anatomically in the brain as an unitary function but through functionally heterogenous multiple regions that jointly integrate to

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[*] Corresponding author at: Sensory-Motor Laboratory (SeMoLa), Jules-Gonin Eye Hospital/Fondation Asile des Aveugles, Department of Ophthalmology/University of Lausanne, Lausanne, Switzerland.

E-mail address: gsppamplona@gmail.com (G.S.P. Pamplona).

[1] Both authors contributed equally.

https://doi.org/10.1016/j.neuroimage.2020.117194
Received 21 March 2020; Received in revised form 7 July 2020; Accepted 20 July 2020

constitute the so-called sustained attention network (SAN) (Langner and Eickhoff, 2013). Conversely, the widely studied default-mode network (DMN) is generally deactivated during attention-demanding tasks (Raichle et al., 2001), but it is active during internally focused cognitive processes, such as mind-wandering (Mason et al., 2007), internal self-referential processes (Gusnard et al., 2001), and episodic memory (Greicius et al., 2003), as well as associated with worsened attentional performance (Weissman et al., 2006). Sustained attention and mind-wandering are viewed as mutually exclusive – based on a definition of mind-wandering as task-unrelated thoughts (Seli et al., 2018) –, which is reflected by a competitive pattern of brain activation in SAN (specifically, the dorsal attention network) and DMN. These two networks are intrinsically anticorrelated (Fox et al., 2005) and are thought to reflect the antagonistic information processing with external versus internal orientation (Spreng, 2012). The more demanding the task is, the more pronounced this dichotomy becomes (Kelly et al., 2008). As evidence for this anticorrelation, better performance in a range of attentional tasks is associated with activation in attention-related regions, while lower performance is linked to DMN activations (Hinds et al., 2013; Lawrence et al., 2003; Ogg et al., 2008; Thompson et al., 2013; Weissman et al., 2006). Furthermore, practitioners of attention-based meditation are better able to deactivate the DMN (Brewer et al., 2011), to activate attention-related regions (Brefczynski-Lewis et al., 2007; Manna et al., 2010), and exhibit higher network anticorrelation even at rest (Josipovic et al., 2012). Taken together, these studies suggest that increased sustained attention is achieved whenever there is a combination of DMN suppression together with SAN activation, an ability that could be enhanced. Following this rationale, we used a differential neurofeedback approach (i.e., feeding back the activity difference between two brain regions/networks) to simultaneously train both SAN up- and DMN down-regulation in order to improve attention.

Enhancing the voluntary control of these two networks may be achieved through fMRI-neurofeedback, a technique that converts current brain activity into sensory feedback to allow for learning to regulate brain activity. Such training has been shown to produce noticeable effects on behavior (Ruiz et al., 2014; Sitaram et al., 2017; Sulzer et al., 2013; Weiskopf et al., 2004). More specifically, learning to simultaneously regulate multiple brain regions associated with different functions was achieved through differential neurofeedback (Robineau et al., 2014; Scharnowski et al., 2015). Several previous studies have attempted to enhance attention using neurofeedback. Findings from EEG-based neurofeedback studies led to inconsistent results, reporting both, the presence and absence (Vollebregt et al., 2014) of attentional benefits from training, indicating that more empirical research is needed. Furthermore, treatments targeting attention-related brain regions rather than specific electrocortical frequencies might be more effective (Langner and Eickhoff, 2013). Using real-time fMRI neurofeedback, sustained attention enhancement was successfully achieved through online monitoring multi-variate brain signatures of attention while performing a specific task and providing feedback to the participants when attention lapses were detected in the brain (deBettencourt et al., 2015). In clinical conditions, fMRI-neurofeedback was applied as an experimental intervention targeting attentional deficits through upregulation of right inferior prefrontal and dorsal anterior cingulate cortex (Alegria et al., 2017; Zilverstand et al., 2017).

The current study aimed to complement and extend these previous approaches by (1) targeting network interactions rather than single brain regions in isolation, and (2) assessing the training effects on a range of attention task rather than the training being linked to a specific task. This was achieved by using differential SAN-DMN network feedback and evaluating the effects of such training on a battery of five behavioral tests that assess different aspects of attention such as attention switching, vigilance, mental rotation, and alertness. We hypothesized that our approach allows to (1) learn control over SAN and DMN activity, (2) exert such control in the absence of feedback (i.e., during transfer runs) after training, and (3) improve attention in participants who learned SAN-DMN self-regulation.

2. Materials and methods

2.1. Participants

Thirty healthy young adult volunteers (10 women, $M = 26.9$, $SD = 3.8$ years old) were recruited via online advertisement and participated in this study. Participants had to be between 18 and 40 years old and needed to read and speak English sufficiently well to follow the instructions. Half the participants were assigned to the neurofeedback (NF) group and the other half were assigned to the test-retest (TR) control group. Both groups were matched for age (paired t-test, $p = .15$) and gender. Exclusion criteria included left-handedness, vision impairments outside of −3 to +3 diopters (when correction by contact lenses was not possible), history of mental and/or cardiovascular disorders, consumption of alcohol or other drugs during the days of the experiment, as well as MRI contraindications (for the NF group only). This study was approved by the local ethics committee of the Canton of Zurich in Switzerland. All participants read and signed the informed consent according to the declaration of Helsinki before taking part in the study.

2.2. MRI acquisition

All MR images were acquired through a Philips Achieva 3T MRI scanner and a 32-channel head coil in the MR center of the Psychiatric Hospital, University of Zürich, Switzerland. Functional images were acquired using a T2*-weighted gradient-echo-planar (EPI) sequence with repetition time/echo time (TR/TE) = 2000/30 ms, flip angle = 80°, and field of view (FOV) = 240 mm × 240 mm. 37 slices were acquired in ascending order to cover the entire cerebrum (voxel size = $3 \times 3 \times 4$ mm^3, gap = 0.5 mm). SofTone mode was activated to reduce acoustic scanner noise. Anatomical T1-weighted brain images were acquired using a 3D MPRAGE (magnetization prepared gradient echo) sequence, TR/TE = 7.2/3.4 ms, 170 slices, voxel size = $1 \times 1 \times 1$ mm^3, flip angle = 8°, FOV = 240 mm × 240 mm, duration = 3.5 min.

Resting-state acquisitions comprised 200 scans (6 min 40 s) during which participants were asked to relax, stay still, breath regularly, look at a central black circle presented on a white screen for visual fixation, and not to think about anything in particular. Neurofeedback training acquisitions comprised 190 scans (6 min 20 s) and no-feedback transfer runs 180 scans (6 min). Before every functional acquisition, five dummy scans were acquired to establish steady-state magnetizations.

Heart rate was measured during functional runs with a pulse oximeter attached to the participants' right index finger (sampling interval = 0.002 s). Breathing rhythm was measured during functional runs by fastening a pneumatic belt to the participants' abdomen. Due to technical problems, heart rate measurements failed for five participants. In the MR scanner, visual stimuli were presented with MR-compatible goggles (Resonance Technology Inc.).

2.3. Experimental design overview

The experimental timeline for the NF group is summarized in Fig. 1. At the beginning of the first and fourth day of the experiment, participants in the NF group were asked to fill out the attention questionnaires and anatomical as well as resting-state fMRI scans were acquired. Subsequently, they were asked to perform a battery of five attention-related tests after having read the instructions.

During the second and third days of the experiment, five 45-min neurofeedback training runs were performed, respectively, after having read instructions explaining the training procedure and suggesting potential self-regulation strategies (for details, see below). Before the first and after the last neurofeedback training run, participants performed

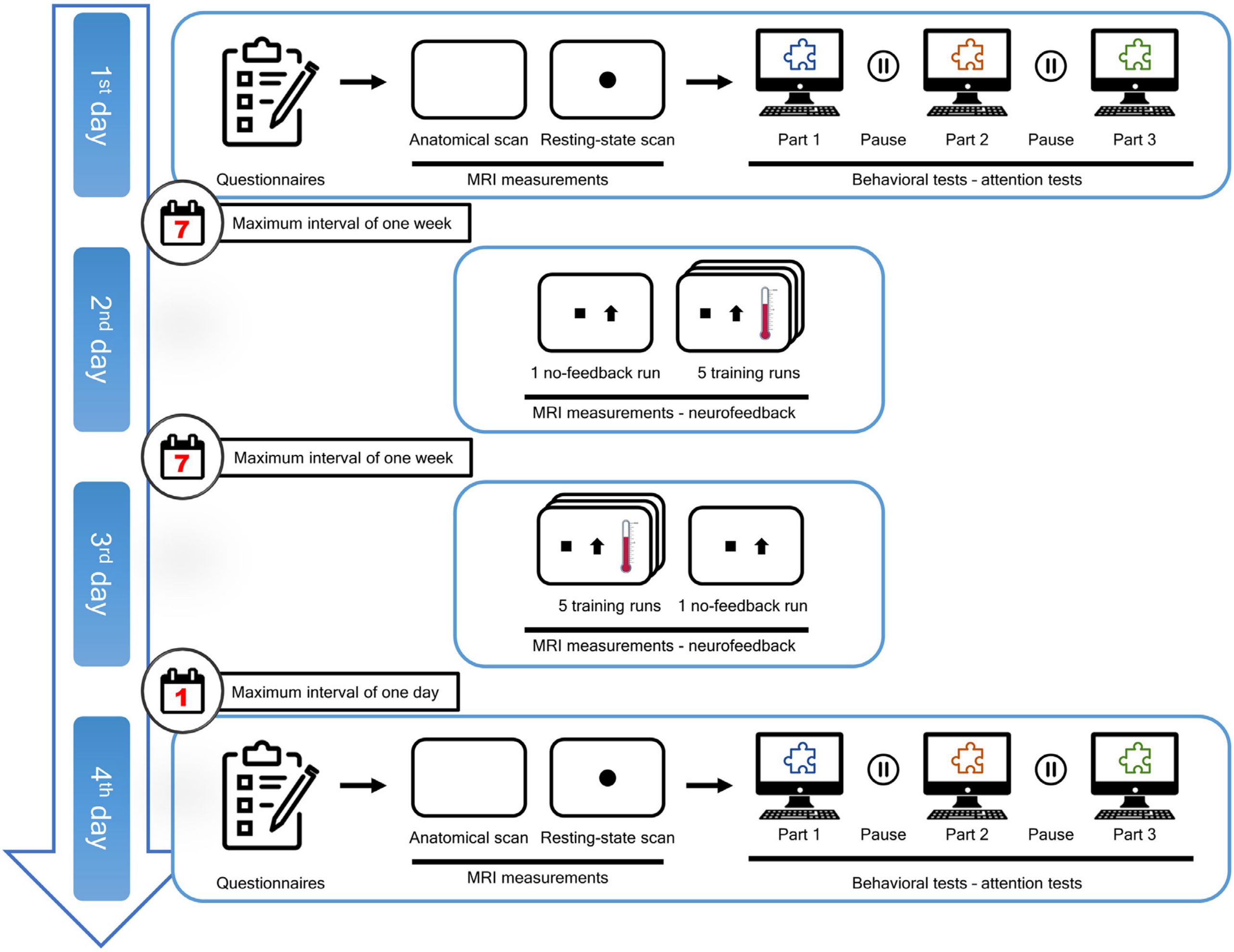

Fig. 1. Experimental timeline over sessions for the NF group.

transfer runs without feedback. The intervals between the first and second days and the second and third days were maximally one week. The interval between the third and fourth days was one day maximum.

Participants in the TR control group were only asked to perform the same behavioral attention tests twice, separated by a two-week interval (which corresponds to approximately the same interval between the pre- and post-training attention tests in the NF group). The TR group did not perform any neurofeedback training.

2.4. Region-Of-Interest (ROI) definitions

To cover the extensive brain activations linked to the different cognitive aspects of attention, the SAN regions that we used consisted of four anatomically distinct regions, respectively (Fig. 2). The SAN regions were defined based on masks from a meta-analysis of sustained attention studies (Langner and Eickhoff, 2013). This approach was chosen to efficiently and robustly delineate the SAN as a network embracing multiple functional aspects, thereby minimizing task-specific biases resulting from idiosyncrasies of any single functional localizer task. SAN1 comprised the anterior midcingulate cortex (aMCC), which is involved in detecting and/or solving processing conflicts, errors, and adjusting efforts (Weissman et al., 2006), sustaining intention and preparation, as well as monitoring performance. SAN1 also comprised a portion of the pre-supplementary motor area (pre-SMA), which is associated with cognitive control of motor output (Tanji, 1994), motor preparation, facilitation, and inhibition (Langner and Eickhoff, 2013), preplanned movement (Cunnington et al., 2002); and enhanced vigilance (Hinds et al., 2013). SAN2 corresponds to the right inferior frontal junction (IFJ), which is associated with discrimination (i.e. go versus no-go) and condition-switching tasks (Langner and Eickhoff, 2013). Together, SAN1 and SAN2 were reported to exhibit sustained activities during attentional tasks (Dosenbach et al., 2006). SAN1 and SAN2 were eroded to reduce cluster size so that they are similar in size to SAN3 and SAN4. SAN3 corresponds to the right temporoparietal junction (TPJ), which is related to stimulus-driven bottom-up reorientation of attention (Corbetta and Shulman, 2002; Langner and Eickhoff, 2013; Weissman et al., 2006), and updating of internal representations for response selection (Wolff et al., 2017). SAN4 corresponds to the right intraparietal sulcus (IPS), which is associated with endogenous, goal-oriented, or top-down attentional orienting (Corbetta and Shulman, 2002), spatial orienting, and mental rotation (Harris et al., 2000). In contrast to SAN1 and SAN2, SAN3 and SAN4 are supposedly recruited only transiently during initial attention engagement (Dosenbach et al., 2006). The SAN combines regions from both the frontoparietal control network (Dosenbach et al., 2008) – SAN1 and SAN3 – and the dorsal attention network (Yeo et al., 2011) – SAN2 and SAN4. While the former is related to cognitive control operations and the latter to visual attention (Spreng, 2012), these regions do not need to be co-activated under all circumstances, but they were selected for co-activation training to promote the enhancement of sustained attention.

The DMN can be subdivided and has been shown to be associated with various functions, reflecting the complexity of self-oriented experiences (Andrews-Hanna et al., 2014). Therefore, we chose regions consistently found across DMN studies and that are related to controlling

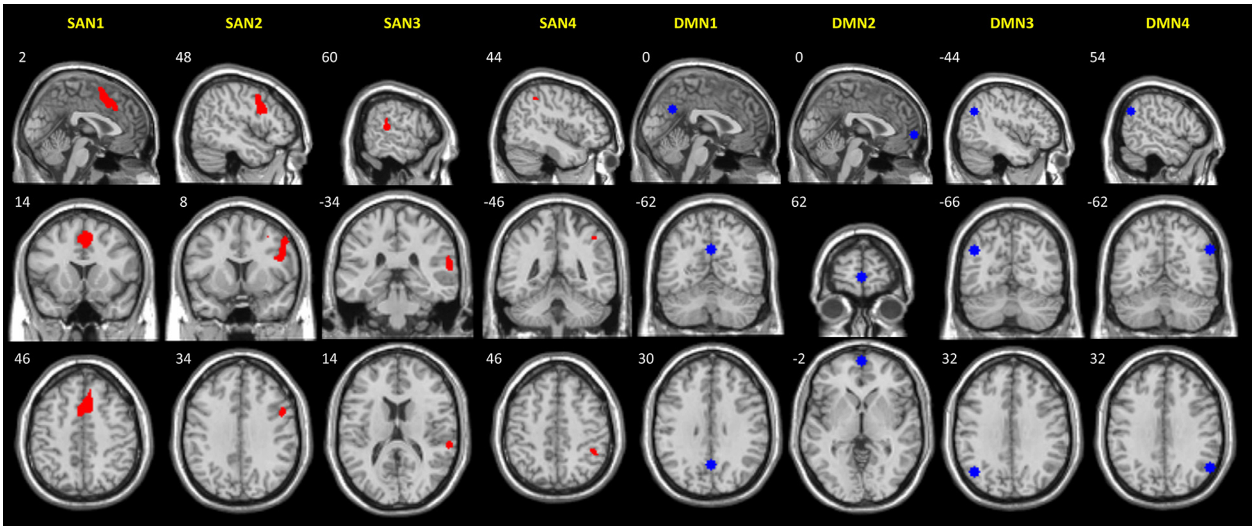

Fig. 2. Selected SAN (red) and DMN (blue) ROIs and their center-of-mass MNI coordinates in sagittal, coronal, and axial views. SAN1 = aMCC, SAN2 = rIFJ, SAN3 = rTPJ, SAN4 = rIPS, DMN1 = PCC, DMN2 = mPFC, DMN3 = lAng, DMN4 = rAng.

attention in self-generated thought, potentially recruiting attention processes that are externally oriented to a task. These characteristics are found in the core network, as defined by Andrews-Hanna et al. (2014), and the DMN nodes chosen as ROIs in this study. DMN1, DMN2, DMN3, and DMN4 represent the posterior cingulate cortex (PCC), the medial prefrontal cortex (mPFC), and the left/right angular gyrus (lAng and rAng), respectively. In order to account for individual differences (Finn et al., 2015; Shen et al., 2013), the subject-specific DMN ROIs were defined using independent component analysis (ICA). Specifically, each participant's anatomical and resting-state fMRI data from the first day were preprocessed and defined as inputs for ICA analysis using the Gift toolbox (http://mialab.mrn.org/software/gift) with a pre-defined number of 30 components. Next, the component representing the dorsal DMN was identified and the four 6-mm-radius spherical DMN ROIs were individually specified using the Personode toolbox (Pamplona et al., 2020; Sohn et al., 2015).

2.5. Real-time fMRI system and feedback calculation

Real-time signal processing was performed on a dedicated personal computer (Intel Core I7, 16GB RAM, Windows 7) using OpenNFT (http://opennft.org/) (Koush et al., 2017a,b). For presenting the feedback, we used Psychtoolbox (http://psychtoolbox.org) for MATLAB (The MathWorks, Natick, MA, USA). To make sure the same brain regions were trained on different days, the MNI (Montreal Neurological Institute)-based ROIs (for details, see below) were transformed into the current native space at the beginning of each run. This was achieved by applying the inverse transformation of a segmented anatomical image of the respective participant to the ROIs using SPM12 (http://www.fil.ion.ucl.ac.uk) and custom-made scripts.

During training and transfer runs, functional images in Analyze^{TM} format were transferred to the real-time processing computer as soon as they were acquired and reconstructed in the MRI scanner computer via the Philips Direct Reconstructor Interface (DRIN) application. On this computer, spatial realignment to the first image, estimation of six movement parameters (translation and rotation), reslicing, and spatial smoothing with an isotropic Gaussian kernel with 5-mm full width at half maximum (FWHM) were performed using OpenNFT. Autoregressive correction of first order was performed online to reduce temporal autocorrelation caused by physiological noise (Lindquist, 2008), and an incremental general linear model (GLM) was used to remove residual motion and linear trends (Hinds et al., 2011). Spike detection and high-frequency noise removal were performed through a modified Kalman filter (Koush et al., 2012).

The feedback was computed as described as follows. First, the average signal from each ROI was extracted separately and processed online. Then, the resulting time-courses were scaled to account for between- and within-subjects variability. Signal limits were rescaled within a sliding window for the last three cycles (baseline and regulation blocks, 105 volumes in total) separately for each ROI. As standard in OpenNFT, inferior $lim^{ROI}_{inferior}$ and superior $lim^{ROI}_{superior}$ limits are the median of the 5% minimum and the median of the 5% maximum, respectively, of signal values previous to the actual volume in the current run (Scharnowski et al., 2012); except for the first 20 volumes, in which $lim^{ROI}_{inferior}$ and $lim^{ROI}_{superior}$ are the minimum and maximum values, respectively (Koush et al., 2012). Both average regulation $\hat{s}^{ROI}_{volume}$ and average baseline $\hat{m}^{ROI}_{baseline}$ signals in the current period are scaled according to (Koush et al., 2012):

$$\hat{\mathrm{m}}^{\mathrm{ROI}}_{\mathrm{baseline}} = \frac{\mathrm{m}^{\mathrm{ROI}}_{\mathrm{baseline}} - \mathrm{lim}^{\mathrm{ROI}}_{\mathrm{inferior}}}{\mathrm{lim}^{\mathrm{ROI}}_{\mathrm{superior}} - \mathrm{lim}^{\mathrm{ROI}}_{\mathrm{inferior}}} \tag{1}$$

and

$$\hat{s}^{ROI}_{volume} = \frac{s^{ROI}_{volume} - lim^{ROI}_{inferior}}{lim^{ROI}_{superior} - lim^{ROI}_{inferior}}. \tag{2}$$

Here, s^{ROI}_{volume} and $m^{ROI}_{baseline}$ are the ROI's signals during regulation and baseline periods, respectively. In the first baseline period, $m^{ROI}_{baseline}$ is the median of the respective ROI time-course and, for subsequent blocks, $m^{ROI}_{baseline}$ considered all previous baseline blocks without the first five volumes of the block. Thus, the normalized signal change nsc^{ROI}_{volume} is

$$nsc^{ROI}_{volume} = \hat{s}^{ROI}_{volume} - \hat{m}^{ROI}_{baseline} \tag{3}$$

and the intermittent feedback signal is finally given by the difference between the average normalized signal change for SAN and DMN ROIs. Differential feedback has also the advantage that global effects such as breathing, heart rate, unspecific changes due to arousal, fatigue and head movements are cancelled out and less likely to cause artifactual self-regulation (Scharnowski et al., 2015; Sorger et al., 2019).

As intermittent feedback after each baseline and regulation block, a thermometer was displayed whose reading was proportional to this computed difference regarding the last block of regulation. The intermittent feedback signal was discretized into 21 steps (10 negative and 10 positive values). For the first run, maximum and minimum thermometer heights were empirically defined as .35 and -.35, respectively.

As additional feedback and motivation after each run, monetary reward of up to 3 CHF was presented. The amount was proportional to the differential signal change during the respective run. To maximize motivation and learning across training runs, both the thermometer maximum/minimum height and the monetary reward were adaptive. Specifically, if the participant's performance in the current run was higher than in the previous one, positive feedback and reward become harder to obtain (in steps of .05, starting from the empirical value of .35). If the participant's performance in the two last runs was less than half of the previous run performance, feedback and reward become easier to obtain (also in steps of .05).

2.6. Neurofeedback training and transfer runs

Neurofeedback training and transfer runs were composed of 30-s baseline blocks interleaved with 40-s regulation blocks and followed by 4-s feedback presentation (Fig. S1). Per run, this cycle was repeated five times. After each run, the monetary reward that the participant earned in the run was displayed for 5 s. The neurofeedback training runs lasted 6 min 15 s and the transfer runs 5 min 50 s (they were without feedback and reward presentation).

We used intermittent feedback (feedback was provided only every 70 s) in order to avoid dual-task interference between self-regulation and processing the feedback and to benefit from improved feedback signal quality due to averaging (Emmert et al., 2017; Hellrung et al., 2018; Johnson et al., 2012). Feedback was presented in form of a thermometer icon with the temperature reading representing the differential signal SAN minus DMN of the previous baseline-regulation block. In addition to the thermometer scale with 21 levels (10 positive, zero, and 10 negative levels), the thermometer reading was also color coded with gradual changes from blue to red for low and high levels, respectively (Fig. S1).

During baseline blocks, a black square was presented, and participants were instructed to relax and let their minds wander. They were explicitly advised not to prepare attention-related strategies for use during the subsequent baseline periods. During self-regulation blocks, a black up-arrow was presented, and participants were asked to regulate their brain activity and increase the subsequent thermometer reading. To facilitate learning, we suggested attention-related mental strategies but, following established neurofeedback procedures, we emphasized that they should find any strategy that works best for them. Suggestions for potential regulation strategies included: (1) paying attention to details on the screen (alignment, shape, color, …) and changing the attention focus every 5-10s, (2) paying attention to the screen and bringing the attention back to the screen whenever the participant realizes mind-wandering (i.e., task-unrelated thoughts), and (3) trying to remain in a state of heightened alertness. These strategies were based on mindfulness studies and have previously been shown to induce the required brain activations (Brefczynski-Lewis et al., 2007; Jang et al., 2011; Josipovic et al., 2012) and worked well during piloting the experiment. Participants were asked to minimize head motion and breathe regularly.

For the first no-feedback transfer run, the participants were asked to choose and apply one of the suggested strategies described above. For the second no-feedback transfer run, participants were asked to apply the strategy that worked best for them during training.

2.7. Self-report and subjective ratings

Right after each neurofeedback training run, we asked every participant the following questions: "(1) From 1 (very bad) to 10 (very good), how do you evaluate your control over the thermometer? (2) From 1 (very hard) to 10 (very easy), how difficult was it to control the thermometer? (3) From 1 (very low) to 10 (very high), how was your concentration level in the last run?". During transfer runs, only the third question was asked. After each run, the participants were also asked to report which strategies they used in order to control the thermometer. Self-report scores from two participants were not collected due to technical issues with the communication system.

In addition to debriefing, participants in both groups completed the Cognitive Failures Questionnaire (CFQ) (Broadbent et al., 1982) and the Dundee Stress State Questionnaire (DSSQ) (Matthews et al., 1999). The CFQ measures stable attentional characteristics of the participant (”traits”), not prone to be altered due to neurofeedback training. Thus, participants responded to the CFQ questionnaire only before training to investigate associations between self-regulation learning and attentional traits. On the other hand, the DSSQ yields information about the current state of attentiveness and stress in real-life situations from a subjective perception, which are prone to fluctuate over time more easily than CFQ scores. To evaluate behavioral changes related to the DSSQ questionnaire, participants filled it in the beginning of the first and the last days of the experiment for the NF group (Fig. 1) and in the beginning of both experimental days for the TR group. The CFQ was applied only to the NF group, whereas the DSSQ was applied to both groups. Due to technical problems, the DSSQ scores of 8-10 participants (depending on the sub-score) were not collected.

2.8. Behavioral tests

Before and after neurofeedback training (i.e., on the 1st and 4th days for the NF group), every participant performed five attention tests outside the MR scanner. Pre- and post-training attention testing was performed at the same time of the day to make performance more comparable. Before every test, written instructions were provided. Attention tests were performed on a dedicated computer and in a separate experimental room with constant luminosity, noise (participants were asked to use earplugs), and temperature levels. Attention tests were presented with the Psychology Experiment Building Language (PEBL) software (Mueller and Piper, 2014), and applied in the following order: Continuous Performance Task (CPT) (Conners et al., 2003; Piper et al., 2016), a go/no-go task with randomly presented targets and non-targets; Task-Switching Performance (Switcher) (Anderson et al., 2012), which requires activating and suppressing attention to switching instructions; Psychomotor Vigilance Test (PVT) (Helton et al., 2007; Loh et al., 2004) to evaluate the readiness to respond to unexpected stimuli onsets (closely related to sustained attention, the main attentional aspect of the study); Mental Rotation Task (Berteau-Pavy et al., 2011; Piper et al., 2015); Attentional Network Test (ANT) (Fan et al., 2002), which is a cognitive flanker effect task designed to measure alertness, orientation, and conflict solving. To avoid fatigue, there were 5-min breaks between the 2nd and 3rd tests and between the 4th and 5th tests.

2.9. Data analysis

fMRI Preprocessing: fMRI data were preprocessed with SPM12 and included slice-timing correction (using the middle slice as the reference), realignment to the mean image, and spatial smoothing using a Gaussian kernel of 8-mm FWHM. The anatomical image was coregistrered to the mean functional image, segmented into tissue class images (gray and white matter, and cerebrospinal fluid compartments (CSF)), and together with the functional images normalized to the MNI space through the forward deformation field.

First-level analysis: For the first-level GLM analysis, the regulation blocks were modeled as boxcar functions convolved with the canonical hemodynamic function of SPM12. In the GLM, the six parameters of movement (translation and rotation) were included as covariates of no interest. For each run of each participant, a positive contrast between regulation and baseline blocks was applied.

Whole-brain analysis: To investigate common de-/activations across participants, second-level whole-brain random-effects analysis included one-sample t-tests for the first and last training runs and for the first and last no-feedback runs. Because of incomplete coverage, three participants were removed from whole-brain analysis of the no-feedback runs. Contrast images were thresholded at $p < .001$ and false discovery rate (FDR)-corrected on cluster level at $p < .05$ plus cluster size > 10 voxels. Moreover, paired t-test contrast maps last minus first training runs and last minus first no-feedback runs were computed and visualized through statistical maps thresholded at uncorrected $p = .001$, and cluster size > 10 voxels. Group-level images were visualized in a sliced brain using MRIcroGL (http://www.nitrc.org/projects/mricrogl/).

ROI analysis: Average contrast values of each ROI were extracted using MarsBaR (http://marsbar.sourceforge.net; Brett et al., 2002). We considered, as the magnitude of the regulation success, the slope of the learning curve, in which the contrast of the signal over the ten training runs is fitted to a linear function (deBettencourt et al., 2015). This was done for the individual ROIs of the SAN and the DMN (contrast values of the respective ROIs were averaged for each network) and the differential signal (SAN-DMN). We also calculated paired t-tests of contrast values to examine regulation success over training days and transfer runs. In order to analyze whether neurofeedback improved sustained activity across time, we extracted the average percent signal change (PSC) time-courses across all participants from each ROI for the first and last training runs using MarsBaR. For this, we considered the 20 TRs of the regulation blocks for the entire run and the following 10 TRs. For the SAN regions, where either maintenance of sustained activity or transient activity would be expected (please refer to "ROI Definitions" section and Dosenbach et al., 2006), we performed repeated-measures ANOVA specifying run (first and last training runs) and time-course (TRs starting after the seventh scan after the regulation epoch and terminating at the end of it, in order to not account for the start-related activity (Dosenbach et al., 2006)) as within factors. Parametric statistics were performed using RStudio (and the ggpubr library). Normality was verified using Shapiro-Wilk tests (and non-parametric tests were applied if required).

Questionnaires and physiological signal analysis: Regarding the CFQ analysis, the overall CFQ score was computed for each NF group's participant before and after neurofeedback training. Then, we computed the correlation between the overall CFQ scores before training and slopes of the neurofeedback learning curve across participants to verify whether attentional traits might be related to neurofeedback learning. We also compared overall CFQ scores before versus after neurofeedback training to check for attentional traits changes. Regarding the DSSQ analysis, instead of considering every possible scale derived from this questionnaire, we only analyzed the ones thought to be involved in our study's hypotheses: motivation, self-focused attention, concentration, control and confidence, task-related interference. We first checked for changes in the DSSQ scales specific to the NF group after neurofeedback training by computing the interaction between day and group through generalized linear models, in order to account for categorical values and repeated measures. Secondly, we computed correlations between the slope of neurofeedback learning curve and the percentage difference of the pre-selected DSSQ scales. Regarding the self-report scores, normalized-to-z Pearson correlation coefficients were estimated for each participant between control, ease, and concentration and contrasts of differential activity (a measure of regulation performance) across runs. Task engagement levels, computed from DSSQ scales, were also computed and compared between days of application (paired t-tests) and between groups (two-sample t-tests). Physiological signals were processed and computed using PhysIO (Kasper et al., 2017) and paired t-tests were conducted to check for differences in baseline versus regulation blocks in terms of heart rate and "respiration volume per time" (RVT) across participants. Finally, we computed the normalized-to-z Pearson correlation coefficients between percentage differences of RVT measures and contrasts of differential activity for each participant across runs (due to incomplete RVT acquisition, two participants were removed from this analysis). One-sample t-tests were performed to examine whether correlations were significantly different from zero for self-report scores and RVT measures (mean correlation values were obtained by converting the distribution back to non-normalized Pearson correlation). All analyses were performed in RStudio and parametric or non-parametric tests were used depending on whether or not data were normally distributed as assessed by the Shapiro–Wilk test.

Behavioral effects: For each attention task, accuracy and reaction times were extracted, and reaction times were corrected for outliers (for each run, trials ± 3 standard deviations from the mean were iteratively removed). We analyzed the interactions between groups and days by computing linear mixed models to account for the hierarchical structure of the application of attention tests. We defined the following fixed factors: day, group, and type for the CPT and Switcher task; day, group, and trial for the PVT; group, day, condition, and orientation for the Rotation task; and group, day, cue, and coherence for the ANT. As random factors, we defined: subject and trial for the CPT, Switcher task, and ANT; subject for the PVT; and subject, trial, and stimulus shape for the Rotation task. Differences between groups (NF and TR) and days (second *versus* first applications) were analyzed post-hoc. For the PVT, we also computed the three-way interaction group × day × trial and performed additional post-hoc testing by comparing early and late trials centered as in the Cohen and Cohen convention (average plus the standard deviation compared to the average minus the standard deviation, considering the number of trials) (Cohen and Cohen, 1983; West et al., 1996), to check for differences in the group × day interaction for early and late trials, respectively. All *p*-values were corrected for multiple comparisons by controlling the FDR.

In addition, we predefined scores of interest by summarizing the measures for each attention test according to Paas and Van Merriënboer (1993); that is, we combined accuracies and reaction times for all conditions in the test and both days of application in a single vector (reaction times were inverted to be positively associated to performance), converted those values into z-scores, and computed the average for each day. This was not made for the ANT as it would misrepresent the plurality of its scores. Furthermore, for the PVT only reaction time was considered because this test did not yield accuracy measures. We also built joint measures comprising similar aspects measured by different attention tests. Specifically, we created compound scores by combining scores through the same approach as follows:

(1) Sustained attention: slope of individual CPT reaction times over time, slope of individual PVT reaction times over time, as well as mean RT of the 10% slowest and 10% fastest individual PVT trials, respectively;
(2) Attentional control: overall accuracy in the CPT, conflict speed costs in the ANT, conflict accuracy costs in the ANT, as well as costs of non-prepared task-switches (i.e., reaction time difference between random and non-random trials of the Switcher task);
(3) Phasic alerting: alerting effect on RT in the ANT;
(4) Mixing costs: reaction time difference between three-tasks and two-tasks versions of the Switcher task;
(5) Attentional orienting: orienting effect on RT in the ANT.

Additionally, the coefficient of variation was computed for both CPT and PVT to assess intraindividual within-task variability. Since these measures reflect intra-individual variability but do not vary themselves within subjects in a given session, repeated-measures ANOVAs (instead of linear mixed models) were used to assess the interaction between time of testing (pre-/post-training) and group (NF/TR), followed by post-hoc tests.

Finally, Pearson correlations were computed between the across-session change in each one of the compound scores (i.e., the difference between the second and first days of testing) and the slope of neurofeedback learning for each ROI in the SAN, the whole SAN, the whole DMN, and the SAN–DMN differential activity, respectively.

All obtained results (except by individual-level whole-brain maps) and scripts used for the data analysis are available on the public GitHub repository: https://github.com/gustavopamplona/NF_ATT_public_data. A checklist summary of the consensus on the reporting and experimen-

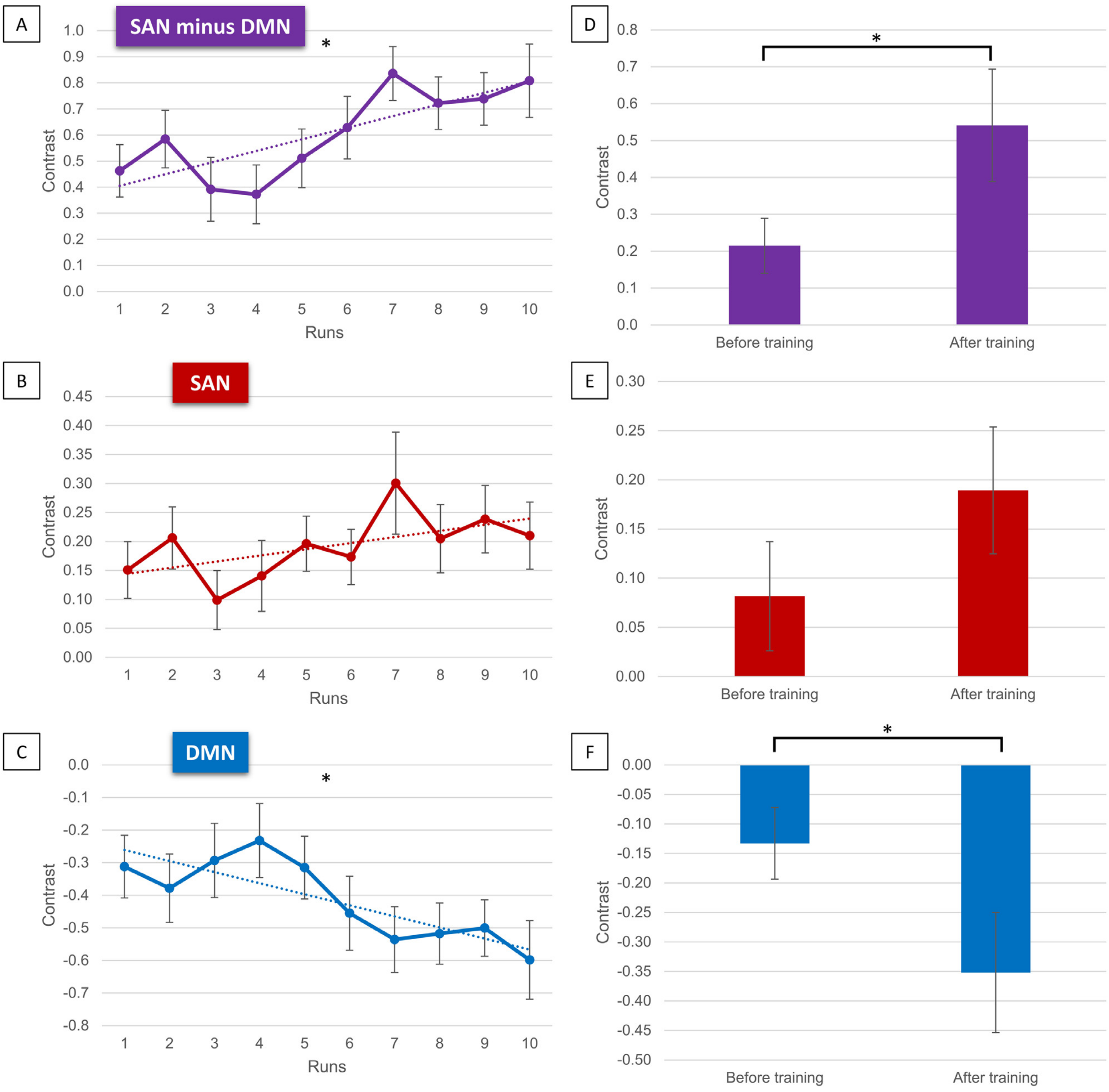

Fig. 3. Left: Contrast regarding the (A) differential signal SAN-DMN, (B) SAN, and (C) DMN across neurofeedback training runs. Right: Contrast of the differential signal SAN-DMN (D), average SAN (E), and average DMN (F) during no-feedback transfer runs before and after neurofeedback training. Asterisks indicate significant differences and slopes and error bars represent ±1 SEM.

tal design of clinical and cognitive-behavioral neurofeedback studies (CRED-nf) was included as supplementary material.

3. Results

3.1. Learning the voluntary control of SAN and DMN

Over the course of the neurofeedback training, participants learned to control differential activity between SAN and DMN (Figure 3). Already in the very first training run, participants showed significant up-regulation of the differential feedback signal (Fig. 3.A, two-tailed Wilcoxon signed-rank test, $Z = .80$, $p = .0020$), and this control increased across training runs (Fig. 3.A, linear regression: $\beta = .04$, $R^2 = .64$, $F(1,8) = 14.2$, $p = .005$). Increased control over the differential SAN-DMN activity is also evident by a significantly better performance during the second compared to the first training day (Fig. S2.A, one-tailed paired t-test, $t(14) = 3.62$, $p = .0014$). Learning control over the differential feedback signal was mediated mainly through significantly decreasing DMN activity (Fig. 3.C, linear regression: $\beta = -.03$, $R^2 = .69$, $F(1,8) = 17.83$, $p = .003$), while the SAN showed modest increases (Fig. 3.B, linear regression: $\beta = .011$, $R^2 = .33$, $F(1,8) = 3.94$, $p = .08$) across training runs. Accordingly, DMN activity reduced significantly from training day 1 to day 2 (Fig. S2.C, SAN; one-tailed paired t-test, $t(14) = -2.81$, $p = .007$), and SAN activity increased slightly (Fig. S2.B, one-tailed paired *t*-test, $t(14) = 1.19$, $p = .13$). This is also evident when considering the individual ROIs that the SAN and DMN are composed of: Only SAN4 activity increased significantly (Fig. S3, SAN4: $\beta = .028$, $R^2 = .72$, $F(1,8) = 20.2$, $p = .0020$), whereas all 4 DMN ROIS decreased significantly across training runs (Fig. S4, DMN1: $\beta = -.03$, $R^2 = .42$, $F(1,8) = 5.89$, $p = .04$; DMN2: $\beta = -.05$, $R^2 = .80$, $F(1,8) = 31.9$, $p <$

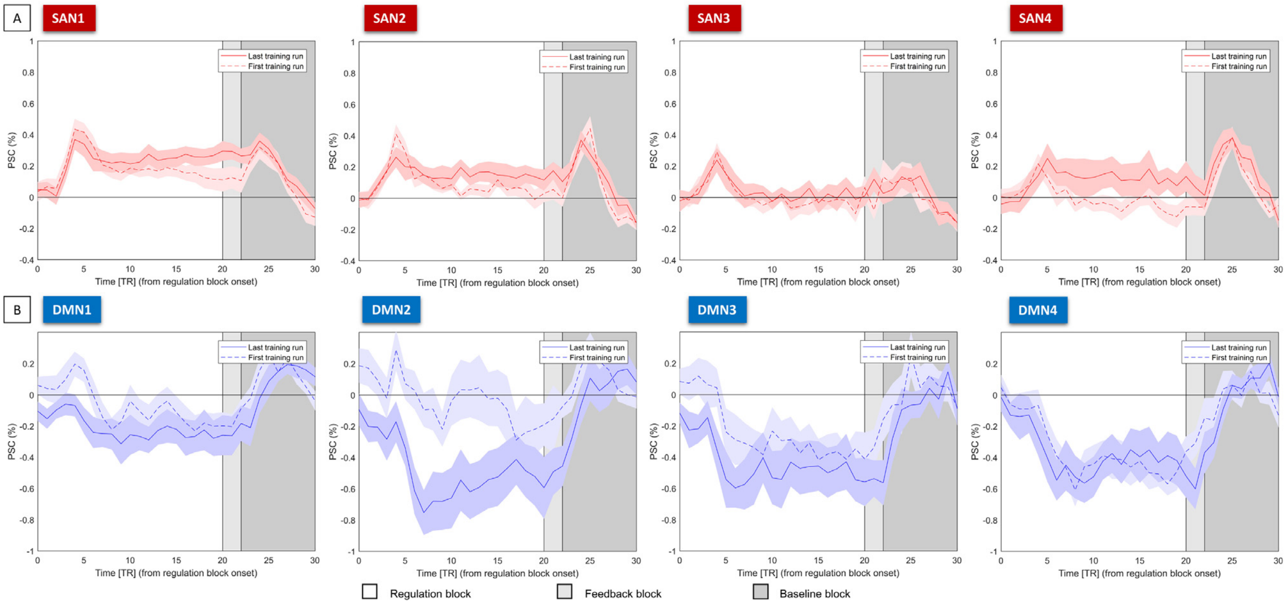

Fig. 4. Average percent signal change (PSC) time-courses for each SAN (A) and DMN (B) region for the last (solid lines) and the first training run (dashed lines). Shaded areas in red represent ±1 SEM. The background colors represent the baseline blocks (white), intermittent feedback blocks (light gray), and part of the subsequent baseline blocks (dark gray).

.001; DMN3: β = -.03, R^2 = .56, $F(1,8)$ = 10.06, p = .013; DMN4: β = -.029, R^2 = .54, $F(1,8)$ = 9.34, p = 0.016).

ROI time-courses locked to the onset of regulation illustrate the activity differences between the first and last training runs (Fig. 4). SAN activations and DMN deactivations were clearly observed. Amongst the SAN ROIs, SAN1 was the only one to show higher maintenance of sustained activity due to neurofeedback training, according to run × time interactions from repeated-measures ANOVAs (Fig. 4: SAN1: $F(16)$ = 1.94, p = .02; SAN2: $F(16)$ = .83, p = .6; SAN3: $F(16)$ = 1.14, p = .3; SAN4: $F(16)$ = .41, p = 1).

This learned ability to control SAN–DMN activity was subsequently maintained during transfer runs in the absence of neurofeedback. Compared to pre-training, post-training transfer run activity differences between SAN and DMN increased significantly, which was mainly mediated by decreasing DMN activity (Fig. 3, D-F, SAN-DMN: $t(14)$ = 1.74, p = .05; SAN: $t(14)$ = 1.19, p = .13; DMN: $t(14)$ = -1.19, p = .13) (see also Fig. S5 for individual ROI analyses of transfer run activity).

While there were no significant differences in heart rate between regulation and baseline blocks across runs (Fig. S6.A, two-tailed paired t-test, heart rate: $t(14)$ = -.05, p = 1), respiration differences were observed between baseline and regulation periods (Fig. S6.B, two-tailed paired t-test, heart rate: $t(14)$ = -2.14, p = .05). However, differential regulation did not correlate with the breathing rhythm differences across training runs (one-sample t-test; *mean* r = .09, $t(12)$ = .76, p = .5). Hence, the observed learning results cannot be explained by differential breathing strategies.

3.2. Neural processes underlying SAN–DMN differential self-regulation

Whole-brain analyses of the last training run showed significant activation in pre-SMA, bilateral inferior occipital gyrus, bilateral thalamus, right inferior frontal gyrus, and left superior parietal lobule as well as deactivations in the DMN (Fig. 5A and Table S1A). During the first training run, we found activations in pre-SMA, bilateral middle and inferior occipital gyrus, bilateral precentral gyrus, and right thalamus as well as deactivations in right angular gyrus (Fig. 5B and Table S1B). The contrast between the last and first training runs revealed significantly stronger deactivations in the precuneus and medial prefrontal cortex (Fig. 5C). A similar pattern emerged for whole-brain analysis of the transfer run, with significant activations in the dorsal attention network during the last no-feedback run (Fig. S7A and Table S2A); activations in bilateral middle and inferior occipital gyrus, as well as left precentral gyrus during the first no-feedback run (Fig. S7B and Table S2B), and larger deactivations in bilateral middle occipital gyrus and right posterior insula in the last compared to the first transfer run (Fig. S7C).

3.3. Mental strategies underlying self-regulation and questionnaires

To successfully control the feedback signal, participants reported attempting a variety of mental strategies. Some strategies (n = 8) were linked to visual content of the screen, such as focusing on the shape of the arrow, the center or the tip, counting the edges of the arrow, mentally describing the geometry of the arrow. Furthermore, imagining threatening or stressful situations (e.g. pretending to be in danger or holding an emotional speech in front of many people), and mental arithmetic were reported to work well. During baseline blocks, participants reported imagining future planning (e.g., what to eat for dinner), relaxing situations (laying by the beach), affective experiences with family or friends, feeling calm and relaxed, trying to think of nothing, and introspective thoughts (making up a story about themselves, imagery of swimming, singing internally or listening to the sound of one's own breath). Most successful strategies for regulation and baseline blocks are reported in Table S3.

Self-reported everyday-life attentional ability was not associated with neurofeedback learning and did not change after neurofeedback training, as indicated by the Pearson correlation between overall CFQ scores and slope of neurofeedback learning curve ($r(13)$ = .008, p = 1) and a paired t-test between the overall CFQ scores before and after the training ($t(14)$ = -.4, p = .7). None of the DSSQ scales improved for the NF group in the second application (after neurofeedback training) compared to the TR group (generalized linear model time × group interaction: all p-values > .05). Task engagement levels, measured by the DSSQ, did not differ between days or groups (all p-values > .05). Pearson and Spearman correlations between percentage differences of pre- and post-training DSSQ scores for the NF group and the slope of the learning curve revealed no significant associations (all p-values > .05).

Self-reported subjective feeling of controlling the feedback signal, subjective level of difficulty, and subjective ratings of how concen-

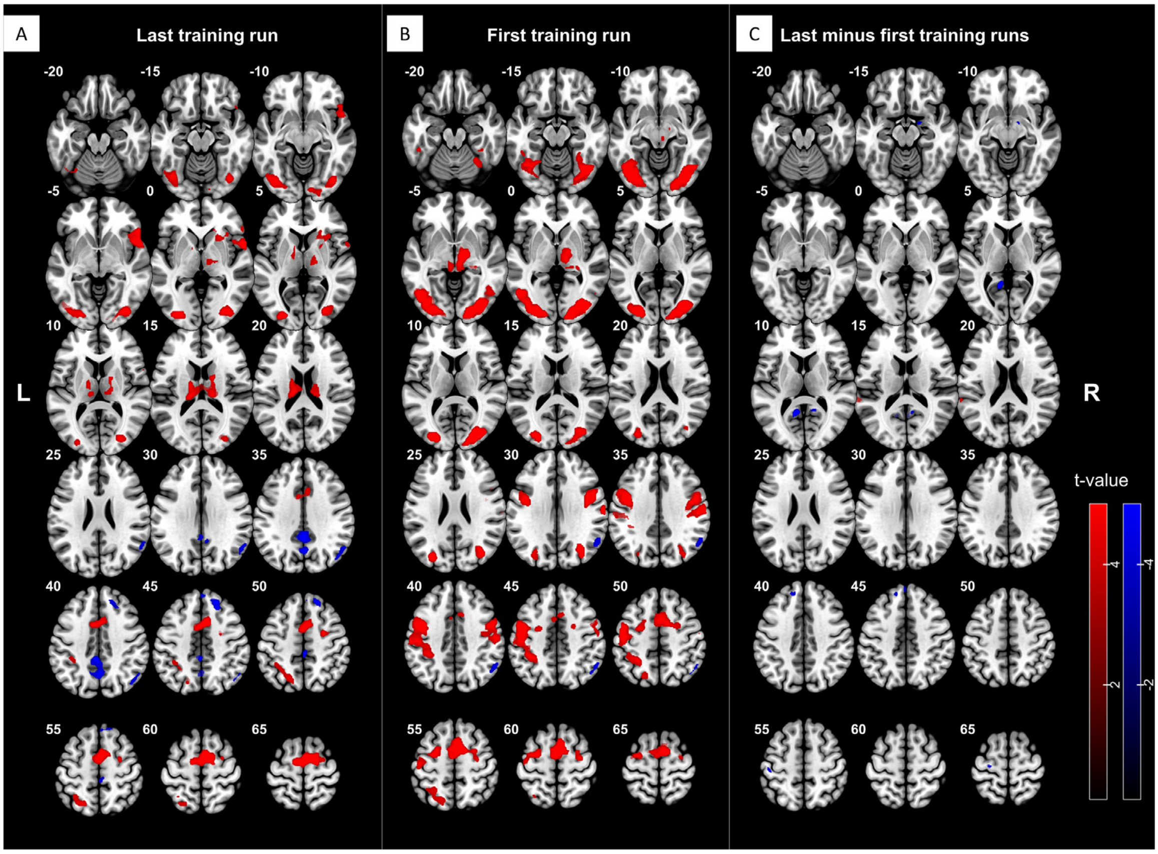

Fig. 5. Whole brain analysis of the training runs. Axial slices show activations (red) and deactivations (blue) during last (A) and first (B) training runs. (C) Axial slices show contrast map from a paired t-test, wherein last > first (red) and first > last (blue). Contrast in A and B are thresholded at $p < .001$ (voxel-level) and FDR-corrected on cluster level at $p < .05$; contrast in C is thresholded at uncorrected $p = .001$. Images visualized using MRIcroGL.

trated participants were during neurofeedback runs were all correlated with neurofeedback learning success (one-sample t-tests; control: *mean* $r = .34$, $t(12) = 2.38$, $p = .03$; ease: *mean* $r = .42$, $t(12) = 3.43$, $p = .005$; concentration: *mean* $r = .22$, $t(12) = 2.51$, $p = .03$). The mean Pearson correlations between self-report scores and contrast values for individual the SAN ROIs, the SAN and DMN as a whole, and the differential signal are reported in Table S6.

3.4. Behavioral effects of self-regulation

We observed significant group × day interactions in linear mixed model analyses for all attention tests (CPT: $F(1,17689) = 98.57, p < .001$; Switcher task: $F(1,5861) = 8.90$, $p = .004$; PVT: $F(1,6808) = 12.94$, $p < .001$; Rotation task: $F(1,6232) = 9.58$, $p = .003$; ANT: $F(1,15119) = 8.07, p = .004$, FDR-corrected p-values). However, according to post-hoc analyses, the performance of participants in both NF and TR groups improved significantly in the second testing session for CPT, Switcher task and ANT (Table 1). These improvements were specific to reaction times and not seen for accuracy measures.

Since behavioral effects in the PVT were observed only for the NF group, we analyzed the differences between groups and days in terms of time on task (i.e., comparing early and late trials). A graph of the three-way interaction group × day × trial is shown in Fig. 6. According to post-hoc analyses comparing early and late trials, NF group participants were faster in the second than in the first testing session in early trials ($t(6808) = 3.68$, $p = .0019$, FDR-corrected) but not in late trials ($t(6808) = 1.77$, $p = .2$, FDR-corrected). Conversely, TR group participants were faster in the second than in the first testing session in late trials ($t(6808) = 3.29$, $p = .004$, FDR-corrected) but not in early trials ($t(6808) = .22$, $p = .8$, FDR-corrected). There were no differences between groups in either early or late trials (all p-values > .05).

Table 1
Estimates of fixed effects from linear mixed effects of second minus first applications. Results for reaction times and accuracy are shown. Asterisks represent significant differences (FDR-corrected p-values < .05). Green and red cells indicate improved and worsened performance, respectively; NF: neurofeedback group; TR: test-retest group.

	Reaction time		Accuracy	
	NF group	TR group	NF group	TR group
CPT	-11.21*	-29.58*	0.19	-0.27
Switcher	-254.50*	-371.22*	0.22	-0.05
PVT	-13.23*	3.50	-	-
Rotation	-370.29*	-138.65	-1.71	-14.33*
ANT	-39.86*	-47.25*	-0.46	0.20

According to (non-hierarchical) repeated-measures ANOVAs, we did not observe any significant group × day interactions for the combined attention scores (Table S4). We also did not observe significant correlations between the slopes of neurofeedback learning curves (for SAN, DMN, and differential SAN–DMN activity) and differences between the second and first days of test application (Table S5) after ROI/network-based FDR correction.

4. Discussion

4.1. Neurofeedback training

The present study demonstrates the successful learning of differential activity modulation in two brain networks by means of fMRI-neurofeedback training (Fig. 3). To the best of our knowledge, this is the first study to show that subjects can learn to simultaneously control

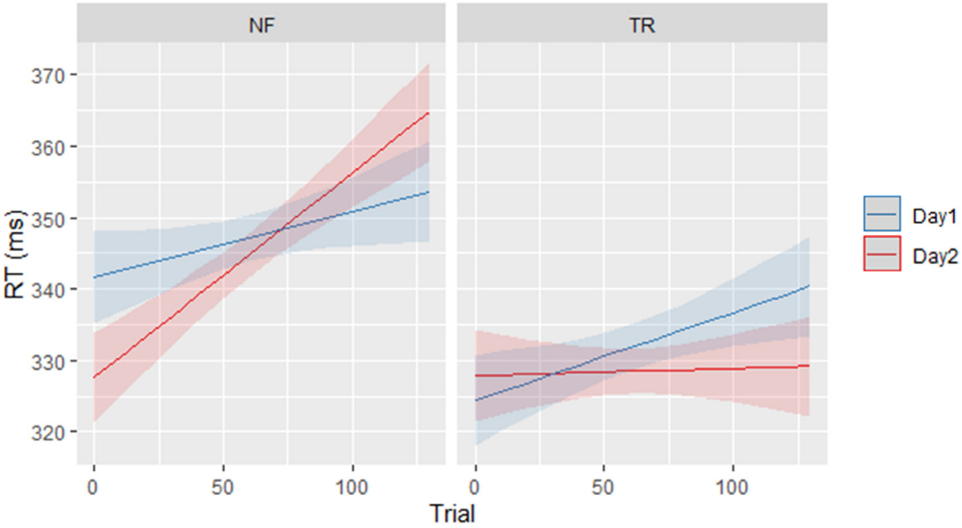

Fig. 6. Fitted model terms of the three-way interaction group x day x trial for reaction times in PVT. Blue and red curves refer to first and second applications, respectively. NF: neurofeedback group, TR: test-retest group.

SAN (activation) and DMN (deactivation) through fMRI-neurofeedback. It is worth noting that neurofeedback was able to boost the regulation ability over training, even though participants already mastered the volitional control of the differential activation in the first training run (Fig. 3A). Despite the frequently found BCI illiteracy phenomena, according to which a subset of participants fails to learn self-regulation of brain activity (Dickhaus et al., 2009), all participants in our experiment eventually succeeded in performing self-regulation. Since successful differential neurofeedback regulation can be achieved in different ways (Robineau et al., 2014; Sitaram et al., 2008), we inspected each network separately in order to better understand the neural processes underlying self-regulation.

Although we observed increased SAN activity throughout neurofeedback training runs (Fig. 3.B) and days (Fig S2.B), the activity increases in this network across neurofeedback training were only modest. On the other hand, down-regulation of the DMN increased significantly (Fig. 3.C). Hence, the learning effects in terms of increased control over the differential feedback signal were mainly due to down-regulation of the DMN, likely reflecting strategies related to the suppression of default mental processes (Dosenbach et al., 2006; Weissman et al., 2006) during self-regulation blocks.

Analyzing regionally specific (de)activations of the individual ROIs that the networks are composed of might further elucidate this result. Amongst the SAN regions, only the right intraparietal sulcus (SAN4) showed self-regulation learning effects (Fig. S3): This might be associated with enhanced top-down attentional orienting over training (Corbetta and Shulman, 2002), which is supported by the most commonly reported strategies of overt and constant focused attention on the screen elements. For the DMN, all ROIs became increasingly down-regulated across training (Fig. S4). Therefore, learning effects were observed throughout the DMN, rather than being node-specific. This was an expected result because DMN deactivations are largely task-independent, varying little in location for a wide range of tasks (Mayeli et al., 2020; Raichle et al., 2001). The larger contribution of DMN down-regulation (compared to SAN up-regulation) is in line with a study showing that DMN regions are easier to regulate through neurofeedback than other regions such as, for example, visual ROIs (Harmelech et al., 2015). This may be due to the fact that DMN processes internally generated information and, since neurofeedback control is essentially an internally driven task, it might make this network more susceptible to intentional control than an externally oriented network. Regarding the down-regulation of the DMN, an earlier neurofeedback study on meditation effects reported that only experienced meditators were able to learn to volitionally deactivate the PCC, which is an important hub of the DMN (Garrison et al., 2013). In contrast, our study shows that participants sampled not specifically from experienced meditators are also able to learn DMN deactivation through neurofeedback training, which is in line with Skouras and Scharnowski (2019) as well as Zhang et al. (2013). We also demonstrated that participants better maintained increased activity levels during the regulation epoch in aMCC after neurofeedback training, as compared to the first training run (Fig. 4). In fact, the aMCC and rIFJ were expected to exhibit sustained attention-related activity, while the rTPJ and rIPS were expected to be recruited only transiently at regulation onset (Dosenbach et al., 2006). The activity time-courses revealed that DMN deactivation was larger in late training runs than was SAN activation, mainly for the mPFC. Interestingly, aMCC, rIFJ, and rIPS showed peaks of activation related to the feedback onset, reflecting neural process of activity interruption (Dosenbach et al., 2006).

From the whole-brain activity maps of the last training runs (Fig. 5A), activations and deactivations observed after the neurofeedback training are evidently related to a neural system underpinning various aspects of attention. Activation in aMCC/preSMA (SAN1), regions related to conflict detection and solution (Weissman et al., 2006), is linked to the ability of differentiating between relevant stimulus input and distraction. Interestingly, the aMCC is a region that has been repeatedly reported in several neurofeedback studies (albeit often somewhat imprecisely labelled “anterior cingulate cortex”), indicating that it plays a role in the regulation mechanism of evaluation of feedback and explicit processing of reward (Amiez et al., 2012; Sitaram et al., 2017). We also observed activations in bilateral inferior occipital gyrus, possibly related to a better perceptual representation of behaviorally relevant stimuli (Weissman et al., 2006); bilateral thalamus, which is thought to be involved in mediating between brainstem and cortical arousal systems during sustained attention (Langner and Eickhoff, 2013); inferior frontal gyrus, which has been linked to the stimulus-driven reorienting of attention (Weissman et al., 2006); bilateral superior parietal lobule, involved in top-down attentional control (Corbetta and Shulman, 2002; Kelly et al., 2008; Miller et al., 2016). Conversely, lapses of attention have been found associated with weaker task-related DMN deactivation (Weissman et al., 2006), also present in the whole-brain results (Fig. 5A).

Because this is an attention-related neurofeedback study, some special considerations were taken concerning the experimental design. For instance, we chose intermittent (instead of continuous) feedback presentation, because this enabled our participants to temporally separate the self-regulation task and the feedback appraisal, avoiding dual-task interference (Johnson et al., 2012). Moreover, intermittent feedback prevents noisy computation of feedback by averaging and filtering more available data points, and there are no concerns about hemodynamic delay (Johnson et al., 2012). Another point was the choice of the nature of feedback computation. In theory, the anticorrelation between SAN and DMN could have been used as a functional-connectivity-based feedback alternative (Ruiz et al., 2014). However, we argue that the feedback based on network activation differences instead of correlation is preferable and more direct, as measuring correlation is noisier than measuring direct network differences. This is mainly the case when short temporal windows are used; network differences may be a more direct and instant proxy for attention manifestation than its anticorrelation. Further, although dorsal attention network and DMN are intrinsically anticorrelated, the SAN in fact combines both dorsal attention and frontoparietal control networks, possibly making their joint anticorrelation with the DMN a sub-optimal proxy target for neurofeedback.

Overall, we observed clear regionally specific activations during neurofeedback-based regulation and learning of higher differential SAN–DMN activity, which was mainly driven by the improved down-regulation of the DMN as a whole. This, in turn, might reflect the internally oriented nature of the cognitive processes presumably subserved by this network. In the SAN, only IPS showed increased activity intensity, while aMCC showed improved maintenance of sustained activity after training. Additionally, other brain regions were activated (besides the pre-selected ROIs) due to neurofeedback training, supporting attentional mechanisms and feedback appraisal and control. We conclude that the feedback approach used here was able to induce the targeted regulation, and we will now discuss the brain changes and behavioral effects induced by this training in some more detail.

4.2. Transfer of self-regulation ability

We found that the participants were able to transfer the acquired differential self-regulation ability to a no-feedback environment (Fig. 3.D–F), which is closer to real-life situations. Although there was a trend of improvement of up-regulation of SAN, no-feedback differential regulation was more significantly driven by the DMN. This result was similar to what it was observed during feedback runs. When looking at specific ROIs, transfer effects could be measured in the rIPS (SAN4) and the PCC (DMN1) (Fig. S5). As previously pointed out, top-down attention is controlled by rIPS (Corbetta and Shulman, 2002) and the PCC is known to be a hub within the DMN and plays a central role in introspective functions (Schilbach et al., 2012).

Visually comparing the whole-brain activation maps of the first and last no-feedback runs (Fig. S7) suggests that the participants used less vision-related self-regulation strategies and more strongly relied on the dorsal attention network. Although not specifically selected as a network to be activated during neurofeedback training, this network has an important role in top-down attentional control (Corbetta and Shulman, 2002).

4.3. Strategies and questionnaires

Although providing mental strategy suggestions is not necessary for learning with neurofeedback (Linden et al., 2012; Sepulveda et al., 2016; Shibata et al., 2011), we hoped to facilitate learning by providing participants with strategy suggestions related to the trained networks (Scharnowski et al., 2015). Most strategies adopted by the participants were linked to focused attention, which are related to the SAN/DMN dissociation (Fox et al., 2005; Hinds et al., 2013; Josipovic et al., 2012). Other successful strategies were more closely related to SAN functions, such as mental imagery of threatening situations, where vigilance is associated with initial shifts of attention towards the threat (Klumpp and Amir, 2009), or doing mental math, which is linked to sustained attention (Anobile et al., 2013). For baseline blocks, participants mainly adopted strategies related to DMN activation, such as planning of the future (Mason et al., 2007), reflecting on introspective thoughts (Schilbach et al., 2012), or reporting purely relaxing strategies. It is worth mentioning that very repetitive and monotonous strategies such as word repetition, counting backwards, or mentally reciting the alphabet did not work well when applied during the regulation blocks. This might be because they cause habituation, which tends to activate the DMN (Mason et al., 2007). Some participants reported mental-imagery-based strategies in both baseline and regulation blocks, whose variability is likely related to the nature of the individual internal/external imagery representation, influencing the directionality of DMN activity.

Attentional performance in real life, as assessed with the CFQ before the neurofeedback training, was not associated with self-regulation learning. Together with the fact that learning success was high in all subjects, one might speculate that SAN–DMN-based neurofeedback learning is independent of attentional traits and might also work well in clinical populations. We did not observe changes in CFQ or DSSQ scores due to neurofeedback training and controlled by the TR group (although the results of the DSSQ should be treated with caution due to the reduced sample size). While the CFQ reflects stable individual characteristics, the DSSQ reflects attentional state and is, therefore, prone to short-term fluctuation. The absence of training-induced differences in the DSSQ scores indicates that the proposed neurofeedback training does not alter subjective attentional states.

Associations between self-reported regulation ratings (control, ease, and concentration), provided after every neurofeedback training run, and self-regulation performance show how feedback was experienced by participants. The positive correlation between self-report scores related to the control over feedback and self-regulation performance indicates that participants had an authentic perception of their control over their actual regulation, demonstrating that the feedback computation techniques used and the experimental design were in fact able to provide coherent feedback. The positive correlation between the ratings of the perceived ease in controlling feedback and self-regulation performance shows that the easier it was perceived by the participants to control the feedback, the better self-regulation performance was. This, in turn, might reflect the improved ability to intentionally apply a successful modulation strategy without much subjective effort. Finally, the positive correlation between the self-report ratings of the level of concentration during neurofeedback and self-regulation performance reflects that the more participants perceived themselves as focused, the better their self-regulation was. This is hardly surprising given the networks involved, but it attests to the commitment of our participants and to the attentional nature of the strategies used for successful SAN–DMN regulation.

4.4. Behavioral effects

We observed a post-training reduction of PVT mean reaction time in early trials relative to the pre-training measurement only for the NF group, which suggests that neurofeedback training of differential SAN-DMN activity regulation can improve the performance in tasks taxing sustained attention (Fig. 6). However, this effect was temporally limited. This attentional function was the basis for the choice of networks/ROIs. The training-induced ability of differentially regulating regional brain activity, mainly driven by DMN, suggests a causal relationship with the behavioral effect of improved sustained attention performance. However, the fact that we only observed this improvement in early trials might reflect that the short duration of the training (6 min 20 s) is insufficient to convey benefits for maintaining the attentional focus over longer periods, such as the duration of the PVT (17 min), or to prevent fatigue effects over such longer time intervals. This might indicate a duration-specific feature of the neurofeedback training. By analogy, just like a training of 1 km runs does not prepare one for a marathon, our short-duration neurofeedback training might only improve sustaining attention over shorter periods. Higher mean reaction time in late trials of the PVT observed in the NF but not the TR group after training might indicate that an augmented, successful use of resources to keep the task focus (i.e., achieve low reaction times) during early trials might lead to an accelerated performance decrement towards late periods. Curiously, the TR group showed improved reaction times in late trials of the PVT during the second testing session, without neurofeedback training. This could not be explained by differences of engagement to the task, as measured by the DSSQ (although the results of the DSSQ should be treated with caution due to the reduced sample size).

We did not observe clear behavioral effects of neurofeedback training on other attentional functions. Upon closer scrutiny, the seeming improvement in mental rotation performance (see Table 1) appears to be due to the presence of outliers in the NF group (Fig. S8). The fact that IPS activation was learned through neurofeedback and that this region is closely related to mental rotation (Harris et al., 2000) suggests a causal link to the observed performance improvement through neurofeedback but should be addressed in a separate study. We also did not observe greater improvements in the combined attention scores for the NF group, as compared to the TR group, on top of the clear practice effects (Table S4). Moreover, we did not find significant correlations between neurofeedback regulation learning and attentional improvements (Table S5). Perhaps the reduction of PVT reaction time in early trials could be enhanced with a test that is more similar to the feedback provided (deBettencourt et al., 2015). Alternatively, it may signify that our kind of network/ROI training does not improve sustained attention performance in general due to narrow, highly specific links between cognitive task subprocess and particular brain regions, many of which were not included in the trained SAN ROIS. Additionally, the small to absent behavioral effects observed in this study indicate that an improvement in down-regulating the DMN is not directly related to performance and is not a sufficient condition for improved performance in the attentional functions assessed here, despite previous evidence for DMN deactivation during attentional tasks. Thus, future neurofeedback studies might consider accommodating only the SAN – but applying a more comprehensive coverage.

Another reason behind the rather small behavioral transfer effects might have been ceiling effects in regulatory abilities in the NF group. That is, participants in training group could already well control the differential activation in early neurofeedback runs (Fig. 3). This may indicate a decoupling between differential activation and behavioral performance above a certain point. On the other side, the experiment had two training sessions with a relatively short period of training (also the case in Garrison et al., 2013; Harmelech et al., 2015; Marxen et al., 2016; Scheinost et al., 2013; Sepulveda et al., 2016; Zhang et al., 2013). In Fig. 3.C, no plateauing of the learning curve can be observed, which contrarily suggests that ceiling self-regulation performance had not yet been reached and additional runs could have led to even higher levels of self-regulation competence (Robineau et al., 2014), which, in turn, might have been needed to see stronger transfer effects on attentional performance.

Finally, the limited behavioral effects of our neurofeedback training might also have been partly due to behavioral ceiling effects: healthy participants may show attentional performance levels that are too good to be significantly improved by a short-term training like the one employed here. As a corollary, the potential benefits that could be achieved through such training might be much larger in clinical populations with reduced attentional functioning. Likewise, such a clinical population also might show reduced initial competence in voluntary differential SAN–DMN regulation. In fact, the NF group showed PVT performance levels comparable to the best group in Hwang et al., 2017. Thus, despite the limited transfer effects observed here, neurofeedback training might still turn out to be effective in serving as a non-invasive and non-pharmacological tool for cognitive enhancement in patients suffering from attentional deficits (Langner and Eickhoff, 2013).

4.5. Limitations

Practice effects on performance in attention tests, as observed in the absence of neurofeedback training (Table 1), might have complicated the detection of training-induced behavioral effects. Here, we used the widely applied PEBL software (Mueller and Piper, 2014) for assessing performance by means of a computerized battery of tasks taxing various attentional functions. However, data regarding test–retest reliability of some tests included in PEBL is sparse (Piper et al., 2015), which can be problematic for repeated-measure designs like ours. On the other hand, it could be argued that noticeably improved maintenance of vigilance can only be achieved with longer regulation blocks. However, in our study, the duration of the regulation blocks was short to (1) consider participant comfort in the MR environment, to (2) be able to collect more training runs for better assessing self-regulation learning, but (3) long enough to train not only transient signal changes but also sustained activity (Dosenbach et al., 2006) (e.g., increased sustained activity in the aMCC, cf. Fig. 4).

Some of the results observed during late training runs were absent or lower for no-feedback runs after training, namely, differences of DMN deactivation (see Figs. S4 and S5) and less de-/activation clusters in whole-brain analyses (see Figs. 5 and S7). Because the second no-feedback run was performed after an entire neurofeedback training session, possible transfer effects might have been affected by fatigue towards the end of the training. In our study, we did not collect measures of fatigue during the experiment so we can only speculate about how fatigue might have affected our results. Mental fatigue and physical discomfort are common not only in neurofeedback, but in MRI experiments in general, which require minimal head movement and sometimes also a high degree of concentration (Sulzer et al., 2013). A more extensive design that repeatedly includes no-feedback runs throughout training might be suitable to address this potential confound.

Whereas the DMN ROIs were defined based on subject-specific functional localizer data, the SAN ROIs were defined based on meta-analytic coordinates. It cannot be ruled out that this difference in ROI definition might have contributed to the stronger learning effect observed in the DMN compared to the SAN. Like other factors such as ROI size, ROI shape, etc., the influences that functional vs. meta-analytical factors might have on neurofeedback learning have not been empirically investigated. A very recently published meta-analysis points towards the importance of functionally defined ROIs (Haugg et al., 2020), whereas a current mega-analysis was unable to reveal potential benefits of functionally defined ROIs (Haugg et al., 2019). In absence of empirical data, one might speculate that the functional localization facilitates performance, particularly because it allows for subject-specific ROIs. Meta-analytic coordinates are based on group statistics, and one has to a priori select suitable information from existing studies. In our case, the SAN ROIs were defined based on our own work (Langner and Eickhoff, 2013), but other studies would have also been suitable (e.g., Rosenberg et al., 2016, or Falahpour et al., 2018, or Lawrence et al., 2003). One the other hand, also functional localizer tasks can vary. For example, whereas ICA analysis of resting state fMRI for the definition of DMN ROIs is relatively standardized, various tasks are aiming at the different facets of sustained attention. Running several functional localizers to capture the multiple functional aspects of such complex cognitive processes can be time consuming, potentially causing fatigue or taking away valuable scanning time from actual neurofeedback training. Hence, in such cases a meta-analytically derived ROI definition can be more efficient and potentially minimizes task-specific biases resulting from idiosyncrasies of any single task. Future research might more systematically address the question of how much different approaches to defining functional ROIs influence the success of neurofeedback learning.

This study was designed to learning control over the SAN-DMN difference to benefit sustained attention (Hinds et al., 2013; Kelly et al., 2008; Lawrence et al., 2003). The functional dichotomy between dorsal attention and default-mode networks is also reflected by the different instructions during regulation and baseline blocks. Therefore, the phenomenology of this experiment is linked to both baseline and regulation blocks and associated with the bidirectionality of the modulation: strategies that either activate SAN, deactivate DMN, or both were equally valid. It is also noteworthy that reported strategies for the baseline varied more, which might be due to instructions for the baseline block being less specific. Nevertheless, despite their plurality, the mental strategies during baseline shared mind-wandering characteristics in the sense that they were task-unrelated thoughts (Seli et al., 2018).

Finally, the design of this study did not allow for an optimal control of all training parameters. In particular, as only one group performed veridical feedback-based training in the MR scanner, the improved sustained attention in early PVT trials observed after training could be a result of differences of motivation, physiological specificity, placebo effects etc. (Sorger et al., 2019; Thibault et al., 2017). The only control group was of the type no-training control, solely providing a comparative baseline for behavioral effects.

4.6. Conclusions

To the best of our knowledge, this is the first study to show that individuals can acquire intentional control over the activity difference between SAN and DMN regions through fMRI-neurofeedback training. This differential network approach might make self-regulation learning more efficient than using a single-network approach, and it could also be applicable to other network interactions. Apart from the expected de-/activations due to neurofeedback training, activity related to training was observed in occipital, parietal, and frontal areas, and thalamus. These structures have been associated with sustaining attention, reorientation and arousal, feedback control, and imaginary strategies. Although some sustained-attention improvement due to neurofeedback training was observed, the effects were temporally limited and other training-induced general attentional improvements were absent. These limited effects were likely due to several factors, among them the limited reliability of performance measures, the limited number of neurofeedback training runs, and the short duration of the runs. As these obstacles can be overcome in future studies, our finding that differential self-regulation of the SAN and DMN can be learned indicates that this novel approach might become a non-invasive and non-pharmacological tool to mitigate attention deficits in neurological and psychiatric population.

Declaration of Competing Interest

The authors declare no competing interests. All obtained results and scripts used for the data analysis are available on the public GitHub repository: https://github.com/gustavopamplona/NF_ATT_public_data.

Acknowledgments

We thank Prof. Jorge Moll, Dr. Griselda Garrido, Dr. Rodrigo Basilio, and Dr. Philipp Stämpfli for technical support. We also thank Drs. Arron Metcalfe, Sofia Osimo, and Simon Schwab for statistical advice. This work was supported by the Brazilian National Council for Scientific and Technological Development (CNPq), the Brazilian National Council for the Improvement of Higher Education (CAPES), the Swiss National Science Foundation (BSSG10_155915, 100014_178841, 32003B_166566, and PP00P1_170506/1), the Foundation for Research in Science and the Humanities at the University of Zurich (STWF-17-012), the Baugarten Stiftung, and the Swiss Government.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117194.

References

Alegria, A.A., Wulff, M., Brinson, H., Barker, G.J., Norman, L.J., Brandeis, D., Stahl, D., David, A.S., Taylor, E., Giampietro, V., Rubia, K., 2017. Real-time fMRI neurofeedback in adolescents with attention deficit hyperactivity disorder. Hum. Brain Mapp. 38, 3190–3209. https://doi.org/10.1002/hbm.23584.

Amiez, C., Sallet, J., Procyk, E., Petrides, M., 2012. Modulation of feedback related activity in the rostral anterior cingulate cortex during trial and error exploration. Neuroimage 63, 1078–1090. https://doi.org/10.1016/j.neuroimage.2012.06.023.

Anderson, K., Deane, K., Lindley, D., Loucks, B., Veach, E., 2012. The effects of time of day and practice on cognitive abilities: the PEBL Tower of London, Trail-making, and Switcher tasks.

Andrews-Hanna, J.R., Smallwood, J., Spreng, R.N., 2014. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann. N. Y. Acad. Sci. 1316, 29–52. https://doi.org/10.1111/nyas.12360.

Anobile, G., Stievano, P., Burr, D., 2013. Visual sustained attention and numerosity sensitivity correlate with math achievement in children. J. Exp. Child Psychol. 116, 380–391. https://doi.org/10.1016/j.jecp.2013.06.006.

Bellgrove, M.A., Hawi, Z., Kirley, A., Gill, M., Robertson, I.H., 2005. Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: Sustained attention, response variability and spatial attentional asymmetries in relation to dopamine transporter (DAT1) genotype. Neuropsychologia 43, 1847–1857. https://doi.org/10.1016/j.neuropsychologia.2005.03.011.

Berteau-Pavy, D., Raber, J., Piper, B., 2011. Contributions of Age, But Not Sex, to Mental Rotation Performance in a Community Sample PEBL Technical Report Series.

Brefczynski-Lewis, J.A., Lutz, A., Schaefer, H.S., Levinson, D.B., Davidson, R.J., 2007. Neural correlates of attentional expertise in long-term meditation practitioners. Proc. Natl. Acad. Sci. 104, 11483–11488. https://doi.org/10.1073/pnas.0606552104.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.-B., 2002. Region of interest analysis using an SPM toolbox. In: 8th International Conference on Functional Mapping of the Human Brain. Sendai, p. 497.

Brewer, J.A., Worhunsky, P.D., Gray, J.R., Tang, Y.-Y., Weber, J., Kober, H., 2011. Meditation experience is associated with differences in default mode network activity and connectivity. Proc. Natl. Acad. Sci. 108, 20254–20259. https://doi.org/10.1073/pnas.1112029108.

Broadbent, D.E., Cooper, P.F., FitzGerald, P., Parkes, K.R., 1982. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br. J. Clin. Psychol. 21, 1–16. https://doi.org/10.1111/j.2044-8260.1982.tb01421.x.

Cohen, J., Cohen, P., 1983. Applied Multiple Regression/correlation Analysis for the Behavioral Sciences. Taylor & Francis Group https://doi.org/10.4324/9780203774441.

Conners, C.K., Epstein, J.N., Angold, A., Klaric, J., 2003. Continuous performance test performance in a normative epidemiological sample. J. Abnorm. Child Psychol. 31, 555–562. https://doi.org/10.1023/A:1025457300409.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215. https://doi.org/10.1038/nrn755.

Cunnington, R., Windischberger, C., Deecke, L., Moser, E., 2002. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. Neuroimage 15, 373–385. https://doi.org/10.1006/nimg.2001.0976.

deBettencourt, M.T., Cohen, J.D., Lee, R.F., Norman, K.A., Turk-Browne, N.B., Cohen, D, J., Lee, R.F., A Norman, K., B Turk-Browne, N., 2015. Closed-loop training of attention with real-time brain imaging. Nat. Neurosci. 18, 470–478. https://doi.org/10.1038/nn.3940.

Dosenbach, N.U.F., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cognit. Sci. 12, 99–105. https://doi.org/10.1016/j.tics.2008.01.001.

Dosenbach, N.U.F., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E., 2006. A core system for the implementation of task sets. Neuron 50, 799–812. https://doi.org/10.1016/j.neuron.2006.04.031.

Emmert, K., Kopel, R., Koush, Y., Maire, R., Senn, P., Van De Ville, D., Haller, S., 2017. Continuous vs. intermittent neurofeedback to regulate auditory cortex activity of tinnitus patients using real-time fMRI – a pilot study. NeuroImage Clin. 14, 97–104. https://doi.org/10.1016/j.nicl.2016.12.023.

Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion 7, 336–353. https://doi.org/10.1037/1528-3542.7.2.336.

Falahpour, M., Chang, C., Wong, C.W., Liu, T.T., 2018. Template-based prediction of vigilance fluctuations in resting-state fMRI. Neuroimage 174, 317–327. https://doi.org/10.1016/j.neuroimage.2018.03.012.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I., 2002. Testing the efficiency and independence of attentional networks. J. Cognit. Neurosci. 14, 340–347. https://doi.org/10.1162/089892902317361886.

Finn, E.S., Shen, X., Scheinost, D., Rosenberg, M.D., Huang, J., Chun, M.M., Papademetris, X., Constable, R.T., 2015. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat. Neurosci. 1–11. https://doi.org/10.1038/nn.4135.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. 102, 9673–9678. https://doi.org/10.1073/pnas.0504136102.

Garrison, K.A., Scheinost, D., Worhunsky, P.D., Elwafi, H.M., Thornhill, T.A., Thompson, E., Saron, C., Desbordes, G., Kober, H., Hampson, M., Gray, J.R., Constable, R.T., Papademetris, X., Brewer, J.A., 2013. Real-time fMRI links subjective experience with brain activity during focused attention. Neuroimage 81, 110–118. https://doi.org/10.1016/j.neuroimage.2013.05.030.

Green, M., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330. https://doi.org/10.1176/ajp.153.3.321.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. 100, 253–258. https://doi.org/10.1073/pnas.0135058100.

Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E., 2001. Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. Proc. Natl. Acad. Sci. 98, 4259–4264. https://doi.org/10.1073/pnas.071043098.

Harmelech, T., Friedman, D., Malach, R., 2015. Differential magnetic resonance neurofeedback modulations across extrinsic (Visual) and intrinsic (default-mode) nodes of the human cortex. J. Neurosci. 35, 2588–2595. https://doi.org/10.1523/jneurosci.3098-14.2015.

Harris, I.M., Egan, G.F., Sonkkila, C., Tochon-Danguy, H.J., Paxinos, G., Watson, J.D.G., 2000. Selective right parietal lobe activation during mental rotation: a parametric PET study. Brain 123, 65–73. https://doi.org/10.1093/brain/123.1.65.

Haugg, A., Sladky, R., Skouras, S., McDonald, A., Craddock, C., Kirschner, M., Herdener, M., Koush, Y., Papoutsi, M., Keynan, J.N., Hendler, T., Kadosh, K.C., Zich, C., MacInnes, J., Adcock, A., Dickerson, K., Chen, N.-K., Young, K., Bodurka, J., Yao, S., Becker, B., Auer, T., Schweizer, R., Pamplona, G., Emmert, K., Haller, S., Van De Ville, D., Blefari, M.-L., Kim, D.-Y., Lee, J.-H., Marins, T., Fukuda, M., Sorger, B., Kamp, T., Liew, S.-L., Veit, R., Spetter, M., Weiskopf, N., Scharnowski, F., 2020. Can we predict real-time fMRI neurofeedback learning success from pre-training brain activity? Hum. Brain Mapp..

Haugg, A., Steryl, D., Götzendorfer, S., Lor, C., Nicholson, A., Sladky, R., Skouras, S., McDonald, A., Craddock, C., Hellrung, L., Kirschner, M., Herdener, M., Koush, Y., Keynan, J., Hendler, T., Kadosh, K., Zich, C., MacInnes, J., Adcock, A., Dickerson, K., Chen, N.-K., Young, K., Bodurka, J., Marxen, M., Shuxia, Y., Becker, B., Auer, T., Schweizer, R., Pamplona, G., Lanius, R., Emmert, K., Haller, S., Van De Ville, D., Kim, D.-Y., Lee, J.-H., Marins, T., Fukuda, M., Sorger, B., Kamp, T., Papoutsi, M., Liew, S.-L., Veit, R., Spetter, M., Weiskopf, N., Scharnowski, F., 2019. Factors influencing neurofeedback learning – a machine learning mega-analysis. Real-Time Functional Imaging and Neurofeedback. Maastricht, The Netherlands.

Hellrung, L., Dietrich, A., Hollmann, M., Pleger, B., Kalberlah, C., Roggenhofer, E., Villringer, A., Horstmann, A., 2018. Intermittent compared to continuous real-time fMRI neurofeedback boosts control over amygdala activation. Neuroimage 166, 198–208. https://doi.org/10.1016/j.neuroimage.2017.10.031.

Helton, W.S., Hollander, T.D., Warm, J.S., Tripp, L.D., Parsons, K., Matthews, G., Dember, W.N., Parasuraman, R., Hancock, P.a, 2007. The abbreviated vigilance task and cerebral hemodynamics. J. Clin. Exp. Neuropsychol. 29, 545–552. https://doi.org/10.1080/13803390600814757.

Hinds, O., Ghosh, S., Thompson, T.W., Yoo, J.J., Whitfield-Gabrieli, S., Triantafyllou, C., Gabrieli, J.D.E., 2011. Computing moment-to-moment BOLD activation for real-time neurofeedback. Neuroimage 54, 361–368. https://doi.org/10.1016/j.neuroimage.2010.07.060.

Hinds, O., Thompson, T.W., Ghosh, S., Yoo, J.J., Whitfield-Gabrieli, S., Triantafyllou, C., Gabrieli, J.D.E., 2013. Roles of default-mode network and supplementary motor area in human vigilance performance: evidence from real-time fMRI. J. Neurophysiol. 109, 1250–1258. https://doi.org/10.1152/jn.00533.2011.

Hwang, J., Castelli, D.M., Gonzalez-Lima, F., 2017. The positive cognitive impact of aerobic fitness is associated with peripheral inflammatory and brain-derived neurotrophic biomarkers in young adults. Physiol. Behav. 179, 75–89. https://doi.org/10.1016/j.physbeh.2017.05.011.

Jang, J.H., Jung, W.H., Kang, D.H., Byun, M.S., Kwon, S.J., Choi, C.H., Kwon, J.S., 2011. Increased default mode network connectivity associated with meditation. Neurosci. Lett. 487, 358–362. https://doi.org/10.1016/j.neulet.2010.10.056.

Johnson, K.A., Hartwell, K., Lematty, T., Borckardt, J., Morgan, P.S., Govindarajan, K., Brady, K., George, M.S., 2012. Intermittent “Real-time” fMRI feedback is superior to continuous presentation for a motor imagery task: a pilot study. J. Neuroimaging 22, 58–66. https://doi.org/10.1111/j.1552-6569.2010.00529.x.

Josipovic, Z., Dinstein, I., Weber, J., Heeger, D.J., 2012. Influence of meditation on anti-correlated networks in the brain. Front. Hum. Neurosci. 5, 1–11. https://doi.org/10.3389/fnhum.2011.00183.

Kasper, L., Bollmann, S., Diaconescu, A.O., Hutton, C., Heinzle, J., Iglesias, S., Hauser, T.U., Sebold, M., Manjaly, Z.-M., Pruessmann, K.P., Stephan, K.E., 2017. The PhysIO toolbox for modeling physiological noise in fMRI data. J. Neurosci. Methods 276, 56–72. https://doi.org/10.1016/j.jneumeth.2016.10.019.

Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2008. Competition between functional brain networks mediates behavioral variability. Neuroimage 39, 527–537. https://doi.org/10.1016/j.neuroimage.2007.08.008.

Klumpp, H., Amir, N., 2009. Examination of vigilance and disengagement of threat in social anxiety with a probe detection task. Anxiety Stress Coping 22, 283–296. https://doi.org/10.1080/10615800802449602.

Koush, Y., Ashburner, J., Prilepin, E., Sladky, R., Zeidman, P., Bibikov, S., Scharnowski, F., Nikonorov, A., De Ville, D.Van, 2017a. OpenNFT: an open-source Python/Matlab framework for real-time fMRI neurofeedback training based on activity, connectivity and multivariate pattern analysis. Neuroimage 156, 489–503. https://doi.org/10.1016/j.neuroimage.2017.06.039.

Koush, Y., Ashburner, J., Prilepin, E., Sladky, R., Zeidman, P., Bibikov, S., Scharnowski, F., Nikonorov, A., Van De Ville, D., 2017b. Real-time fMRI data for testing OpenNFT functionality. Data Brief 14, 344–347. https://doi.org/10.1016/j.dib.2017.07.049.

Koush, Y., Zvyagintsev, M., Dyck, M., Mathiak, K.A., Mathiak, K., 2012. Signal quality and Bayesian signal processing in neurofeedback based on real-time fMRI. Neuroimage 59, 478–489. https://doi.org/10.1016/j.neuroimage.2011.07.076.

Langner, R., Eickhoff, S.B., 2013. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol. Bull. 139, 870–900. https://doi.org/10.1037/a0030694.

Lawrence, N.S., Ross, T.J., Hoffmann, R., Garavan, H., Stein, E.A., 2003. Multiple neuronal networks mediate sustained attention. J. Cognit. Neurosci. 15, 1028–1038. https://doi.org/10.1162/089892903770007416.

Linden, D.E.J., Habes, I., Johnston, S.J., Linden, S., Tatineni, R., Subramanian, L., Sorger, B., Healy, D., Goebel, R., 2012. Real-time self-regulation of emotion networks in patients with depression. PLoS One 7, 1–10. https://doi.org/10.1371/journal.pone.0038115.

Lindquist, M.A., 2008. The statistical analysis of fMRI data. Stat. Sci. 23, 439–464. https://doi.org/10.1214/09-STS282.

Loh, S., Lamond, N., Dorrian, J., Roach, G., Dawson, D., 2004. The validity of psychomotor vigilance tasks of less than 10-minute duration. Behav. Res. Methods Instrum. Comput. 36, 339–346. https://doi.org/10.3758/BF03195580.

Manna, A., Raffone, A., Perrucci, M.G., Nardo, D., Ferretti, A., Tartaro, A., Londei, A., Gratta, C.Del, Belardinelli, M.O., Romani, G.L., 2010. Neural correlates of focused attention and cognitive monitoring in meditation. Brain Res. Bull. 82, 46–56. https://doi.org/10.1016/j.brainresbull.2010.03.001.

Marxen, M., Jacob, M.J., Müller, D.K., Posse, S., Ackley, E., Hellrung, L., Riedel, P., Bender, S., Epple, R., Smolka, M.N., 2016. Amygdala regulation following fMRI-neurofeedback without instructed strategies. Front. Hum. Neurosci. 10, 1–14. https://doi.org/10.3389/fnhum.2016.00183.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315, 393–395. (80-.) https://doi.org/10.1126/science.1131295 .

Matthews, G., Joyner, L., Gilliand, K., Campbell, S.E., Falconer, S., Huggins, J., 1999. Validation of a comprehensive stress state questionnaire – towards a state “big three”? Personal. Psychol. Eur. 7, 335–350. https://doi.org/10.1177/154193120404801107.

Mayeli, A., Misaki, M., Zotev, V., Tsuchiyagaito, A., Al Zoubi, O., Phillips, R., Smith, J., Stewart, J.L., Refai, H., Paulus, M.P., Bodurka, J., 2020. Self-regulation of ventromedial prefrontal cortex activation using real-time fMRI neurofeedback—influence of default mode network. Hum. Brain Mapp. 41, 342–352. https://doi.org/10.1002/hbm.24805.

Miller, K.L., Alfaro-Almagro, F., Bangerter, N.K., Thomas, D.L., Yacoub, E., Xu, J., Bartsch, A.J., Jbabdi, S., Sotiropoulos, S.N., Andersson, J.L.R., Griffanti, L., Douaud, G., Okell, T.W., Weale, P., Dragonu, I., Garratt, S., Hudson, S., Collins, R., Jenkinson, M., Matthews, P.M., Smith, S.M., 2016. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. 19, 1523–1536. https://doi.org/10.1038/nn.4393.

Mueller, S.T., Piper, B.J., 2014. The psychology experiment building language (PEBL) and PEBL test battery. J. Neurosci. Methods 222, 250–259. https://doi.org/10.1016/j.jneumeth.2013.10.024.

O’Keeffe, F.M., Murray, B., Coen, R.F., Dockree, P.M., Bellgrove, M.A., Garavan, H., Lynch, T., Robertson, I.H., 2007. Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. Brain 130, 753–764. https://doi.org/10.1093/brain/awl367.

Ogg, R.J., Zou, P., Allen, D.N., Hutchins, S.B., Dutkiewicz, R.M., Mulhern, R.K., 2008. Neural correlates of a clinical continuous performance test. Magn. Reson. Imaging 26, 504–512. https://doi.org/10.1016/j.mri.2007.09.004.

Paas, F.G.W.C., Van Merriënboer, J.J.G., 1993. The efficiency of instructional conditions: an approach to combine mental effort and performance measures. Hum. Factors 35, 737–743. https://doi.org/10.1177/001872089303500412.

Pamplona, G.S.P., Vieira, B.H., Scharnowski, F., Salmon, C.E.G., 2020. Personode: a toolbox for ICA map classification and individualized ROI definition. Neuroinformatics 18, 339–349. https://doi.org/10.1007/s12021-019-09449-4.

Piper, B., Mueller, S.T., Talebzadeh, S., Ki, M.J., 2016. Evaluation of the validity of the Psychology Experiment Building Language tests of vigilance, auditory memory, and decision making. PeerJ 2016, e1772. https://doi.org/10.7717/peerj.1772.

Piper, B.J., Mueller, S.T., Geerken, A.R., Dixon, K.L., Kroliczak, G., Olsen, R.H.J., Miller, J.K., 2015. Reliability and validity of neurobehavioral function on the Psychology Experimental Building Language test battery in young adults. PeerJ 3, e1460. https://doi.org/10.7717/peerj.1460.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. 98, 676–682. https://doi.org/10.1073/pnas.98.2.676.

Robertson, I.H., 2003. The absent mind: attention and error. Psychologist 16, 476–479.

Robineau, F., Rieger, S.W., Mermoud, C., Pichon, S., Koush, Y., Van De Ville, D., Vuilleumier, P., Scharnowski, F., 2014. Self-regulation of inter-hemispheric visual cortex balance through real-time fMRI neurofeedback training. Neuroimage 100, 1–14. https://doi.org/10.1016/j.neuroimage.2014.05.072.

Rosenberg, M.D., Finn, E.S., Scheinost, D., Papademetris, X., Shen, X., Constable, R.T., Chun, M.M., 2016. A neuromarker of sustained attention from whole-brain functional connectivity. Nat. Neurosci. 19, 165–171. https://doi.org/10.1038/nn.4179.

Ruiz, S., Buyukturkoglu, K., Rana, M., Birbaumer, N., Sitaram, R., 2014. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. Biol. Psychol. 95, 4–20. https://doi.org/10.1016/j.biopsycho.2013.04.010.

Scharnowski, F., Hutton, C., Josephs, O., Weiskopf, N., Rees, G., 2012. Improving visual perception through neurofeedback. J. Neurosci. 32, 17830–17841. https://doi.org/10.1523/JNEUROSCI.6334-11.2012.

Scharnowski, F., Veit, R., Zopf, R., Studer, P., Bock, S., Diedrichsen, J., Goebel, R., Mathiak, K., Birbaumer, N., Weiskopf, N., 2015. Manipulating motor performance and memory through real-time fMRI neurofeedback. Biol. Psychol. 108, 85–97. https://doi.org/10.1016/J.BIOPSYCHO.2015.03.009.

Scheinost, D., Stoica, T., Saksa, J., Papademetris, X., Constable, R.T., Pittenger, C., Hampson, M., 2013. Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. Transl. Psychiatry 3, e250. https://doi.org/10.1038/tp.2013.24.

Schilbach, L., Bzdok, D., Timmermans, B., Fox, P.T., Laird, A.R., Vogeley, K., Eickhoff, S.B., 2012. Introspective minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One 7, 1–10. https://doi.org/10.1371/journal.pone.0030920.

Seli, P., Kane, M., Smallwood, J., Schacter, D., Maillet, D., Schooler, J., Smilek, D., 2018. Mind-wandering as a natural kind: a family-resemblances view. Trends Cognit. Sci. 22. https://doi.org/10.1016/j.tics.2018.03.010.

Sepulveda, P., Sitaram, R., Rana, M., Montalba, C., Tejos, C., Ruiz, S., 2016. How feedback, motor imagery, and reward influence brain self-regulation using real-time fMRI. Hum. Brain Mapp. 37, 3153–3171. https://doi.org/10.1002/hbm.23228.

Shen, X., Tokoglu, F., Papademetris, X., Constable, R.T., 2013. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. Neuroimage 82, 403–415. https://doi.org/10.1016/j.neuroimage.2013.05.081.

Shibata, K., Watanabe, T., Sasaki, Y., Kawato, M., 2011. Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. Science 334, 1413–1415. (80-.) https://doi.org/10.1126/science.1212003 .

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskopf, N., Blefari, M.L., Rana, M., Oblak, E., Birbaumer, N., Sulzer, J., 2017. Closed-loop brain training: the science of neurofeedback. Nat. Rev. Neurosci. 18, 86–100. https://doi.org/10.1038/nrn.2016.164.

Sitaram, R., Weiskopf, N., Caria, A., Veit, R., Erb, M., Birbaumer, N., 2008. fMRI brain-computer interfaces. IEEE Signal Process. Mag. 25, 95–106. https://doi.org/10.1109/MSP.2008.4408446.

Skouras, S., Scharnowski, F., 2019. The effects of psychiatric history and age on self-regulation of the default mode network. Neuroimage 198, 150–159. https://doi.org/10.1016/j.neuroimage.2019.05.008.

Sohn, W., Yoo, K., Lee, Y.-B., Seo, S., Na, D., Jeong, Y., 2015. Influence of ROI selection on resting state functional connectivity: an individualized approach for resting state fMRI analysis. Front. Neurosci. 9, 280. https://doi.org/10.3389/fnins.2015.00280.

Sood, A., Jones, D.T., 2013. On mind wandering, attention, brain networks, and meditation. Explor. J. Sci. Heal. 9, 136–141. https://doi.org/10.1016/j.explore.2013.02.005.

Sorger, B., Scharnowski, F., Linden, D.E.J., Hampson, M., Young, K.D., 2019. Control freaks: towards optimal selection of control conditions for fMRI neurofeedback studies. Neuroimage 186, 256–265. https://doi.org/10.1016/j.neuroimage.2018.11.004.

Spreng, R., 2012. The fallacy of a “task-negative” network. Front. Psychol. 3, 145. https://doi.org/10.3389/fpsyg.2012.00145.

Sulzer, J., Haller, S., Scharnowski, F., Weiskopf, N., Birbaumer, N., Blefari, M.L., Bruehl, A.B., Cohen, L.G., DeCharms, R.C., Gassert, R., Goebel, R., Herwig, U., LaConte, S., Linden, D., Luft, A., Seifritz, E., Sitaram, R., 2013. Real-time fMRI neurofeedback: progress and challenges. Neuroimage 76, 386–399. https://doi.org/10.1016/j.neuroimage.2013.03.033.

Tanji, J., 1994. The supplementary motor area in the cerebral cortex. Neurosci. Res. 19, 251–268. https://doi.org/10.1016/0168-0102(94)90038-8.

Thibault, R.T., Lifshitz, M., Raz, A., 2017. Neurofeedback or neuroplacebo? Brain 140, 862–864. https://doi.org/10.1093/brain/awx033.

Thompson, G.J., Magnuson, M.E., Merritt, M.D., Schwarb, H., Pan, W.J., Mckinley, A., Tripp, L.D., Schumacher, E.H., Keilholz, S.D., 2013. Short-time windows of correlation between large-scale functional brain networks predict vigilance intraindividually and interindividually. Hum. Brain Mapp. 34, 3280–3298. https://doi.org/10.1002/hbm.22140.

Vollebregt, M.A., Dongen-boomsma, M.Van, Buitelaar, J.K., Slaats-willemse, D., 2014. Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study. J. Child Psychol. Psychiatry 5, 460–472. https://doi.org/10.1111/jcpp.12143.

Weiskopf, N., Scharnowski, F., Veit, R., Goebel, R., Birbaumer, N., Mathiak, K., 2004. Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI). J. Physiol. Paris 98, 357–373. https://doi.org/10.1016/j.jphysparis.2005.09.019.

Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9, 971–978. https://doi.org/10.1038/nn1727.

West, S.G., Aiken, L.S., Krull, J.L., 1996. Experimental personality designs: analyzing categorical by continuous variable interactions. J. Pers. 64, 1–48. https://doi.org/10.1111/j.1467-6494.1996.tb00813.x.

Wilmer, H.H., Sherman, L.E., Chein, J.M., 2017. Smartphones and cognition: a review of research exploring the links between mobile technology habits and cognitive functioning. Front. Psychol. 8, 605. https://doi.org/10.3389/fpsyg.2017.00605.

Wolff, N., Mückschel, M., Beste, C., 2017. Neural mechanisms and functional neuroanatomical networks during memory and cue-based task switching as revealed by residue iteration decomposition (RIDE) based source localization. Brain Struct. Funct. 222, 3819–3831. https://doi.org/10.1007/s00429-017-1437-8.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165. https://doi.org/10.1152/jn.00338.2011.

Zhang, G., Zhang, H., Li, X., Zhao, X., Yao, L., Long, Z., 2013. Functional alteration of the DMN by learned regulation of the PCC using real-time fMRI. IEEE Trans. Neural Syst. Rehabil. Eng. 21, 595–606. https://doi.org/10.1109/TNSRE.2012.2221480.

Zilverstand, A., Sorger, B., Slaats-Willemse, D., Kan, C.C., Goebel, R., Buitelaar, J.K., 2017. fMRI neurofeedback training for increasing anterior cingulate cortex activation in adult attention deficit hyperactivity disorder. An exploratory randomized, single-blinded study. PLoS One 12, e0170795. https://doi.org/10.1371/journal.pone.0170795.