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Rapid acquisition of dynamic control over DLPFC using real-time fMRI feedback

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Abstract

It has been postulated that gaining control over activity in the dorsolateral prefrontal cortex (DLPFC), a key region of the working memory brain network, may be beneficial for cognitive performance and treatment of certain psychiatric disorders. Several studies have reported that, with neurofeedback training, subjects can learn to increase DLPFC activity. However, improvement of dynamic control in terms of switching between low and high activity in DLPFC brain states may potentially constitute more effective self-regulation. Here, we report on feasibility of obtaining dynamic control over DLPFC, meaning the ability to both in- and decrease activity at will, within a single functional MRI scan session. Two groups of healthy volunteers (N=24) were asked to increase and decrease activity in the left DLPFC as often as possible during fMRI scans (at 7 Tesla), while receiving real-time visual feedback. The experimental group practiced with real-time feedback, whereas the control group received sham feedback. The experimental group significantly increased the speed of intentionally alternating DLPFC activity, while performance of the control group did not change. Analysis of the characteristics of the BOLD signal during successful trials revealed that training with neurofeedback predominantly reduced the time for the DLPFC to return to baseline after activation. These results provide a preliminary indication that people may be able to learn to dynamically down-regulate the level of physiological activity in the DLPFC, and may have implications for psychiatric disorders where DLPFC plays a role.

Keywords

Dorsolateral Prefrontal Cortex; fMRI; neurofeedback; biofeedback; working memory function; activity regulation

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Contributors

Authors VandenBoom, Jansma and Ramsey designed the study, Author Jansma wrote the protocol. Author Van den Boom managed the literature searches and analyses. Authors Van den Boom and Jansma undertook the statistical analysis, and author Van den Boom wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

1 Introduction

Working memory (WM) function is conceptually associated with temporary information storage and processing (Baddeley, 2003). Many higher cognitive abilities such as reasoning, planning and problem solving are dependent on WM. A number of behavioral studies have shown that both the storage capacity and the ability to process information are limited (Baddeley and Hitch, 1974; Cowan, 2001; Miller, 1956). With practice of certain WM tasks, performance improves, while brain activity in the associated network of regions declines (Jansma et al., 2001), suggesting that brain activity adjusts to the need for cognitive control (Ramsey et al., 2004). Various psychiatric disorders have been associated with WM dysfunction, in which the dorsolateral prefrontal cortex (DLPFC), a key region of the WM system, could play a role. Patients with schizophrenia show impaired WM performance, where the DLPFC responds differently to WM demands in comparison to healthy people (Jansma et al., 2004; Potkin et al., 2009; van Raalten et al., 2008). Individuals with depression show increased DLPFC activity on WM tasks (Harvey et al., 2005; Wagner et al., 2006). For Major Depression, neuromodulation of the DLPFC using rTMS is currently applied therapeutically (Berlim et al., 2014, 2013). Disruption of WM function has also been associated with drug dependence (Goldstein and Volkow, 2011). As such, the DLPFC can be regarded as a potential target for treatment of WM deficits associated with psychiatric disorders, where the ability to learn to self-regulate activity of the DLPFC is of interest for the development of novel treatment options.

The results of neurofeedback studies suggest the possibility that WM function can be improved through the use of neurofeedback in real-time (rt-) fMRI experiments (Thibault et al., 2016). In such experiments, the blood oxygenation level-dependent (BOLD) signal or pattern in a specific region of interest (ROI) is translated into information that can be used by the subject in real time (Weiskopf, 2012). It has already been shown that self-regulation of activity through neurofeedback can be trained for brain areas such as the anterior cingulate cortex (ACC) (Hamilton et al., 2011), amygdala (Zotef et al., 2011), premotor areas (Sitaram et al., 2012), visuospatial attention (Andersson et al., 2012, 2011) and auditory cortex (Haller et al., 2010).

The DLPFC has been attributed a pivotal role in WM (D'Esposito et al., 1995; Jansma et al., 2013; Ramsey et al., 2006; Wager and Smith, 2003). Neurofeedback studies that target the left DLPFC have predominantly focused on the possibility to increase activity (Shen et al., 2015; Sherwood et al., 2016; Zhang et al., 2015, 2013). However, WM function may also benefit from direct dynamic control of brain activity levels, in other words the capability to increase and decrease activity in brain regions when needed.

In the current study, we used neurofeedback to examine the possibility to learn to dynamically control DLPFC activity. The magnitude of left DLPFC activity, generated during performance of a WM task in a 7-Tesla MRI scanner, was visually presented to healthy volunteers in real time. Training encompassed practice of control over a figurine in a game setting, where the level of activity in left DLPFC determined the vertical position of the figurine. A control group performed the identical task, but with sham instead of real

feedback. We used a 7 Tesla MRI scanner to obtain a sufficiently accurate and strong measure of local neural activity to allow for real-time dynamic control learning.

The DLPFC is part of the dorsolateral prefrontal circuit, which projects from the DLPFC to the dorsolateral caudate nucleus, the lateral dorsomedial globus pallidus and connects via the ventral anterior and mediodorsal thalamus back to the DLPFC. It is possible that neurofeedback on the DLPFC influences other regions in this circuit. Therefore we perform a cluster analysis to see if other brain regions are affected.

We hypothesized that subjects would be able to learn to regulate DLPFC activity using the information provided by the rt-fMRI neurofeedback. In order to understand how neurofeedback practice affected the ability to regulate activity, we analyzed the temporal characteristics of the BOLD signal before and after the practice periods. In addition, we explored whether other regions besides the DLPFC are affected as a result of the neurofeedback.

2 Experimental procedures

Participants

Twenty-four healthy participants between the age of 19 and 30 years (11 male, 13 female; mean age 23.54; SD 2.81 years) were included in the study after giving written informed consent. Exclusion criteria were history of psychiatric illness, pregnancy, metal objects in or around the body or claustrophobia. The study was approved by the local medical ethics committee, in accordance with the Declaration of Helsinki (2013). One participant was excluded from analysis due to scanner failure. Participants were randomly assigned to an experimental or control group. Thirteen participants were included in the experimental group and eleven in the control group. The groups are not exactly equal due to dropout resulting from MRI scanner issues.

MRI

fMRI was performed using a 7T Philips Achieva system, with a 32-channel headcoil. Functional data was recorded using an EPI sequence (TR/TE: 2.0 s/25 ms, FA: 70, 39-axial slices, acquisition matrix 112 voxels x 112 voxels, slice thickness 2.2 mm no gap, 2.19 mm in plane resolution). A T1-weighted image was acquired for anatomy (TR/TE: 7/2.76ms; FA: 8; resolution 0.98 x 0.98 x 1.0mm). Computer tasks were projected onto a mirror attached to the head coil.

Tasks

During the experiment a neurofeedback task and a count-back task were administered. Both tasks require mental calculation to reliably activate the left DLPFC (Vansteensel et al., 2010).

The neurofeedback task consisted of a man on a ladder positioned against an apple tree. The position of the man on the ladder was controlled in real-time by the magnitude of DLPFC activation, allowing it to ascend or descend (see Figure 1). By modulating DLPFC activity, participants were able to pick the apples at the top of the tree and bring them back down,

requiring the crossing of a top and bottom threshold respectively. To activate the DLPFC participants were to covertly count back in steps of 7, and to deactivate participants were to let their mind wander freely. Instruction was to pick as many apples (alternately crossing the two thresholds) as possible in 2.5 minutes. The number of apples picked within each 2.5 minute run was used as a behavioral performance score.

The count-back task was used to assess the pattern of activity in the DLPFC. Participants alternated between 20 seconds of rest and 20 of seconds of counting back for 3 minutes. To assist participants, a random number between 600 and 900 was displayed on the screen as a starting point during count-back blocks.

Procedure

Table 1 gives an overview of the runs and tasks in the experiment. The experiment was single blind with both groups receiving the same instructions. Participants were informed that during the neurofeedback tasks there would be a delay between their cognitive effort (rest vs counting backwards) and the visual representation of the brain signal due to the nature of the BOLD signal. With regard to the training tasks the participants were asked to experiment within the count back paradigm in order to improve their performance on the task.

After giving informed consent participants were positioned inside the scanner. Instructions were given between tasks. During the first (preparatory) scans the participants were asked to relax. They then performed the count-back task for the first time, followed by a 5 minute rest period during which an anatomical scan was acquired. After the anatomical scan they were presented with eight more tasks which started with another count-back task, followed by the neurofeedback task seven times with half a minute of rest in-between each of the tasks. After the last run they would have 5 minutes of rest without scanning. Then finally they had to perform one more count-back task before being taken out of the scanner.

Neurofeedback

Feedback was based on BOLD levels in left DLPFC. The neurofeedback software was written in MATLAB (MathWorks) and integrates functions of SPM8. Since the exact location of brain activity within the DLPFC varies per person, the first count-back task served to localize the most active area in the DLPFC region. To limit the ROI to the DLPFC we used a global DLPFC mask converted from MNI space to native space after the first task. Immediately after the task – while the participant was still in the scanner – the functional scans from the task were aligned, smoothed, a GLM including detrending was performed and a t-map was generated online. Then, the 200 most active voxels within the global DLPFC mask constituted a subject-specific ROI for the neurofeedback tasks.

To translate the BOLD signal within the ROI to a representation/position on the screen, the range of potential values needed to be determined. An additional problem is signal variation across persons, days and even scan runs (McGonigle et al., 2000; Zandbelt et al., 2008). For these reasons neurofeedback related tasks were acquired in one single continuous run, starting with an initial count-back task that was used to determine the range of activation

values, followed by the actual neurofeedback tasks. The neurofeedback tasks of 2.5 minutes each were interleaved with 30-second periods of rest.

During the neurofeedback tasks functional images were retrieved straight from the scanner with the use of the Philips “Drin Data Dumper” tool. As soon as the software running on the task computer would detect a new task image it would be registered to the first image from the first scan run and smoothed (FWHM=12mm) in real-time. Subsequently, the BOLD signal of the voxels within the subject specific ROI were isolated and detrended, removing linear, quadratic and cubic trend from the time-series (Tarvainen et al., 2002). The mean was then taken and translated to the vertical position on the ladder using the upper and lower BOLD boundaries as reference for the top and bottom of the ladder.

Design

The first and last of the neurofeedback tasks served as pre- and post-test, while the five neurofeedback tasks in-between served as training. Both the experimental and control group received feedback on their DLPFC activity during the pre-and post-test. During training only the experimental group continued to receive feedback on their DLPFC activity, while the control group would receive sham-feedback, effectively only practicing counting backwards. The sham-feedback for each participant in the control group was taken from a different and at random selected experimental participant.

Each neurofeedback task resulted in a performance score (i.e. the number of apples picked). To test our hypothesis we used the scores on the neurofeedback tasks before and after training to test for differences within and between groups. Several characteristics of the BOLD signal were analyzed in order to examine the effect of practice on the ability to control DLPFC activity.

The first count-back task was – besides being used to determine the ROI for neurofeedback – also utilized to determine clusters of activation, the subsequent count-back tasks before and after neurofeedback were used to test examine the effect of neurofeedback on brain activity in the DLPFC and other brain regions.

Post-MRI Analyses

The fMRI data from the count-back tasks was processed using SPM8 software. Analysis on DLPFC activity was performed in native space, the scans were corrected for motion and spatially smoothed with a Gaussian filter yielding a full-width at half-maximum (FWHM) of 12 mm in each direction. In order to investigate the effects on other brain regions, the motion-corrected scans were normalized to MNI space using DARTEL and also smoothed at 12mm FWHM. Individual statistical activation maps were generated using a general linear model analysis. A single regressor was used to model activity for the count-back condition against baseline using a block design (20s on, 20s off). To identify other task-relevant brain regions over subjects, a second level analysis was performed on the normalized beta estimation maps of the first count-back task. The resulting group map was thresholded at $p < 0.05$ (correcting for multiple comparisons using the false discovery rate method) to reveal a number of active clusters.

The behavioral effect of the training was determined using a one-tailed paired t-test ($\alpha = .05$), comparing the differences in pre and post-test apple pick scores within each group. To test for group differences we performed a mixed-design analysis of variance on the difference between the pre and post-test apple pick scores (one-tailed, $\alpha = .05$).

The influence of neurofeedback on brain activity in the DLPFC and other brain regions was tested using the regressor weights of the second and third count-back tasks, which were respectively before and after the neurofeedback. DLPFC effects were investigated in native space using the same ROI that was used for neurofeedback. The effect on other task-relevant brain regions was investigated in MNI space using the clusters defined by the first count-back task. To determine the direct effect of neurofeedback on the DLPFC we performed a two-tailed paired t-test ($\alpha = .05$) within each group and a mixed-design analysis of variance (two-tailed, $\alpha = .05$) to test between group differences. In order to investigate the interaction between the DLPFC and clusters we used a repeated measures ANOVA.

Performance and relation to feedback signal parameters

We calculated a number of parameters that describe the BOLD signal for each participant. These parameters reflect the activation velocity, the deactivation velocity, overshoot (over the upper boundary) and undershoot (under the lower boundary). Figure 2a and 2b show examples of such parameters. Every signal parameter was calculated separately for the pre- and post-test per participant. The signal elevation parameters were calculated by taking the BOLD signal's lowest point as the beginning of the trial, up till and including the first point above the upper boundary (top of the ladder) or the highest BOLD value after going above the upper boundary. Vice versa was done for the signal decline parameters. A mean was calculated over the elevating or declining segments and a linear slope was fitted. Another activation/deactivation parameter was generated by taking the average number of measurement points over the segments, and yet another parameter divides the signal change by the number of measurement points. The resulting slope parameters were regarded as the velocity of the decline or elevation.

To calculate the overshoot parameters we took the highest value, the AUC and the average of all points (i.e. scans) above the upper boundary (top of the ladder) of each trial and averaged these across trials. The same was done for the undershoot parameters but vice versa.

For each parameter we deleted outliers (more than 3 interquartile ranges below the 1st quartile or above the 3rd quartile) pre-post pairwise. In some cases a parameter could not be calculated, for example when one of the runs held no successful apple pick trials or when no surface can be calculated from one overshoot point. In these cases we also applied pre-post pair wise deletion for the missing parameter. Then, to validate each parameter we correlated the pre-post difference of the parameter to the pre-post difference in the task performance. Parameters that correlated highly to the apple pick performance were considered contributing factors and were used for further analysis. A two-tailed paired t-test ($\alpha = .05$) was used on the pre and post-test signal parameters within each group and a mixed-design analysis of variance (two-tailed, $\alpha = .05$) was used to test between group differences.

3 Results

Performance

The apple pick task performance within the experimental group improved significantly from 3.31 apples (SD: 1.44) before to 4.92 apples (SD: 2.49) after training ($t(12) = -2.88, p = .007$; see figure 3). In contrast, task performance within the control group did not change ($t(10) = 0.00, ns$) from an average of 4.00 apples (pre SD: 2.24, post SD: 2.49) picked. The difference in training effect between groups was significant ($F(1,22) = 3.38, p = .040$).

Brain activity

The DLPFC activity within the experimental group did not change after neurofeedback (pre vs post, $t(12) = 1.669, ns$), whereas the activity within the control group declined significantly ($t(10) = 4.495, p = .001$). However, this difference was not significant when comparing groups ($F(1, 22) = 1.914, ns$).

A total of seven clusters were found in the first count-back task (see figure 4). A repeated measures ANOVA on ROIs (i.e. the DLPFC and clusters) before and after neurofeedback comparing groups showed there is no 3-way interaction between the different ROIs, training and groups ($F(4.13, 90.85) = .665, ns$).

Parameter correlations

All four parameters describing the decline of the BOLD signal correlated with performance ($p < 0.05$, details in Table 2). Two of the signal elevation parameters - scans needed to pick apple and fitted slope till the highest point above the ladder - correlated with the task performance ($r = .56, p = .015$; $r = .57, p = .022$). Two of the under- and overshoot parameters – average value of undershoots and average value of overshoots - correlated with the apple pick performance ($r = .42, p = .044$; $r = .47, p = .048$).

Parameter tests

Table 3 and 4 contain detailed statistics on all parameters that correlate to the performance. Three of the signal decline parameters – scans needed to pick apple, decrease divided by scans and the fitted slope till the first below ladder - show that the experimental group was able to decrease their BOLD signal significantly faster after practice ($t(9) = 3.388, p = .008$; $t(11) = 2.861, p = .015$; $t(10) = 2.824, p = .018$), while in the control group the same parameters showed no change ($t(10) = -1.147, ns$; $t(10) = -1.106, ns$; $t(6) = -1.582, ns$). The other signal decline parameter – fitted slope till the lowest point below ladder - showed no within-group effect in both the experimental group ($t(11) = 2.099, ns$) and control group ($t(7) = .708, ns$). In the between-group analyses, three of the four signal decline parameters show a significant change in velocity for the experimental group when compared to the control group ($F(1,19) = 5.219, p = .034$; $F(1,21) = 7.484, p = .012$; $F(1,16) = 8.771, p = .009$). These were the parameters based on the scans needed to pick apple, decrease divided by scans and the fitted slope till the first below ladder.

Within-group analysis on the signal elevation parameters show that the fitted slope till the highest point above the ladder parameter changes significantly for the experimental group

($t(9) = -2.925$, $p = .017$) and not in the control group ($t(5) = .072$, $p = .945$). The elevation parameter - scans needed to pick apple - showed no significant changes in the experimental ($t(10) = 1.687$, ns) nor the control group ($t(6) = -.455$; ns). Between group analysis of the elevation parameters show no difference of the experimental group in comparison to the control group ($F(1,14) = .890$, ns ; $F(1,16) = 2.100$, ns). See figure 5a and 5b.

Both the undershoot parameter and the overshoot parameter showed no between-group effect ($F(1,21) = 1.321$, ns ; $F(1,16) = 3.043$, ns) and no within-group effect in the experimental ($t(12) = .295$, ns ; $t(10) = .106$, ns) nor the control group, ($t(9) = 1.019$, ns ; $t(6) = 2.249$, ns).

4 Discussion

The goal of this fMRI study was to investigate whether people can learn to dynamically control activity of the DLPFC, a region that has been shown to be important for WM function (D'Esposito et al., 1995; Jansma et al., 2013; Wager and Smith, 2003), and has been associated with various psychiatric disorders. Results of this real-time neurofeedback study indicate that it is possible to acquire dynamic control of DLPFC after a 15-minute training period. In-depth examination of the effect of training on the dynamic properties of the feedback signal showed a significant correlation between the speed of returning to baseline and neurofeedback performance. In particular, we observed a clear decline in the time needed to return DLPFC activity back to baseline levels, after training with neurofeedback. Although there are overshoot and undershoot parameters that correlate with the neurofeedback performance, they show no significant within- or between-group effect. From this, it can be concluded that improved performance was not simply the result of improved anticipation of the delay of the BOLD response. Other brain regions - including part of the left dorsolateral caudate nucleus and the lateral part of the left dorsomedial globus pallidus, both belonging to the dorsolateral prefrontal circuit - responded to the WM task, but were unaffected by neurofeedback on the DLPFC.

The elevation phase of the feedback signal in the experimental group did not show a significant change after practice compared to the control group. The absence of a practice effect on the elevation phase suggests that control over this phase is relatively difficult to improve with neurofeedback. This phase is mostly linked to the start and execution of the WM task, which immediately activates the left DLPFC and results in a maximum increase in the BOLD signal. As a result, there may not be much room for improvement in the speed of increasing activity. Another explanation could be the (relatively) low number of samples in the control group for the elevation parameters. Theoretically, a larger sample would result in more power and could show a significant effect in signal elevation. However, this scenario is unlikely as the means of the pre- and post-elevation parameter show little difference for the control group.

The training-induced reduction in the time to return to baseline suggests that it is possible to deliberately deactivate the DLPFC. Before training, DLPFC activity appears to linger on between the activity peak (top of the ladder) and dip (bottom of the ladder), which may be due to presence of context-irrelevant functions that cause the DLPFC to stay active. Through

neurofeedback, subjects are able to discontinue such lingering and thereby reduce the time to return the DLPFC activity to baseline. In this context, it should be noted that DLPFC activity might not be the result of just manipulation and maintenance of information in WM, but could also be attributed to the selection of information (Rowe and Passingham, 2001) or an executive control network related to regulation itself (Emmert et al., 2016; Ninaus et al., 2013). This in turn raises the question how such a neurofeedback control mechanism would function: whether the DLPFC is (circularly) involved and learns to more efficiently switch off regulation (i.e. deactivate), or whether such a mechanism is more flexible and can function without DLPFC involvement to lower the activity faster. Regardless, it is conceivable that the neurofeedback enhances awareness of DLPFC activity and allows the trainee to acquire the skill to deactivate at will. This effect, we believe, warrants further investigation into the potential benefits for therapeutic intervention where WM function is implicated.

Our results may provide several new insights. WM is characterized by a capacity constraint, imposing limitations for information processing (Cowan, 2001; Miller, 1956). Therefore, it is important that the WM capacity is used efficiently in order to optimize cognitive performance. Improved control over DLPFC may well constitute (a degree of) control over the WM system, thereby influencing WM function (Sherwood et al., 2016; Zhang et al., 2015, 2013). Improved control over WM, specifically an improved ability to return to rest after WM engagement, may result in better cognitive performance in situations where several tasks have to be performed, in terms of a more efficient allocation to the most pertinent task at hand. Improved control may also affect levels of stress during sustained cognitive demand. Several studies have indicated that cognitive effort elicits a stress response, including a reduced heart rate variability (HRV) (Kennedy and Scholey, 2000; Thayer et al., 2009; Wood et al., 2002). A more rapid termination of activity in the WM system would facilitate (brief) rest states, thereby allowing for physiological energy replenishment (Raichle and Gusnard, 2002), and possibly limiting mental fatigue.

In addition, although speculative, our results may have implications for treatment of brain disorders. In schizophrenia, for instance, WM function has been connected to cognitive deficits (Callicott et al., 2003; Jansma et al., 2004; Karlsgodt et al., 2007; van Raalten et al., 2008). It has been shown that brain activity during WM tasks exhibits over-activation during low-demand WM tasks, whereas WM function and brain activity collapse at high demand, suggesting that schizophrenic patients suffer from inefficient use of WM function (Callicott et al., 2003; Glahn et al., 2005; Jansma et al., 2004; Ramsey et al., 2002). The notion that even brief feedback-training for dynamic control over DLPFC may improve efficiency of WM use, seems to warrant further investigation. Other brain disorders such as Huntington's disease and depression have also been associated with impaired WM (Elliott, 2003; Goldman-Rakic, 1994; Rose and Ebmeier, 2006; Wolf et al., 2009) and the DLPFC, and could conceivably benefit from neurofeedback. For example, the left DLPFC is the target for a novel treatment of depression, involving repeated stimulation with transcranial magnetic stimulation (George and Short, 2014).

The findings may also have implications for another emerging field, namely that of Brain Computer Interface (BCI) for people with severe communication disabilities (e.g. Locked-In

Syndrome). For a BCI, brain activity is detected and used to control external devices. Direct decoding from DLPFC activity has been shown to be feasible for this purpose (Vansteensel et al., 2010), but it is unknown if DLPFC activity remains decodable after extensive use. Some WM studies have indicated that with practice of a WM task (no feedback), activity in the WM network can reduce substantially, even with very short periods of practice (Jansma et al., 2001; Ramsey et al., 2004). The repeated performance of a WM task to control a BCI could conceivably result in reduction of activity and consequently reduced BCI control. Our research shows that providing neurofeedback can in principle prevent this effect. A direct comparison with the controls, where DLPFC activity declined after sham feedback, was not significant, but it could be that the difference becomes more pronounced after longer training, given that WM activity is likely to continue to decline (Ramsey et al., 2004).

Multiple studies have shown that activity in a variety of brain areas can be influenced using neurofeedback and rt-fMRI (deCharms et al., 2004; Haller et al., 2013, 2010; Hamilton et al., 2011; Rota et al., 2011; Sitaram et al., 2012; Zotev et al., 2011), of which only a few studies addressed WM (Sherwood et al., 2016; Zhang et al., 2015, 2013). Zhang et al (Zhang et al., 2015, 2013) and Sherwood (Sherwood et al., 2016) showed that it is possible to up-regulate activity in the left DLPFC in a block-design neurofeedback task, and report an effect on subsequent WM function. Zhang (Zhang et al., 2013) shows improved verbal working memory, attributing it to the up-regulation of left DLPFC activation. On the same data, Zhang (Zhang et al., 2015) shows changes in the functional connectivity due to the up-regulation of the left DLPFC as a new way to improve WM performance. Finally, Sherwood (Sherwood et al., 2016) showed improved performance on a custom made WM task after neurofeedback training. In both studies the aim was to maximize self-induced velocity of DLPFC activation. The current study directly addresses the ability to control DLPFC activity dynamically, focusing on the ability to rapidly elevate and decline activity at will.

While we did show improved control over activity in left DLPFC after neurofeedback, we did not look for improvement in WM performance in our subjects. Given the results, investigation of the relationship between controllability (i.e. state shifts) and performance seems worthwhile. Since we allowed only for one session of training we cannot draw conclusions about the duration of the training effect over time. Neither can we provide information about transferability to other tasks. However, results of previous neurofeedback studies targeting WM and using multiple sessions spread over multiple days indicate that improvement in WM control is indeed transferable over time and over WM tasks (Sherwood et al., 2016; Zhang et al., 2013).

Our results show that it is feasible to accomplish dynamic control over DLPFC activity using neurofeedback. Detailed BOLD signal analyses indicated that training with neurofeedback predominantly resulted in improved ability to return DLPFC activity to a baseline level after activation. The finding that subjects learned to regulate DLPFC activity after a neurofeedback training period of only 15 minutes, suggests that this skill can be rapidly acquired with a real-time dynamic feedback task, and encourages investigation of potential therapeutic applications for patients with psychiatric and neurological disorders that have been associated with WM deficits.

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Figure 1. Neurofeedback task. The DLPFC normalized signal mean translated to a position on the ladder.

Figure 2.

a. Signal slopes, the signal is shown in blue, the upper and lower boundaries of the ladder in orange. The green indicates the part of the signal considered as decline, the red as elevation.

b. Signal over- and undershoots. The circles show measurement points which are used to calculate several over- or undershoot parameters. The red shaded area shows an example of an overshoot AUC, the green the undershoot.

Figure 3.

Neurofeedback behavioral results for the experiment (N=14) and control (N=11) group. The performance is measured in number of apples picked and shown for both the pre- and post-test run. (Bars denote the standard error; * significant at 0.05 level 1-tailed)

Figure 4.

Group-activity (N=24) in the first count-back task (neurological view, left=left). Clusters of activity with Brodmann area and number of voxels in MNI space at 1.5 mm isotropic: Cluster 1 - right inferior frontal gyrus (1629 voxels); Cluster 2 - left inferior frontal gyrus & hippocampal area (6789 voxels); Cluster 3 – right inferior frontal gyrus (417 voxels); Cluster 4 – right inferior frontal gyrus/Broca’s (2101 voxels); Cluster 5 – left inferior parietal lobule (6590 voxels); Cluster 6 – right inferior parietal lobule (6609 voxels); Cluster 7 - anterior cingulate gyrus (8653 voxels).

Figure 5.

a and b. Feedback signal parameters related to performance. Experimental (N=13) against control (N=11), before and after neurofeedback training. Both were tested within group and between groups. (Bars denote the standard error; * significant at the 0.05 level 2-tailed; ** significant at the 0.01 level 2-tailed)

Table 1

Experiment setup

Scan run	Duration	Task	Purpose
0	3 min	-	Preparatory scans and setting the scan field
1 (EPI)	3 min	count-back	Localization of ROI for neurofeedback tasks
2 (T1)	5 min	-	Acquisition of anatomy image
3 (EPI)	30 min	count-back	Determine subject specific range of activation in ROI Pre-test brain activity
		neurofeedback	Pre-test neurofeedback performance
		neurofeedback (5x)	Training
		neurofeedback	Post-test neurofeedback performance
-	5 min		Rest
4 (EPI)	3 min	count-back	Post-test brain activity

Table 2

Correlations between feedback signal parameters and apple pick performance. Only parameters that correlate highly to the performance are considered valid contributors.

Signal decline	
Slope of a linear fitted line based on trials mean (lowest point)	$r = -.61, n = 20, p = .004^{**}$
Mean number of scans until apple picked over trials	$r = -.67, n = 21, p = .001^{**}$
Slope based on the decrease (until below ladder) divided by the number of scans	$r = -.69, n = 23, p < .001^{**}$
Slope of a linear fitted line based on trials mean (first below ladder).	$r = -.69, n = 18, p = .001^{**}$
Signal elevation	
Slope of a linear fitted line based on trials mean (highest point)	$r = -.20, n = 22, p = .364$
Mean number of scans until apple picked over trials	$r = -.56, n = 18, p = .015^*$
Slope based on the decrease (until below ladder) divided by the number of scans	$r = .29, n = 19, p = .226$
Slope of a linear fitted line based on trials mean (first above ladder).	$r = .57, n = 16, p = .022^*$
Undershoot	
Average value of undershoots	$r = .42, n = 23, p = .044^*$
Average of deepest undershoots	$r = .31, n = 24, p = .138$
Average of undershoot area under curve	$r = .02, n = 19, p = .941$
Overshoot	
Average value of overshoots	$r = .47, n = 18, p = .048^*$
Average of highest overshoots	$r = .28, n = 19, p = .252$
Average of overshoot area under curve	$r = .06, n = 16, p = .829$

^{**} Correlation is significant at the 0.01 level (2-tailed)

^{*} Correlation is significant at the 0.05 level (2-tailed)

Table 3

Averages and standard deviations of the signal parameters which relate to apple pick performance.

	Experimental group (N = 13)		Control group (N = 11)	
	Pre	Post	Pre	Post
Signal decline				
Slope of a linear fitted line based on trials mean(lowest point)	M: -0.54 SD: 0.25 N: 12	M: -0.74 SD: 0.33 N: 13	M: -0.45 SD: 0.20 N: 9	M: -0.52 SD: 0.13 N: 10
Mean number of scans until apple picked over trials	M: 9.93 SD: 1.98 N: 13	M: 6.54 SD: 2.25 N: 13	M: 8.75 SD: 4.23 N: 11	M: 11.49 SD: 6.48 N: 11
Slope based on the decrease (until below ladder) divided by the number of scans	M: -0.31 SD: 0.16 N: 13	M: -0.50 SD: 0.19 N: 13	M: -0.42 SD: 0.14 N: 11	M: -0.34 SD: 0.16 N: 11
Slope of a linear fitted line based on trials mean (first below ladder).	M: -0.03 SD: 0.03 N: 11	M: -0.22 SD: 0.22 N: 13	M: -0.20 SD: 0.14 N: 9	M: -0.10 SD: 0.10 N: 9
Signal elevation				
Mean number of scans until apple picked over trials	M: 11.27 SD: 5.26 N: 11	M: 7.93 SD: 3.78 N: 13	M: 5.81 SD: 2.83 N: 10	M: 6.57 SD: 3.01 N: 9
Slope of a linear fitted line based on trials mean (first above ladder).	M: 0.06 SD: 0.06 N: 10	M: 0.24 SD: 0.17 N: 13	M: 0.31 SD: 0.35 N: 8	M: 0.29 SD: 0.32 N: 8
Undershoot				
Average value of undershoots	M: 0.36 SD: 0.19 N: 13	M: 0.37 SD: 0.14 N: 13	M: 0.45 SD: 0.23 N: 11	M: 0.34 SD: 0.14 N: 11
Overshoot				
Average value of overshoots	M: 0.35 SD: 0.16 N: 11	M: 0.35 SD: 0.15 N: 13	M: 0.44 SD: 0.14 N: 10	M: 0.33 SD: 0.20 N: 9

Table 4

Test statistics on performance related feedback signal parameters. A paired t-test was used on the pre and post-test parameters within each group and a mixed-design analysis of variance was used to test between group differences.

	Within group		Between group
	Experimental	Control	
Signal decline			
Slope of a linear fitted line based on trials mean (lowest point)	$t(11) = 2.099$, $p = .060$	$t(7) = .708$, $p = .502$	$F(1,18) = .960$, $p = .340$
Mean number of scans until apple picked over trials	$t(9) = 3.388$, $p = .008^{**}$	$t(10) = -1.147$, $p = .278$	$F(1,19) = 5.219$, $p = .034^*$
Slope based on the decrease (until below ladder) divided by the number of scans	$t(11) = 2.861$, $p = .015^*$	$t(10) = -1.106$, $p = .295$	$F(1,21) = 7.484$, $p = .012^*$
Slope of a linear fitted line based on trials mean (first below ladder).	$t(10) = 2.824$, $p = .018^*$	$t(6) = -1.582$, $p = .165$	$F(1,16) = 8.771$, $p = .009^{**}$
Signal elevation			
Mean number of scans until apple picked over trials	$t(10) = 1.687$, $p = .122$	$t(6) = -.455$, $p = .665$	$F(1,16) = 2.100$, $p = .167$
Slope of a linear fitted line based on trials mean (first above ladder).	$t(9) = -2.925$, $p = .017^*$	$t(5) = .072$, $p = .945$	$F(1,14) = .890$, $p = .361$
Undershoot			
Average value of undershoots	$t(12) = -.295$, $p = .773$	$t(9) = 1.019$, $p = .335$	$F(1,21) = 1.321$, $p = .263$
Overshoot			
Average value of overshoots	$t(10) = .106$, $p = .918$	$t(6) = 2.249$, $p = .066$	$F(1,16) = 3.043$, $p = .100$

^{**} Significant at the 0.01 level (2-tailed)

^{*} Significant at the 0.05 level (2-tailed)