Differential impact of reward and punishment on functional connectivity after skill learning

Adam Steel[1,2], Edward H. Silson[2], Charlotte J. Stagg[1,3,$], Chris I. Baker[2,$]

[1]Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU, UK

[2]Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, 20814

[3]Oxford Centre for Human Brain Activity (OHBA), Wellcome Centre for Integrative Neuroimaging, University Department of Psychiatry, University of Oxford, Oxford, UK, OX3 9DU, UK

[$]Joint Senior Authors

Corresponding Author: Adam Steel, FMRIB Centre, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom; Tel. +44 (0) 1865 222493; email: adam.steel@nih.gov

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Abstract

Reward and punishment shape behavior, but the mechanisms underlying their effect on skill learning are not well understood. Here, we tested whether the functional connectivity of premotor cortex (PMC), a region known to be critical for learning of sequencing skills, after training is altered by reward or punishment given during training. Resting-state fMRI was collected before and after 72 participants trained on either a serial reaction time or force-tracking task with reward, punishment, or control feedback. In each task, training-related change in PMC functional connectivity was compared across feedback groups. Reward and punishment differentially affected PMC functional connectivity in a task-specific manner. For the SRTT, training with reward increased PMC connectivity with cerebellum and striatum, while training with punishment increased PMC-medial temporal lobe connectivity. For the FTT, training with control and reward increased PMC connectivity with parietal and temporal cortices after training, while training with punishment increased PMC connectivity with ventral striatum. These findings suggest that reward and punishment influence spontaneous brain activity after training, and that the regions implicated depend on the task learned.

Keywords: Sequence learning, Motor learning, Consolidation, Motivation, Premotor cortex

The potential to use reward and punishment, collectively referred to as valenced feedback, during training has been pursued in recent years as a potential method to increase skill learning and retention (Wachter T et al. 2009; Abe M et al. 2011; Galea JM et al. 2015; Steel A et al. 2016). Prior behavioral studies of motor adaptation suggest that reward and punishment have differing effects on motor learning. For example, punishment increased learning rate in a cerebellar-dependent motor adaptation task (Galea JM *et al.* 2015), while reward prevented forgetting after adaptation (Shmuelof L et al. 2012; Galea JM *et al.* 2015). Reward also restored adaptation learning in patients with cerebellar degeneration (Therrien AS et al. 2016) and stroke (Quattrocchi G et al. 2017). Results in other skill-learning contexts outside of adaptation have been mixed, with reward either increasing offline gains (Abe M *et al.* 2011) or having no effect (Steel A *et al.* 2016). However, despite the inconsistencies with regard the impact on memory, reward and punishment have reliably dissociable effects on performance during learning (Abe M *et al.* 2011; Steel A *et al.* 2016).

One potential explanation for the differential effects of reward and punishment on behavior is the recruitment of different learning systems. For example, it has been suggested that punishment leads to the recruitment of fast learning systems [e.g. medial temporal lobe (MTL)], while reward recruits slow learning systems [e.g. caudate via dopaminergic signaling (Wachter T *et al.* 2009; Peterson EJ and CA Seger 2013)]. In support of this hypothesis, functional imaging studies have reported that reward increases caudate activity in a behaviorally-relevant manner (Wachter T *et al.* 2009; Peterson EJ and CA Seger 2013). In contrast, punishment increases activity in the anterior insula (Wachter T *et al.* 2009; Shigemune Y et al. 2014) and MTL (Murty VP et al. 2012; Murty VP, KS LaBar, et al. 2016). Others have shown memory benefits for reward mediated by MTL activity in the post-encoding phase in episodic memory (Gruber MJ et al. 2016; Murty VP, A Tompary, et al. 2016), but this has not been studied in a skill learning context. Taken together, these studies provide evidence to support the theory that reward and punishment recruit different memory systems, but prior work has been limited to focusing on a single task in a given study. Thus, the extent to which feedback might elicit similar effects across tasks is not known.

Thus, we sought to determine how valenced feedback affects neural processing immediately after training across two different tasks. Currently, no studies have examined the extent to which the effect of valenced feedback on brain activity evokes activity in brain regions that are common across task. To address this knowledge gap, participants in the present study trained on one of two skill learning tasks (serial reaction time task [SRTT] or force tracking task [FTT]) augmented with reward, punishment, or uninformative (control) feedback. These two tasks were chosen because although both are sequencing tasks, they have distinct task demands, with the SRTT requiring appropriate action selection and the FTT requiring smooth motor control. Before and after training we collected 20-minutes of resting-state fMRI data (Figure 1a-d). We have previously presented our behavioral results, which suggested that feedback differentially impacted on performance during learning in the two tasks and that all groups showed equal retention (Steel A *et al.* 2016). We wished to extend these findings by analyzing brain activity change due to training. To that end, we examined the change in functional connectivity after training on each task.

We focused on premotor cortex (PMC) as the key region for evaluating post-encoding connectivity in both tasks, based on its well-documented critical role as a memory-encoding region for sequence learning (Hardwick RM et al. 2013). In addition, PMC shows reward-related activity after movement (Ramkumar P et al. 2016). We predicted that PMC functional connectivity would be differentially modulated by training with reward and punishment, with connectivity between the PMC and the anterior insula, MTL, cerebellum, and caudate providing distinct contributions to skill retention. We found that reward and punishment did differentially impact PMC functional connectivity after training, but that task demands modulated the impact of feedback; after training on the SRTT, reward and punishment differentially recruited the striatal and motor systems and the MTL. However, after training on the FTT, these differences were concentrated among frontal and parietal cortical regions. This suggests that feedback valence strongly affects neural processing after learning, and that the influence of reward and punishment is limited to regions involved in task performance rather than a core set of feedback processing hubs.

Materials and methods

Overview

Participants were trained on either the serial reaction time task (SRTT) or the force-tracking task (FTT) with reward, punishment, or uninformative feedback (Figure 1A). No participant was trained in both tasks. A detailed description of the tasks and training procedure can be found in (Steel A *et al.* 2016) and is summarized below. Before and after the training session, 20-minutes of resting-state fMRI was collected.

Participants

78 participants (47 female, mean age = 25 years ± std. 4.25) were recruited and participated in the study. All participants were right-handed, free from neurological disorders, and had normal or corrected-to-normal vision. All participants gave informed consent and the study was performed with National Institutes of Health Institutional Review Board approval in accordance with the Declaration of Helsinki (93-M-0170, NCT00001360). Data from six individuals were removed from the study due to inattention during training (defined as non-responsive or inaccurate performance on greater than 50% of trials; n=3) or inability to complete the imaging session due to discomfort or fatigue (n=3). This left 72 participants with complete data sets included in the analyses presented here.

Training procedure

Both tasks followed the same behavioral training procedure. Trials were presented over 15 blocks with a 30-second break separating each. Unbeknownst to the participants, during some blocks ("fixed-sequence blocks") the stimulus would appear according to a repeating pattern (described below for each task). During other blocks the appearance of the stimulus was randomly determined ("random-sequence blocks").

To familiarize participants to the task, and establish their baseline level of performance, the task began with three random-sequence blocks without feedback ("familiarization blocks"). Participants were unaware of the forthcoming feedback manipulation during the familiarization blocks. Then the feedback period began, starting with a pre-training probe (three blocks, random – fixed – random), then the training blocks (six consecutive fixed-sequence blocks), and, finally, a post-training probe (three blocks, random – fixed – random). The difference in performance between the mean of the two random blocks compared to the fixed sequence block, during these probes was used to index sequence knowledge (Robertson EM 2007). Participants were presented with only one sequence during the fixed-sequence blocks.

To test the impact of reward and punishment on skill learning, participants were randomised into one of 3 feedback groups: reward, punishment, or uninformative (control). During the feedback period, reward, punishment, or control feedback was provided based on the participant's ongoing performance. The feedback paradigm for each task is outlined separately below.

Training was conducted inside the MRI scanner, and functional MR images were collected during the training period. These training period data are outside the scope of the present manuscript and are not presented here.

Serial reaction time task (SRTT)

The version of the SRTT used here adds feedback to the traditional implementation. At the beginning of each block participants were presented with four "O"s, arranged in a line, at the center of the screen. These stimuli were presented in white on a grey background (Figure 1B). A trial began when one of the "O"s changed to an "X". Participants were instructed to respond as quickly and accurately as possible, using the corresponding button, on a four-button response device held in their right hand. The "X" remained on screen for 800 ms regardless of whether the subject made a response, followed by a 200 ms fixed inter-trial interval, during which time the four "O"s were displayed. While this trial timing may foster some degree of explicit awareness in some subjects, making this variant of the SRTT not a purely motor learning task, this timing was necessary to accommodate the constraints of collecting fMRI data during training.

A block consisted of 96 trials. During fixed-sequence blocks, the stimuli appeared according to one-of-four fixed 12-item sequences, which repeated 8 times (e.g. 3-4-1-2-3-1-4-3-2-4-2-1). For each participant, the same 12-item sequence was used for the duration of the experiment. Each fixed block began at a unique position within the sequence, to help prevent explicit knowledge of the sequence from developing (Schendan HE et al. 2003). In the random blocks, the stimuli appeared according to a randomly generated sequence, without repeats on back-to-back trials, so, for example, subjects would never see the triplet 1-1-2.

Breaks between blocks lasted 30-seconds. Initially, participants saw the phrase "Nice job, take a breather". After five seconds, a black fixation-cross appeared on the screen. Five seconds before the next block began, the cross turned blue to cue the subjects that the next block was about to start.

During the post-training retention probes, participants performed three blocks (random – fixed – random), outside the scanner on a 15-inch Macbook Pro using a button box identical to the one used during training. During these retention probes, the next trial began 200 ms after the participant initiated their response rather than after a fixed 800 ms as during training. No feedback was given during the retention blocks.

Force-tracking task

In the force-tracking task (FTT), participants continuously modulated their grip force to match a target force output (Floyer-Lea A and PM Matthews 2005; Floyer-Lea A et al. 2006). In the traditional implementation, participants are exposed to a single pattern of force modulation repeated each trial. This design does not allow discrimination between general improvement (i.e. familiarization with the task and/or the force transducer) and improvement specific to the trained sequence of force modulation. Therefore, we adapted the traditional FTT method to align it with the experimental design that is traditional for the SRTT, i.e. by including random sequence blocks.

A given trial consisted of a 14 second continuous pattern of grip modulation. At the beginning of a trial, participants were presented with three circles on a grey background projected onto a screen: a white circle (Cursor, 0.5 cm diameter), a blue circle (Target, 1.5 cm diameter), and a

black circle (Bottom of the screen, 2 cm diameter, indicating the position corresponding to minimum pressure; Figure 1C). Participants held the force transducer (Current Designs, Inc., Philadelphia, PA) in the right hand between the four fingers and palm (Figure 1D, bottom). Participants were instructed to squeeze the force transducer (increasing force moving the cursor upwards) to keep the cursor as close to the center of the target as possible as the target moved vertically on the screen. During fixed blocks, participants were randomly assigned to one of six sequences (Figure 1D, left). During random blocks, the target followed a trajectory generated by the linear combination of four waveforms, with periods between 0.01 and 3 Hz. The combinations of waveforms were constrained to have identical average amplitude (target height), and the number and value of local maxima and minima were constant across the random blocks.

For data analysis, the squared distance from the cursor to the target was calculated at each frame refresh (60 Hz). The first 10 frames were removed from each trial. The mean of the remaining time points was calculated to determine performance, and trials were averaged across blocks.

Feedback

All participants were paid a base remuneration of $80 for participating in the study. At the start of the feedback period, participants were informed they could earn additional money based on their performance.

For full details of our tasks please see (Steel et al, 2016a). In the SRTT, performance was defined as the accuracy (correct or incorrect) and reaction time (RT) of a given trial. Feedback was given on a trial-by-trial basis (Figure 1C,D). This was indicated to the participant when the white frame around the stimulus changed to green (reward) or red (punishment). In the reward group, the participants were given feedback if their response was accurate and their RT was faster than their criterion RT, which indicated that they earned money ($0.05 from a starting point of $0) on that trial. In the punishment group, participants were given feedback if they were incorrect, or their RT was slower than their criterion, which indicated that they lost money ($0.05 deducted from a starting point of $55) on that trial. Participants in the control-reward and control-punishment groups saw red or green color changes, respectively, at a frequency matched to punishment and

reward, respectively. Control participants were told that they would be paid based on their speed and accuracy. Importantly, to control for the motivational differences between gain and loss, participants were not told the precise value of a given trial. This allowed us to assess the hedonic value of the feedback, rather than the level on a perceived-value function. Between blocks, for the reward and punishment groups, the current earning total was displayed (e.g. "You have earned $5.00"). Control participants saw the phrase, "You have earned money." The criterion RT was calculated as median performance in the first familiarization block. After each block, the median + standard deviation of performance was calculated, and compared with the criterion. If this test criterion was faster (SRTT) or more accurate (FTT) than the previous criterion, the criterion was updated. During the SRTT, only the correct responses were considered when establishing the criterion reaction time.

Feedback in the FTT was based on the distance of the cursor from the target (Figure 1C). For the reward group, participants began with $0. As participants performed the task, their cursor turned from white to green when the distance from the target was less than their criterion. This indicated that they were gaining money at that time. In the punishment group, participants began with $45, and the cursor turned red if it was outside their criterion distance. This indicated that they were losing money. For reward-control and punishment control, the cursor changed to green or red, respectively, but was unrelated to their performance. For control, the duration of each feedback instance, as well as cumulative feedback given on each trial, was matched to the appropriate group. Between each block, participants were shown their cumulative earnings. Control participants saw the phrase "You have money."

MRI acquisition

This experiment was performed on a 3.0T GE 750 MRI scanner using a 32-channel head coil (GE Medical Systems, Milwaukee, WI).

Structural scan

For registration purposes, a T1-weighted anatomical image was acquired (magnetization-prepared rapid gradient echo (MPRAGE), TR = 7 ms, TE = 3.4 ms, flip-angle = 7 degrees, bandwidth = 25.000 kHz, FOV = 24x24 cm^2, acquisition matrix = 256 x 256, resolution = 1 x 1 x 1 mm, 198

slices per volume). Grey matter, white matter, and CSF maps for each participant were generated using Freesurfer (Fischl B et al. 2002).

EPI scans

Both task and resting state fMRI scans were collected with identical parameters and slice prescriptions. Multi-echo EPI scans were collected with the following parameters: TE = 14.9, 28.4, 41.9 ms, TR = 2, ASSET acceleration factor = 2, flip-angle = 65 degrees, bandwidth = 250.000 kHz, FOV = 24 x 24 cm, acquisition matrix = 64 x 64, resolution = 3.4 x 3.4 x 3.4 mm, slice gap = 0.3 mm, 34 slices per volume covering the whole brain. Respiratory and cardiac traces were recorded. Each resting state scan lasted 21-minutes. The first 30 volumes of each resting-state scan were discarded to control for the difference in arousal that occurs at the beginning of resting state scans. This left the final 20-minutes of rest in each scan for our analysis. This procedure has been used in other studies where long-duration resting state runs were collected (Gonzalez-Castillo J et al. 2014).

Resting state fMRI preprocessing

Data were preprocessed using AFNI (Cox RW 1996). The time series for each TE was processed independently prior to optimal combination (see below). Slice-time correction was applied (3dTShift) and signal outliers were attenuated [3dDespike (Jo HJ et al. 2013)]. Motion correction parameters were estimated relative to the first volume of the middle TE (28.4 msec), and registered to the structural scan (3dSkullStrip, 3dAllineate). These registration parameters were then applied in one step (3dAllineate) and the data were resampled to 3 mm isotropic resolution.

The optimal echo time for imaging the BOLD effect is where the TE is equal to T2*. Because T2* varies across the brain, single echo images are not optimal to see this variation. By acquiring multiple echoes, this enables the calculation of the “optimal” T2* weighted average of the echoes, which allows one to recover signals in dropout areas and improves contrast-to-noise ratio (Posse S et al. 1999; Poser BA et al. 2006; Kundu P et al. 2014; Evans JW et al. 2015). The following is a summary of methods implemented in the ME-ICA procedure.

The signal at an echo, *n* varies as a function of the initial signal intensity S_0 and the transverse susceptibility T2* = 1/R2* and is given by the mono-tonic exponential decay:

$$S(TE_n) = S_0 exp(-R_2 * TE_n),$$

where R2* is the inverse of relaxation time or 1/T2*. This equation can be linearized to simplify estimation of T2* and S_0 as the slope using log-linear transformation. The time courses can be optimally combined by weighted summation by a factor, w, described by the following equation:

$$w(T^*_{2(fit)})_n = \frac{TE_n \cdot exp(-TE_n/T^*_{2(fit)})}{\sum_n TE_n \cdot exp(-TE_n/T^*_{2(fit)})}.$$

Where T_2(fit) is the transverse relaxation time estimated for each voxel using the equation above. The OC time series can then be treated as a single echo, as it is here for the resting state data.

After optimal combination, we applied the basic ANATICOR (Jo HJ et al. 2010) procedure to yield nuisance time series for the ventricles and local estimates of the BOLD signal in white matter. All nuisance time-series (six parameters of motion, local white matter, ventricle signal, and 6 physiological noise regressors (AFNI: RetroTS)) were detrended with fourth order polynomials. These time series, along with a series of sine and cosine functions to remove all frequencies outside the range (0.01-0.25 Hz) were regressed out in a single regression step (AFNI program 3dTproject). Time points with motion greater than 0.3 mm were removed from the data [scrubbing, see Power JD et al. (2012)] and replaced with values obtained via linear interpolation in time. Data were transformed into standard space (@auto_tlrc) and smoothed with a 6mm FWHM Gaussian kernel. For group data analysis and calculation of global connectedness, a group-level grey matter by mask was created by calculating voxels in standard space determined to be grey matter in 80% of participants (Gotts SJ et al. 2012) fMRI data analysis

For group tests, the average smoothness of the data was estimated (3dFWHMx). Data were corrected for multiple comparisons using Monte-Carlo simulations to (3dClustSim, AFNI compile date July 9, 2016). Cluster size correction was applied to achieve an $\alpha = 0.05$ ($p < 0.005$, $k = 55$) unless otherwise indicated.

Left premotor cortex functional connectivity

We focused our analysis on the left premotor cortex based on this regions well-described central role in sequence production in response to visual cues (Mushiake H et al. 1991), sensorimotor learning, and sequence learning (Hardwick RM *et al.* 2013; Hardwick RM et al. 2015). Given that the participants were performing the task with their right hand, we further focused on the left PMC. Left dorsal and ventral premotor cortex (PMd and PMv) were defined based on a publicly available diffusion-MRI based parcellation of premotor cortex (Tomassini V et al. 2007), which are matched for size. The mean time series from both dorsal and ventral premotor cortices were extracted separately from each participant and each rest period, and the whole brain correlation maps (Pearson's r) for both PMd and PMv during the pre- and post- training resting state MRI scans were then calculated based on these time series. For each resting state scan, global correlation [GCOR; @compute_gcor: Saad ZS et al. (2013)] and magnitude of motion across runs (@1dDiffMag) were calculated and included as nuisance covariates for group analysis.

The resulting maps were then submitted to a linear mixed effects model (3dLME) with ROI (PMd/PMv), Rest (pre-/post-), Group (Control/Reward/Punishment). Based on the intrinsic differences between the SRTT and FTT and the differences in task-performance during the learning period, the two tasks were analyzed separately. The precise model fit at the group level in R-syntax (nlme) was 'Group*Rest*ROI+motion+gcor'. Group analysis maps were cluster-corrected for multiple comparisons to achieve a $\alpha = 0.05$ using the ACF model in 3dClustSim ($p < 0.005$, $k = 54$). To determine the extent of overlap across the two tasks, the overlap of the significant clusters from the Rest x Condition interaction from both tasks was calculated.

Results

To identify task-independent effects of feedback on functional connectivity immediately following training, we used a seed-based analysis focused on the left PMC. For each task, we implemented a voxel-wise linear mixed effects (LME) model (Chen G et al. 2013) with Rest (Pre-/Post- training), Group (Reward /Punishment /Control), and ROI (ventral-/dorsal- premotor cortex) as factors and looked for regions showing a significant interaction between Rest x

Condition. No regions showed a Rest x Condition x ROI interaction in either task. Full results from this model for both tasks can be found in Table 1.

Reward and punishment evoke dissociable changes in PMC connectivity patterns after SRTT training

Following training on the SRTT task, several regions showed a modulation of PMC functional connectivity that differed by the feedback given during training (Rest x Group interaction; Figure 2a). These included bilateral thalamus and striatum, right cerebellar vermis, supplementary motor area (SMA), bilateral medial temporal lobe, and left inferior frontal gyrus. In order to examine the nature of the interaction, we extracted the estimated mean PMC functional connectivity change due to training from each cluster (Figure 2b). This revealed a pattern that was distinct across the feedback groups. After training with reward, functional connectivity increased between PMC and thalamus and striatum, cerebellar vermis, and SMA, but PMC functional connectivity decreased with medial temporal lobe and inferior frontal gyrus. The punishment group showed the opposite pattern; PMC connectivity with medial temporal lobe and inferior frontal gyrus increased after training with punishment. The control group showed in intermediate pattern between the reward and punishment groups. In the control group, PMC connectivity increased with the thalamus, striatum, and cerebellar vermis after training, but decreased with SMA, medial temporal lobe, and inferior frontal gyrus. Thus, in the context of the SRTT, there is evidence multiple streams can support memory formation, which can be dissociated by augmenting training with reward or punishment.

Punishment promotes PMC-striatal connectivity after FTT training

After training on the FTT, PMC connectivity change with bilateral lateral occipital temporal cortex, precuneus, left culmen, cerebellum, right striatum, and right medial frontal gyrus differed across the feedback groups (Figure 3a). Extracting the estimated mean PMC functional connectivity change of these regions revealed that two primary modes of change in these regions (Figure 3b). PMC connectivity with the lateral occipital cortex, precuneus, culmen, and cerebellar lobule VI, decreased after training with punishment, but increased after training with control feedback. In

contrast, connectivity of the PMC with right striatum and right medial frontal gyrus increased after training with punishment. PMC connectivity to right medial frontal gyrus decreased after training with control. Overall, in the regions showing the interaction between functional connectivity change after training and feedback group, reward had a smaller influence compared to control or punishment. This suggests that punishment induces marked changes in functional connectivity change after FTT training, which was consistent with the behavioral effects observed at the end of training (Steel A *et al.* 2016).

Influence of reward and punishment on PMC-striatal connectivity depends on task

In order to better understand the correspondence between the feedback and the change in PMC functional connectivity after training between the two tasks, we calculated the overlap between the sets of regions that showed the Rest x Group interaction for each task separately. Given the reduced power to detect general effects that might be weak but consistent across tasks, for this qualitative assessment, we considered the conservative threshold reported above ($p < 0.005$, $k = 54$), as well as a liberal threshold ($p < 0.01$, $k = 54$; Figure 4a). The mean connectivity change with PMC for clusters greater than 20 voxels in extent is shown in Figure 4b. At the conservative threshold, one region in the striatum showed overlap (Cluster 1). When we extracted the estimated mean connectivity change after training for each task, we found that the pattern of connectivity change across the feedback groups was diametrically opposed. In the SRTT, connectivity between the PMC and the overlapping region increased after training with reward but decreased after training with punishment. In contrast, after training on the FTT, connectivity between PMC and the overlapping region increased after training with punishment but increased after training with reward. In both tasks, connectivity between PMC and the overlapping region increased after training with control feedback.

At the liberal threshold, we detected three other clusters in the right anterior temporal lobe, the right cerebellum, and right dorsal thalamus. In each of these clusters, the pattern of connectivity change with PMC exhibited by the Reward and Punishment groups was also not consistent across tasks. Thus, we find no evidence for regions showing consistent effects of reward and punishment across tasks.

Discussion

The present study sought to investigate the effect of valenced feedback on brain activity during the period immediately after training on the SRTT and FTT. We found that reward and punishment differentially impacted change in PMC functional connectivity, and this impact was influenced by task. After training on the SRTT, functional connectivity between PMC with striatum, cerebellum, and SMA increased after training with reward, while functional connectivity between PMC connectivity with medial temporal lobe and inferior frontal gyrus increased after training with punishment. Training on the FTT induced a different pattern of connectivity change. After training on the FTT, functional connectivity between PMC and parietal cortices increased after training with control feedback but decreased after training with punishment; however, after training on the FTT with punishment, functional connectivity between PMC with the striatum and medial frontal gyrus increased after training. Finally, we looked for regions that showed an overlap in the Rest x Feedback group interaction across tasks. At our conservative threshold, only the ventral pallidum showed an overlap for this interaction and training the two tasks reward and punishment had opposing effects on connectivity between PMC and this region. After training on the SRTT, connectivity between the PMC and the pallidum increased after training with reward but decreased after training with punishment; the opposite pattern was true after training with the FTT: connectivity between the PMC and the pallidum increased after training with punishment but decreased after training with reward. Taken together, these results suggest that training with valenced feedback has differential effects on functional connectivity after training, and that these effects primarily manifest in the regions involved in task performance.

Reward and punishment differentially impacted PMC functional connectivity with the striatum and medial temporal lobe after training on the SRTT. It is widely known that the SRTT learning engages the motor system, including motor cortex and premotor cortex (Keele SW et al. 2003; Schubotz RI and DY von Cramon 2003; Hardwick RM *et al.* 2013; Wiestler T and J Diedrichsen 2013; Kornysheva K and J Diedrichsen 2014; King BR et al. 2017), parietal cortex (Keele SW *et al.* 2003; Breton J and EM Robertson 2017), basal ganglia (Carbon M et al. 2004; Seger CA 2006;

Albouy G, S Fogel, et al. 2013; Debas K et al. 2014), and medial temporal lobe (Schendan HE *et al.* 2003; Albouy G, BR King, et al. 2013). The contribution of the motor, parietal, and subcortical systems may be based on the goal of the learner, or based on the statistical complexity of the sequence being learned (Robertson EM 2007). However, it is clear that these memory systems interact during the learning process and, given particular task constraints, it is possible to bias activity towards one system or another [e.g. (Keele SW *et al.* 2003)] or to induce competitive interactions among the memory systems (Brown RM and EM Robertson 2007; Tunovic S et al. 2014). There has been evidence to suggest that valenced feedback could also dissociate the memory systems involved during learning (Wachter T *et al.* 2009), and the present data show that reward and punishment do recruit separable neural networks after SRTT learning.

Following training on the FTT, we observed differences amongst the feedback groups in functional connectivity between PMC and posterior parietal, lateral occipital, and prefrontal cortices, as well as the ventral striatum and the cerebellum. The control and, to a lesser extent, reward groups showed increases in connectivity between PMC and the parietal, occipital, and cerebellar regions, but decreasing connectivity between PMC and ventral striatal and medial frontal gyrus. Punishment showed the opposite effect: functional connectivity between PMC and parietal, occipital, and cerebellum decreased after training and increased with the striatum and medial frontal gyrus. FTT learning is generally associated with decreased BOLD activity in the cortical motor network, prefrontal cortex, and caudate nucleus, but increased BOLD activity in the cerebellum and putamen (Floyer-Lea A and PM Matthews 2004, 2005). While training did not modulate BOLD activity of lateral occipital cortex, this region is strongly associated with action representation (Kable JW et al. 2005; Kable JW and A Chatterjee 2006; Lingnau A and PE Downing 2015), is potentially consistently engaged while learning the novel visuomotor association for learning on the FTT.

Overall, we observed very little overlap between the FTT and SRTT with respect to the influence of feedback on functional connectivity change due to training. At our conservative threshold, the only region where feedback modulated functional connectivity change due to training after training on both tasks was the ventral pallidum. In this region, reward and punishment feedback had opposing effects in the two tasks. After training on the SRTT, functional connectivity between

the PMC and ventral pallidum increased after training with reward and decreased after training with punishment. The opposite was true after training on the FTT, wherein we observed increased functional connectivity between PMC and the ventral pallidum after training with punishment, but a decrease after training with reward. The ventral pallidum contains cell populations that respond to both appetitive and aversive stimuli (Saga Y et al. 2017). Behavioral response to appetitive and aversive stimuli are mediated by glutamatergic and GABAergic neurons in the ventral pallidum, and project to the ventral tegmental area and lateral habenula, respectively (Faget L et al. 2018). Therefore, given that this area has cells that respond to positive and negative stimuli, it may not surprising to find this area recruited by both reward and punishment following training in our study. Across both tasks, in the pallidum, the observed pattern of behavior matched the observed functional connectivity change: the Feedback Group performing better at the end of training showed diminished functional connectivity with ventral pallidum. On the SRTT, punishment was performing better (i.e. had a faster overall reaction time) compared to the reward and control groups, and, here we observed a decrease in functional connectivity between ventral pallidum and PMC after training with punishment. On the other hand, in the FTT, the punishment group performed worse (i.e. made more tracking error) than the reward and control groups behaviorally, and, in this case, the connectivity between PMC and ventral pallidum increased after training with punishment. Thus, with respect to the pallidum, it may be that the connectivity of this region to PMC depends on the experience of the learner (either absence of reward or presence of punishment) in the environment, and this activity may persist after training. In line with this hypothesis, a meta-analysis of decision making studies using valenced feedback found surprise, valence, and signed prediction error information converged specifically in the ventral pallidum (Fouragnan E et al. 2018).

Even at a liberal threshold, the regions that showed overlap across the two tasks showed opposite patterns of connectivity change based on the feedback given. Similar to the pallidum, the differential effect of feedback on functional connectivity between PMC and these regions may be due to the qualitative differences in performance. More generally, the minimal overlap and opposing patterns suggest that reward and punishment have strong impacts on post-training brain activity and that this effect is strongly influenced by the task that was performed.

Valenced feedback processing is often characterized as being mediated by a set of regions that would be common across tasks; for example, in the context of statistical learning and decision making, distinct networks for valence, surprise, and signed-prediction error have been suggested (Fouragnan E *et al.* 2018). Regions activated in response to surprise and valence information include the striatum and insular cortex, which differentially responded to positive and negative surprises, respectively (Fouragnan E *et al.* 2018). This fits well with the regions that showed differential PMC-connectivity after training on the SRTT, which can be classified as a statistical learning task (Robertson EM 2007). However, after training on the FTT, the patterns of connectivity change across the feedback groups was not consistent with what would be expected after statistical learning. Indeed, in the FTT, we observed increased functional connectivity between PMC and ventral striatum after training with punishment, which is opposite to the predicted response to the positive prediction error. Instead, we found that task-relevant regions, including the lateral occipital, parietal, and cerebellar activity (Imamizu H et al. 2000; Krakauer JW et al. 2004; Grafton ST et al. 2008; Hardwick RM *et al.* 2013) showed feedback related changes in functional connectivity. Motivational adjustments to movement and performance are roles generally ascribed to the basal ganglia, but there is evidence that the cerebellum also plays a role in motivational aspects of correction during motor learning (Turner RS et al. 2003; Turner RS and M Desmurget 2010; Bostan AC and PL Strick 2018). Our data provide further evidence that, rather than utilize a core feedback-processing network segregated on the basis of valence, rewards and punishments are processed in a distributed fashion amongst the brain regions that are active during the task. This hypothesis is consistent with behavioral findings that suggest reward and punishment may have differential effects depending on task demands (Steel A *et al.* 2016).

Several aspects of the present study are worth noting. First, we did not distinguish between dorsal and ventral premotor cortex in our analyses because no regions showed a Rest x Group x ROI interaction in either task. Dorsal and ventral premotor cortex are highly interconnected and although feedback may differentially impact dorsal and ventral premotor cortex, we may have been underpowered to detect any effect. Second, it should be noted that our implementation of the SRTT included a fixed trial length rather than a self-paced trial duration, which might foster explicit knowledge. Explicit learning may recruit different neural networks after learning (Sami S

et al. 2014). No participants included in the study spontaneously reported sequence knowledge. When tested at 3+ weeks, participants showed no evidence of explicit awareness (for further discussion, see Steel et al., 2016a). Third, we did not observe and differences in retention across the feedback groups in either task. However, we did observe differences in the acquisition and performance during training. Therefore, we are not able to say whether any specific PMC connections facilitate better memory formation. Finally, it is widely known that sleep interacts with memory formation and offline memory processes (Robertson EM, A Pascual-Leone and RC Miall 2004; Robertson EM, A Pascual-Leone and DZ Press 2004; Albouy G, S Fogel*, et al.* 2013). In our study, we did not measure sleep quality. Whether sleep interacts with the effect of reward and punishment on retention may be an interesting avenue for future research.

In summary, we found that training with reward and punishment differentially affects functional connectivity after training in a task-specific manner. This suggests that rather than a critical feedback-processing network, feedback may be processed within those systems specifically engaged by the task requirements.

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Tables

Number of voxels	**Volume**	**x**	**y**	**z**	**Region**
SRTT					
Main effect Rest					
1909	51543	-4.5	-22.5	11.5	Left Thalamus
949	25623	52.5	1.5	-6.5	Right superior temporal gyrus
477	12879	1.5	-73.5	-24.5	Right cerebellar vermis
299	8073	-55.5	-1.5	-3.5	Left superior temporal gyrus
68	1836	25.5	-13.5	-12.5	Right parahippocampal cortex
Rest x Condition					
828	22356	-16.5	1.5	-0.5	Left pallidum
215	5805	28.5	1.5	-18.5	Right parahippocampal cortex
195	5265	-10.5	-34.5	59.5	Left supplementary motor area
154	4158	-4.5	-37.5	-24.5	Left cerebelllum
77	2079	-16.5	-13.5	-18.5	Left parahippocampal cortex
59	1593	-31.5	19.5	15.5	Left inferior frontal gyrus
FTT					
Main effect Rest					
3545	95715	-4.5	-22.5	11.5	Left thalamus
148	3996	7.5	-31.5	59.5	Right supplementary motor area
118	3186	-1.5	55.5	-6.5	Left medial frontal gyrus
112	3024	43.5	-61.5	-3.5	Left middle occipital gyrus
112	3024	1.5	-61.5	17.5	Right posterior cingulate cortex
60	1620	16.5	-73.5	29.5	Right precuneus

Rest x Condition

639	17253	46.5	-49.5	-15.5	Right fusiform gyrus
395	10665	-49.5	-64.5	8.5	Left middle temporal gyrus
147	3969	-10.5	-91.5	5.5	Left cuneus
124	3348	25.5	-73.5	38.5	Right precuneus
74	1998	13.5	1.5	5.5	Right pallidum
63	1701	19.5	-61.5	-21.5	Right cerebellum lobule VI
60	1620	-7.5	-64.5	2.5	Left lingual gyrus
55	1485	7.5	61.5	2.5	Right medial frontal gyrus

Captions

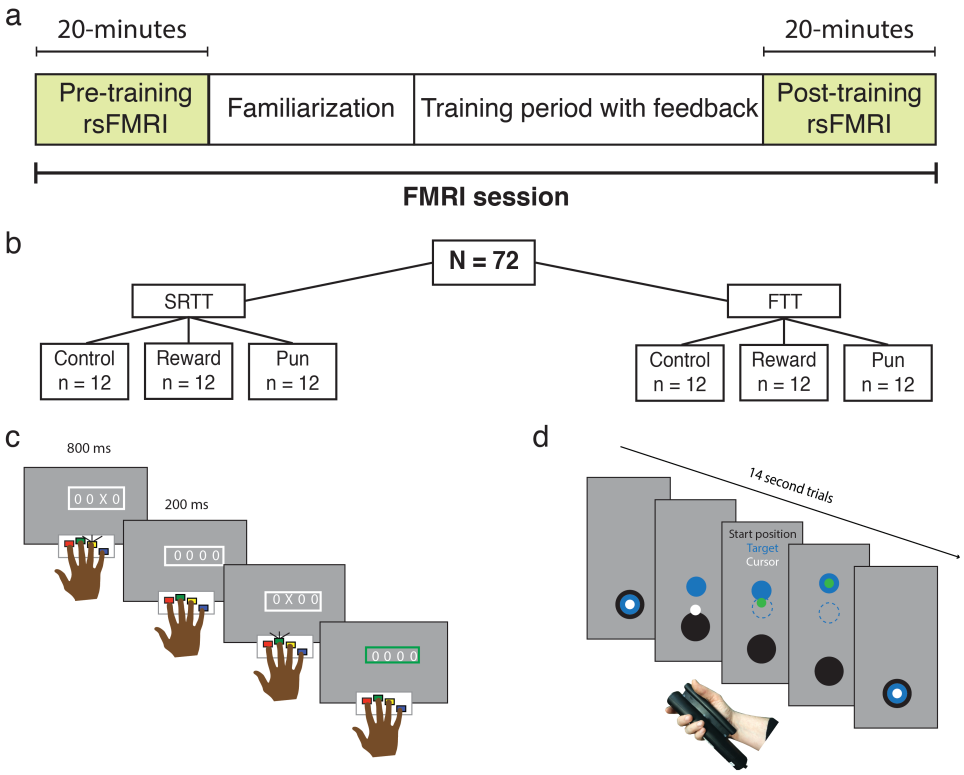

Figure 1. Experimental design and skill memory retention. (a,b) Participants underwent 20 minutes of resting state fMRI before and after training on either the serial reaction time task (SRTT) or the force tracking task (FTT) while receiving REW, PUN, or CONT feedback. In the SRTT (c), participants responded to a cue appearing in one of four locations on a screen. In the FTT (d), participants modulated their grip force to track a moving target. In both tasks, the stimulus could follow either a random or fixed sequence, and skill memory was assessed by comparing performance during random and fixed trials.

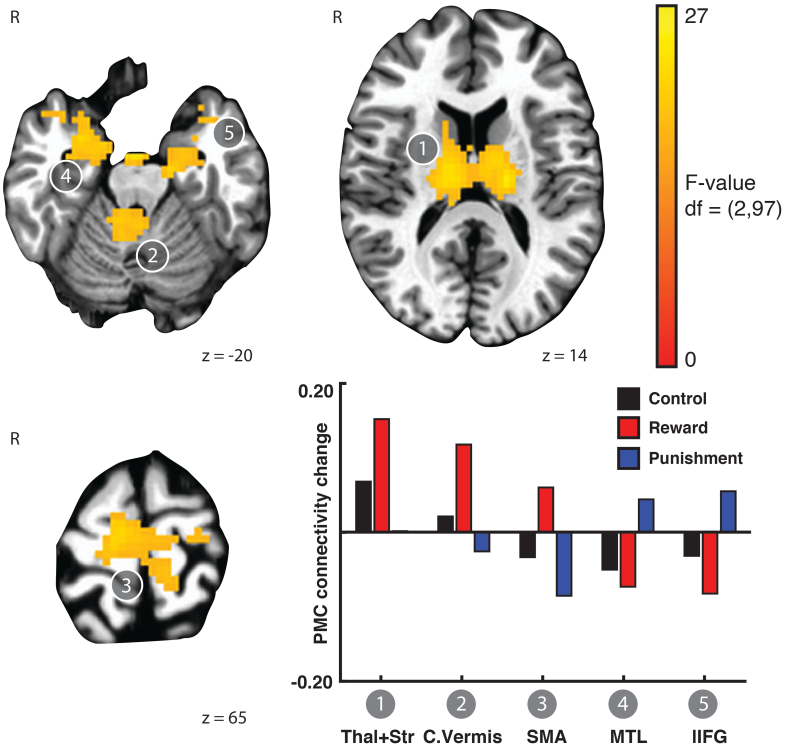

Figure 2. Reward and punishment differentially effect PMC functional connectivity change after training on the SRTT. Linear mixed effects model revealed brain regions exhibiting a Rest x Feedback group interaction in the functional connectivity of left PMC. Functional connectivity between PMC and the thalamus and striatum, cerebellum, and SMA increased after training with reward and control feedback but decreased after training with punishment. In contrast, functional connectivity between medial temporal lobe and left inferior frontal gyrus increased after training with punishment but decreased after training with reward and control feedback. Bars show mean connectivity change after training estimated by the linear mixed effects model.

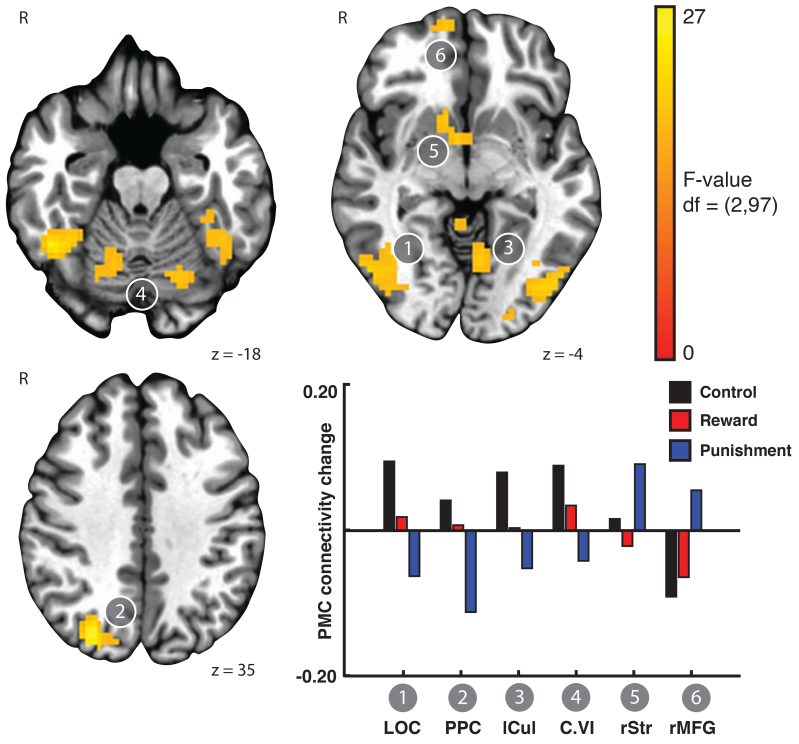

Figure 3. Punishment promotes PMC-striatal connectivity after FTT training. Linear mixed effects model revealed brain regions exhibiting a Rest x Feedback group interaction in the functional connectivity of left PMC. Functional connectivity between the PMC and lateral occipital cortex, posterior parietal cortex, culmen, and cerebellum increased after training with control feedback, but decreased after training with punishment. In contrast, PMC connectivity with Right ventral striatum and right medial frontal gyrus increased after training with punishment but decreased after training with reward and control feedback. Bars show mean connectivity change after training estimated by the linear mixed effects model.

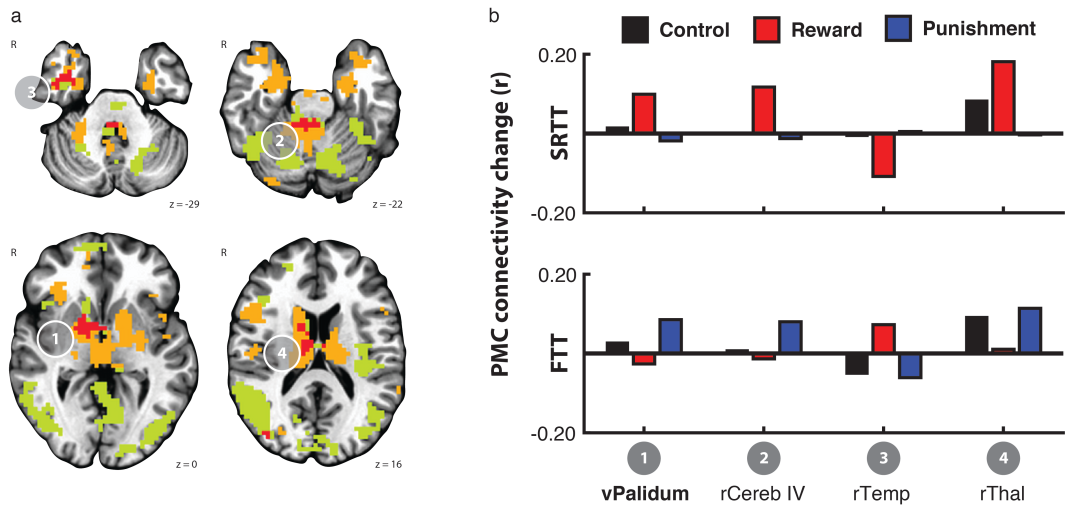

Figure 4. Regions showing PMC functional connectivity change after training were had limited overlap across tasks. Clusters that showed a PMC connectivity change after training that differed by the feedback group in the SRTT (orange) and the FTT (green) showed limited overlap, even at a liberal cluster threshold ($p < 0.01$, $k = 54$). Only the ventral pallidum (Cluster 1, bold) showed an overlap at the threshold reported above ($p < 0.005$, $k = 54$). In all clusters, the Reward and Punishment groups exhibited opposite patterns of connectivity change with PMC due to training on the SRTT (upper) and FTT (lower). Bars show mean connectivity change after training estimated by the linear mixed effects model.