How hard do you want to work?: How the ACC influences motivation

by

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M.S. Biomedical Engineering, U. Iowa 2011

A thesis submitted to the

Faculty of the Graduate School of the

University of Colorado in partial fulfillment

of the requirements for the degree of

Master of Arts

Department of Psychology

2015

This thesis entitled:
How hard do you want to work?: How the ACC influences motivation
written by Prescott Mackie
has been approved for the Department of Psychology

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

Mackie, Prescott (M.A. Psychology)

How hard do you want to work?: How the ACC influences motivation

Thesis directed by Prof. Randall O'Reilly

Animals integrate motivational states with signals from the environment (e.g. learned cues) and signals from the body (e.g. muscle fatigue) to make decisions about how much effort to exert for different possible rewards. Previous research has implicated the anterior cingulate cortex (ACC) in processing information during effort-related decision-making. Here, we use fMRI to record activity in the ACC and other prefrontal cortical areas while subjects integrate motivation, stimulus cues, and bodily signals during the moments leading up to a decision regarding exerting high physical effort to obtain a secondary reward. We show that caudal ACC areas co-activate with premotor areas prior to a decision to exert high physical force. On the other hand, more rostral ACC areas co-activate with lateral OFC prior to a decision to avoid high effort. We also show that mid-rostral dACC co-activates with LPFC areas during presentation of the high-reward/high-effort cues, which suggests ACC involvement in recruiting attention systems in response to cues predicting reward.

Contents

Chapter

0.1 Introduction

Our lives are filled with a constant weighing of effort expended against potential gain. How does this process operate in the brain? By answering this question, can we obtain deeper insight into the nature of this fundamental calculus, and how it may go awry in various conditions? Making the choice to exert effort involves the application of a decision-making process that emerges from intricate interactions between multiple prefrontal cortical (PFC) regions, including areas in the ventral and medial regions, such as the anterior cingulate cortex (ACC) and orbital frontal cortex (OFC), which encode affective value (among other things) [15, 14, 19]. There is growing evidence for a gradient along the rostral-caudal axis in the PFC, where anterior regions code for higher-order, abstract, cognitive representations and posterior regions code for lower-level, concrete, motor representations [1, 2, 24]. Research has also suggested a functional distinction between ventral and dorsal cortex, where ventral regions process the 'what' characteristics of stimuli, and the dorsal regions process the 'how'/'where' of interacting with stimuli [24]. In this paper, we find evidence for a similar rostral-caudal organization for decisions involving cost-benefit calculations, organized over multiple time scales, within the ACC. Importantly, this topographical organization carries an interaction of functions that are observed between anterior-posterior and ventral-dorsal gradients.

Different areas of the ACC have been implicated in various aspects of effort. Previous research has found that the ACC is selectively active during simple experimental tasks involving effortful decision-making. An fMRI BOLD response in the ACC has been observed during a choice involving execution of a difficult task [27, 20], during the presentation of a cue that predicts effort [9], and during a discounting response for a cue that predicts a poor cost-benefit outcome [7]. Research has also shown effort related signals during cost-benefit reward training in macaques [16]. However, these studies have only suggested a general activation location for effort-related decisions.

Moreover, studies have implicated more ventral mPFC areas (medial PFC) in affective decision making processes. These studies focus on the cortical region ventral to the ACC, which is analogous to orbital cortex. These medial orbital regions show enhanced activity before an animal makes a

decision to reach for a rewarding food item [15]. Very rostral regions of ACC (pregenual ACC) have been shown to be active during the experience of pain or expectation of pain [29]. Given the role of ventral mPFC in processing value, the role of dorsal ACC and recruiting appropriate motor response, the high interconnectivity of the mPFC, and the functional connectivity between the mPFC and lateral PFC, there is likely to be a predictable flow of activity within that guides decision-making and behavioral response. Here, we demonstrate a gradient of mPFC regions that link goal-centered zones with regions that drive behavioral responses by categorizing three stages of strategy execution.

Our task involves a long sequence of decisions about whether to choose a high-effort, high-reward action, versus a low-effort, low-reward action, with pseudo-random variability in the specific effort and reward values over time. Within each trial, we presented the two options sequentially, followed by a decision event, followed by actual exertion of effort (using a pneumatic hand force grip system). At the end of the trial, an outcome event displayed a success cue (amount of points they achieved based on their choice) or a failure cue (subtraction points). Analysis of brain activity and subject behavior was completed only for the presentation events, as strong physiological BOLD activity (relating to increased cardiac output) was observed in all other events.

Decision stages were determined by contrasts of critical moments during each of the presentation events. During each presentation event, subjects were either looking at the high reward, high effort cue (HIGH) (representing the high option), or looking at the low reward, low effort cue (LOW) (representing the low option). Moreover, for any given presentation event, subjects were either about to either select the high option (HOS) or select the low option (LOS).

The **preparation** (PREP) stage was represented in the presentation events as the contrast of ultimately deciding HOS over LOS. This represents the subjects' state of preparing to achieve the high amount of points, as was the main objective of the task. At this level of achieving immediate, concrete goals, we found that posterior ACC and motor frontal areas were most strongly activated.

The **evaluation** (EVAL) stage was represented in the presentation events as the contrast of viewing the HIGH cue vs. viewing the LOW cue. This represents the subjects' state of evaluating

the level of effort and the level of payout of a potential option. At this level of decision processing, we found that posterior dorsal (pd) ACC and right middle frontal gyrus (MFG) were most strongly activated.

The **strategy updating** (STRAT) stage was represented in the presentation events as the contrast of ultimately deciding HOS over LOS. This is the reverse contrast of the PREP stage. Importantly, it represents the state during which subjects felt that the main objective (to achieve maximum points) was not feasible. Therefore, it can be assumed they selected some other strategy for confronting the task event, since they did not end up selecting the HO. At this level of decision processing, we found that anterior dorsal (ad) and pregenual (pg) ACC and right lateral orbital frontal cortex (LOFC) were most strongly activated. This lateral PFC activity can be linked to the 'what' goal processing proposed for ventral frontal cortex.

0.2 Methods

0.2.1 Participants

Subjects were recruited from the Paid Psychology Research System through the University of Colorado at Boulder. Thirty-one (15 female; 16 male) right-handed individuals between the ages of 18 and 35 with no history of neurological or psychiatric disorders were scanned for this experiment. All gave written, informed consent to participate in this study. This study was approved by the Institutional Review Board of the University of Colorado at Boulder. Five subjects were removed from analysis because of scanner malfunction, two removed for brain artifacts, and two removed for improper calibration. This left 22 subjects (10 female) to be used for the main effects imaging analysis.

0.2.2 Image Acquisition and Preprocessing

Functional imaging was conducted on a 3-Tesla Siemens Trio (Erlangen, Germany) scanner equipped with a 32-channel head coil. Multiband sequencing was implemented for the purposes

of increasing SNR. Multiband parameters included: multiband acceleration factor = 3; GRAPPA acceleration factor = 2. In each run, 456 images containing 48 slices (2 mm thick) were acquired. Each run lasted approximately 10 min. Imaging parameters were as follows: repetition time (TR) 1300 ms, echo time (TE) 28 ms, flip angle 50ř, field of view (FOV) of 220 mm, and voxel size of 2 x 2 x 2 mm. A T1 weighted structural data set was collected for the purpose of anatomical localization. The parameters were as follows: TR 2530 ms, FOV 256 mm, voxel size of 1 x 1 x 1 mm.

Functional images were examined for severe motion and artifacts. Images involving movement were modeled separately as nuisance regressors. Runs during which subjects moved more than a voxel (>2mm) were not included in the analysis. fMRI data processing was carried out using MatLab fMRI SPM Toolbox with analysis code developed by CAN (Cognitive and Affective Neuroscience) lab (Tor Wager PhD) at University of Colorado Boulder `http://wagerlab.colorado.edu/wiki/doku.php/help/fmri_tools_documentation`. The following preprocessing methods were applied: motion correction; spatial smoothing; mean intensity normalization; high pass temporal filtering. No slice timing acquisition correction was implemented due to unique acquisition sequence run with the multiband scanning protocol. Registration to high resolution structural images was carried out with SPM's mutual information coregistration. Functional and structural images were manually aligned with the anterior commissure according to the Montreal Neurological Institute. All registrations were manually inspected to ensure proper alignment.

0.2.3 Procedure

Before the experimental run in the scanner, subjects were familiarized with the pressure-sensitive handgrip device. Once in the scanner, subjects were instructed 3 times to exert their hardest grip for 2 seconds. The maximum force during this calibration phase was used as the baseline maximum during the experimental task. Each trial consisted of 5 events: first option presentation (2 sec), second option presentation (2 sec), decision (3 sec), task (6 sec), and outcome (1 sec) (Figure 1). At the beginning of each trial, subjects were presented with the first task option. The screen displayed a scale of reward and a scale of effort to complete in order to achieve the

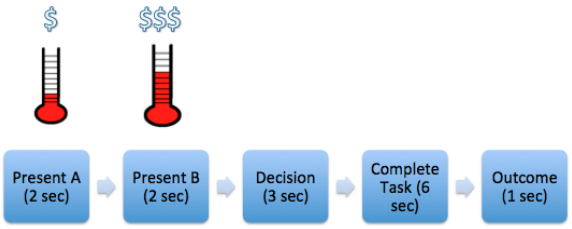

Figure 1: Experimental Paradigm. Each trial consisted of the following 5 events: presentation of first option, presentation of second option, 3-second cue to select task with button box, task event, and result of task by presenting reward if success, failure if failed. The entire trial lasted approx. 30 seconds when accounting for jitter. Fixation cross was presented during time between events.

reward for two seconds. After a 2-4 second baseline screen of a visual fixation cue, the second task option was displayed with the same factors for two seconds (Figure 2).

Every trial consisted of a high option cue (HIGH) and a low option cue (LOW). The HIGH entailed presentation of a high level of reward and a high level of effort. The LOW entailed presentation of a low level of reward and a low level of effort. The order of option presentation was random. On normal trials, the level of reward and effort in the HIGH was represented by a distribution: N(0.75,0.005). The level of reward and effort in the LOW had the distribution: N(0.25,0.005). Reward level is the proportion of maximum points allowed for one trial (100 points). The effort level is the proportion of the maximum force calculated during the calibration phase prior to the experiment.

For every HIGH presentation, the reward and effort levels were always greater than 0.5, while the reward and effort levels were always less than 0.5 for the LOW presentation. This was done by selecting a value between only 5 standard deviations. For each option, the reward and effort levels were selected separately within their respective distribution. Values for each factor were multiplied by 10 and rounded to the nearest integer in order to be presented on the screen with the given scales.

The subjects were then presented with a decision screen. Here, they chose either the first task to complete, or the second, using a button box that was placed in their left hand. Following the decision, the task event began. Subjects had 1 second to match or go above the selected force that

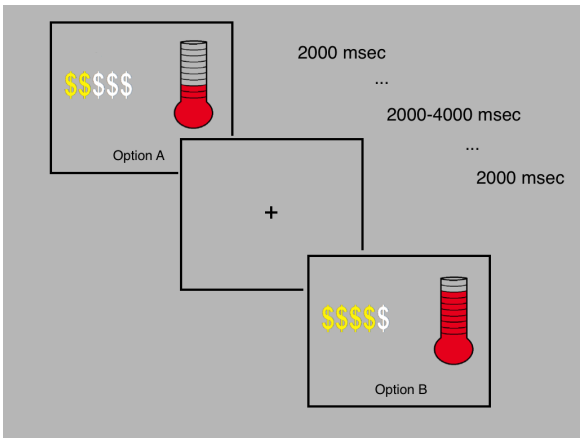

Figure 2: Presentation events with options. This example shows the first two events of a trial. In this case, the low option is presented first (reward and effort levels below half) while the high option is presented second (reward and effort levels above half). Low/High option order was random and counterbalanced. Each trial had exactly one low option and exactly one high option.

was presented on a scale on the left of the screen. They had to maintain that level of force for 5 seconds. Their exertion level was presented in real-time feedback on a scale on the right side of the screen. If they dropped below the chosen effort level during the critical 5-second task duration, the scale turned red. Afterwards, we presented the reward as an increment of points if they succeeded, or a loss of points if they failed. Task failures resulted in a 100 point deduction in the first run, and a 200 point deduction in all other runs.

Between each event, there was a 2-4 second jitter, uniformly distributed. There was also a 2-4 second ITI between each trial. With the given event times, each trial had a duration of approximately 29 seconds. There were 4 runs with 20 trials each. For any given trial, this meant that subjects spent about 5 seconds exerting a physical force, and about 24 seconds in a resting state. The pilot experiments revealed that the relatively short task time allowed subjects to consistently choose the high effort option with little to no effect of fatigue. As a result, subjects had selected 5 or less LO tasks out of the 80 total trials.

In order to encourage switching behavior, two modifications were made to the reward and effort values for each option. Both modifications were put in place for trials after two or more consecutive HO-completed trials. First, the scale of required force was slightly altered. This modification was designed so that the force required to reach the maximum on the presented scale was a small increment more than the previous trial. When the modification was not present, the scale maximum was set to the subject's calibrated maximum force recorded just before the experiment. The change was small such that the subject would not be able to detect it. We implemented this moving scale instead of just using a constant-difficult scale so that participants did not think that any level of the force meter was physically impossible to achieve. After each consecutive HO trial, the small increase in maximum force was added to the last. Eventually, the scale would approach a point beyond the physical limit of the individual. Thus, in order to avoid task failure, the subject would have to exhibit switch behavior.

Second, we implemented a value modification such that for every trial after two or more consecutive HO selections, the presentation level of reward and effort followed a preset scheme. For

every trial after two or more consecutive high effort tasks, the high option effort (HE) value and the low option reward (LR) value increased 0.05 from 0.75 and 0.25, respectively. In addition, the high option reward (HR) value and the low option effort (LE) value decreased 0.05 from 0.75 and 0.25, respectively.

After the experiment and outside the scanner, the subject completed a questionnaire that measured behavioral characteristics focused on levels of persistence. The persistence rating was calculated by taking the mean of 16 of 20 questionnaire item self-rated scores after reversing necessary items. Four of the items were dropped due to large variance in scores or due to low or negative correlation with the other items.

0.2.4 Materials

Subjects squeezed a simple pressure-sensitive handgrip device in order to experience the expenditure of various levels of physical effort. The device was built from two polymer rods that clamp down on a compressible, polyvinyl air tube. The air tube connects to an air pressure sensor (Honeywell 40PC001B1A) outside the MRI scanner room. The sensor sends a signal to an analog-to-digital converter (NI USB-6009), which then sends a signal to analysis software on a computer in the control room. The design was replicated from [20].

0.2.5 Analysis of Behavioral Data

Due to the force and presentation level modification throughout the experiment, the reward and effort level for different presentations [trials] were not independent. Each level was dependent on the previous choice history of the subject. This was especially the case for LOS trials: 72% involved force and value manipulation due to previous consecutive HOS trials.

Other behavioral variables were analyzed in a multi-level mixed models analysis. Reaction time was entered as a predictor in a linear regression with option selection type (OST) as the outcome. A logistic regression was also run with choice history markers as predictors for high or low option selection type. Choice history markers were represented as options selected (HOS vs. LOS)

for previous trial (Prev1), two trials back (Prev2), and three trials back (Prev3). Beta parameters were calculated for each variable for each subject and were entered in a group-level linear model. Group level regression predictor variables included strength (measured during calibration), gender, and persistence. Failed trials (trials where subjects did not select an option in the designated 3 second decision window and trials where subjects did not maintain the required force for 5 seconds) were removed for the behavioral analysis.

0.2.6 Imaging Analysis

Statistical models were run using a multi-level linear regression analysis. ROI data was acquired by calculating the BOLD group level statistics within each mask. Each event was run as a separate regressor with each presentation event and decision event filtered by option selection (OS) and presentation level (PL) type. The interval between the Decision and Task events as well as the interval between the Task and Outcome events were run as regressors in the model to remove preparation and relaxation effects from the baseline. Trials that resulted in a failed task (N=55 for all subjects) occurred only for HOS trials. All failed task trials were still run in the analysis as a HOS trial. Missed response trials (N=4 for all subjects) were run as LOS trials. While we do not know the intention of the subject because no option was selected, the subject still enjoyed 6 seconds of rest during the task event. Only presentation events (i.e. PresA and PresB) were used in the analysis. BOLD signals were extremely high in nearly all regions of the brain for the Decision event and the Task event for HO trials. This may be due to an increase in adrenaline, and consequently, cardiac output as a response for preparation for high physical effort exertion.

0.2.7 Decision Stages

As previously mentioned, we analyzed BOLD activity during the lead up to the decision moment, namely, the two presentation events for each trial. During a given presentation event, the subject was either viewing the HIGH cue, or the LOW cue. In addition, the subject was either about to select to attempt the high effort, high reward option (HOS) or to select to attempt the low

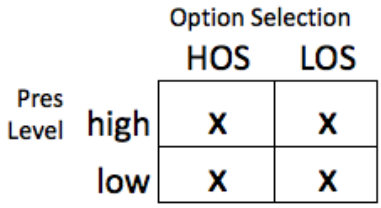

Figure 3: Four possible event types for any given presentation event. Subjects were either looking at the HIGH cue or LOW cue, and simultaneously about to select the high option (HOS) or to select the low option (LOS).

effort, low reward option (LOS). This results in a 2x2 combination of event types. Specifically, any given presentation event would fall into one of these four event types shown in figure 3. For each trial, there would be a HIGH presentation event and a LOW presentation event. However, both presentation events in that trial would be either HOS or LOS.

In order to breakdown stages of the decision-making process, we created contrasts of these event types. Since the main objective of the experiment for the subjects was to attain as many points as possible, the **preparation** (PREP) stage consisted of contrasting the HOS events with the LOS events (top contrast in figure 4). This would show which mPFC and lateral PFC (lPFC) regions were active as the subject prepared to engage in the effortful main objective.

Moreover, the **evaluation** (EVAL) stage represented the part of the decision process where subjects are evaluating the information given to them so that they can make an informed decision. We contrasted the HIGH events with the LOW events in order to show which mPFC and lPFC regions are active for cues containing (or not containing) the information critical for maximizing reward points (bottom contrast in figure 4).

Lastly, the **strategy selection** (STRAT) stage represented a change in strategy representation. Here, subjects did not feel as if the maximum points of the trial were achievable. They ultimately selected to engage in the task that offered the lower amount of points. For any reason, they updated their strategy to something else. We contrasted the LOS events with the HOS events in order to show which mPFC and lPFC regions were active during this strategy update (reverse of top contrast in figure 4).

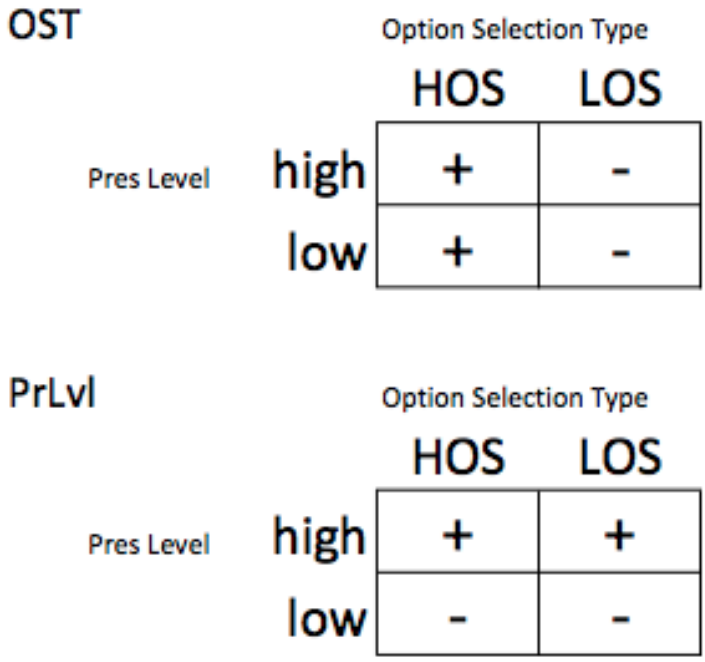

Figure 4: 2x2 categorical analysis involved labeling each presentation event by option selection type (OS) and by presentation level (PrLvl). Imaging analysis involved 2 models: comparing events by ultimate task selection (OS), or comparing events by reward/effort presentation (PrLvl).

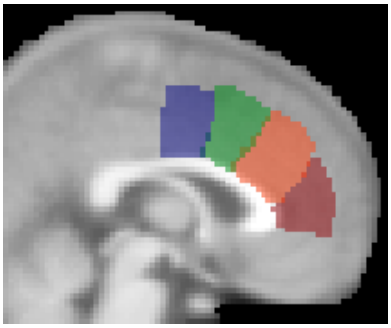

Figure 5: ACC ROIs. Blue = Middle cingulate cortex. Green = posterior dorsal (pd) ACC. Orange = anterior dorsal (ad) ACC. Red = pregenual (pg) ACC.

0.2.8 Region of Interest (ROI) Masks

Imaging analysis resulted in a matrix of statistical scores that reflected the strength of significant BOLD signal in all 2mm voxels with respect to the MNI brain map (MNI152, T1, 2mm). These scores for each voxel were captured in designated ROI masks. As mentioned, the anterior cingulate cortex was divided into 4 separate zones for analysis (Figure 5). All ACC zones were hand-drawn using the mask tool in FSLView. All zones were also created to cover specific areas from the Harvard-Oxford cortical map (2mm voxel, probability/overlap threshold > 0.25). Only three regions from this labeled image were used: Juxtapositional Lobule Cortex (SMA; Area 26), Cingulate gyrus, anterior division (Area 29), and the Paracingulate gyrus (Area 28).

The most posterior region, the middle cingulate cortex (MCC) consisted of the inferior SMA ($z<63$) as well as the Cingulate gyrus region below the SMA. The next rostral area, the posterior dorsal ACC (pdACC), consisted of the Cingulate and Paracingulate gyrus regions within $74>y>66$. As mentioned, the ACC ROIs were hand-drawn in order to fit the contour of the cingulate gyrus around the corpus callosum. Therefore, the anterior and posterior borders formed diagonal margins in the sagittal plane. The anterior border of the pdACC began at $y=70$, and ended at $y=77$. Next, the anterior dorsal ACC (adACC) covered the Cingulate and Paracingulate regions rostral to the pdACC. The anterior border of the adACC began at $y=79$, and ended at $y=86$. Finally, the pregenual ACC (pgACC) encompassed the Harvard-Oxford Cingulate and Paracingulate regions anterior to the genu of the corpus callosum ($z>34$). The width of all ACC zones fell within $52>x>38$.

Other areas of the brain were also of interest in this study as to understand the activity patterns relative to the ACC. Several prefrontal areas, subcortical areas, and a region within the parietal cortex were targets of analysis for this experiment. Tested ROIs included left and right caudate, putamen, nucleus accumbens (from Harvard-Oxford subcortical map), insula, lateral orbital frontal cortex, middle frontal gyrus (DLPFC), motor cortex, and parietal cortex as well as medial structures such as medial superior frontal gyrus, and anterior PFC (frontal pole), and ventral medial PFC. All ROIs were formed from the corresponding Harvard-Oxford cortical map regions. The anterior PFC region in this map was fairly large; therefore, we divided it into a dorsal ($z>38$) and ventral ($z<39$) half.

0.3 Results

0.3.1 Behavioral

Reaction times to select an option ranged from 50 to 2910 ms, with a mean = 580 ms and std = 280 ms (for successful trials). The multi-level linear regression analysis showed that reaction time did not significantly predict choice behavior. Group level parameters, baseline strength, gender, and persistence score also showed no effect on probability of selecting the high option.

Logistic regression of the previous trial choices showed that only two of three preceding trials significantly predicted selection of the high task option on the current trial at the group level when controlling for gender, baseline strength, and persistence score. Prev1 (on the previous trial, selecting the high =1, selecting low = 0) significantly predicted the current trial task selection ($F(3,18) = 5.51$; $p < 0.05$). Also, Prev2 (two trials back, selecting the high =1, selecting low = 0) significantly predicted current trial task selection ($F(3,18) = 5.13$; $p < 0.05$). However, only controlling for baseline strength (not controlling for gender or persistence at the group level, Prev3 highly predicted current trial task selection.

0.3.2 Imaging

Participants showed high persistence to accumulate points. Due to the promised monetary bonus for total points at the end of the experiment, subjects likely had a general strategy to accumulate maximum points each trial. Given the observed variables in the experiment (i.e. option selection and presentation level), 'alternating' the strategy stage could be defined as the presentation events that ultimately led to low option selection. The 'evaluation' strategy stage could be defined as the presentation events that consisted of the subject viewing the high effort, high reward cue. Finally, the 'preparation' strategy state could be defined as the events associated with a high option selection.

0.3.2.1 Option Selection

All trials across all subjects (n=22) resulted in 74% HOS (high option selected) with the remaining as LOS (low option selected) or missed responses (only 4 missed trials over all subjects). The first column of Figure 6 shows the ROI signal results comparing across option selection type conditions during the first presentation event (PresA). Here, subjects showed significantly greater activity bilaterally in all striatal regions when the high option was ultimately chosen compared to events when the low option was ultimately chosen. The option selection type contrast also demonstrated significantly greater activity in bilateral parietal and motor regions as well as MCC for first presentation events that led to HOS (Figure 8A).

The second column of Figure 7 shows the ROI signal results comparing across option selection type conditions during the second presentation event (PresB). Here, subjects showed significantly greater activity in bilateral parietal and motor cortices as well as MCC during events leading to HOS compared to events leading to LOS (Figure 8B). On the other hand, second presentation events leading to LOS showed greater BOLD signal in the right LOFC as well as the anterior dorsal (ad) ACC when compared to second presentation events leading to HOS (Figure 8C,E).

Activity during Presentation A: HOS > LOS

Region	X	Y	Z	Mean Z Score
Left Caudate*	-14	0	20	4.6656
Right Caudate*	18	14	12	5.4289
Left Putamen**	-28	-10	-4	9.0601
Right Putamen***	24	12	4	12.4609
Left Nucleus Accumbens***	-8	10	-8	12.8881
Right Nucleus Accumbens***	8	10	-8	12.3904
Left Insula^	-40	0	-2	3.1329
Right Insula^	36	8	6	3.0276
Left LOFC^	-30	30	-12	4.3264
Right LOFC				
Left Middle Frontal Gyrus*	-28	34	36	5.1076
Right Middle Frontal Gyrus^	36	34	36	3.0276
Left Parietal Cortex***	-26	-46	62	10.3684
Right Parietal Cortex***	28	-46	62	12.1104
Left Primary Motor Cortex***	-24	-16	64	11.3569
	-20	-8	64	
	-24	-24	58	
Right Primary Motor Cortex*	32	-16	66	7.6176
	12	-8	68	
	28	-24	62	
Middle Cingulate Cortex***	4	-2	40	11.8336
posterior dorsal ACC^	4	10	38	4.3264
anterior dorsal ACC				
pregenual ACC				

Figure 6: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. ROI BOLD effects comparing first presentation events (PresA) for which the high option task was ultimately selected to first presentation events for which the low option task was selected

Activity during Presentation B: HOS > LOS

Region	X	Y	Z	Mean Z Score
Left Caudate				
Right Caudate				
Left Putamen				
Right Putamen				
Left Nucleus Accumbens				
Right Nucleus Accumbens				
Left Insula				
Right Insula				
Left LOFC				
Right LOFC*	**34**	**22**	**-12**	**-5.5696**
Left Middle Frontal Gyrus				
Right Middle Frontal Gyrus				
Left Parietal Cortex*	-26	-50	64	6.6564
Right Parietal Cortex***	26	-50	64	10.6929
Left Primary Motor Cortex**	-44	-12	52	9.4864
	-10	-2	66	
Right Primary Motor Cortex***	38	-12	50	10.4329
	26	-6	68	
	10	0	58	
Middle Cingulate Cortex***	0	-6	46	14.1376
posterior dorsal ACC				
anterior dorsal ACC*	**4**	**32**	**28**	**-7.5625**
pregenual ACC^	**4**	**44**	**8**	**-4.1616**

Figure 7: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. ROI BOLD effects comparing second presentation events (PresB) for which the high option task was ultimately selected to second presentation events for which the low option task was selected

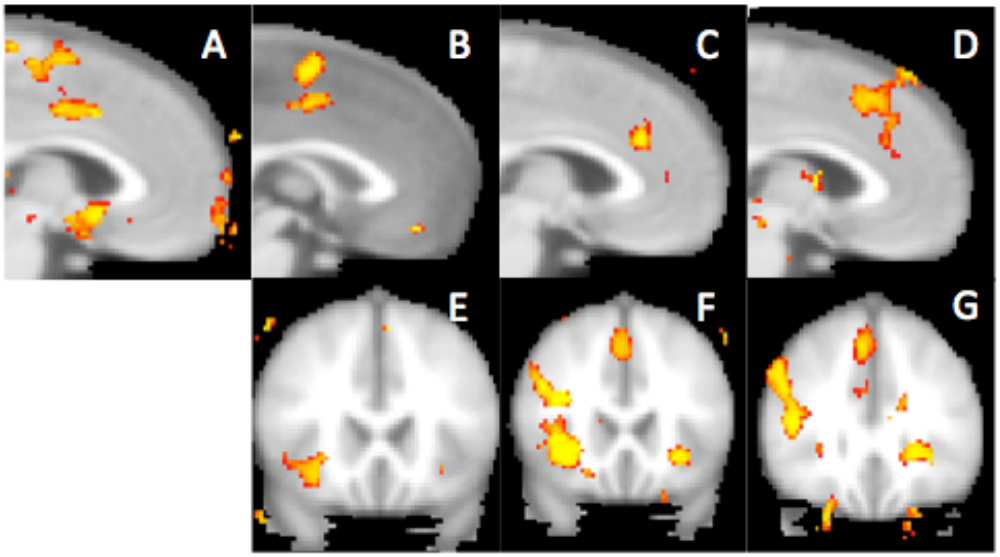

Figure 8: A-D) significant mPFC activity for all conditions. A) (x=4; p<0.004), HOS>LOS during first presentation event. B) (x=0; p<0.0044), HOS>LOS during second presentation event. C) (x=4; p<0.025), LOS>HOS during second presentation event. D) (x=4; p<0.0023), high>low during second presentation event. E) (y=22; p<0.0044), LOS>HOS during second presentation event F) (y=22; p<0.0023), high>low during second presentation event. G) (y=30, p<0.0023), high>low during second presentation event.

0.3.2.2 Presentation Level

Figure 9 shows the ROI signal results comparing across presentation level type conditions for the first and second presentation events. No significant differences were observed during the first presentation event. However, large significant effects were seen in right LOFC, right MFG, left parietal cortex, and posterior dorsal (pd) ACC for events when the high option was presented compared to events when the low option was presented right before the decision event. Smaller significant results were seen in right caudate, right parietal cortex, and adACC.

0.3.2.3 Option Selection x Presentation Level (PresA, PresB)

In order to demonstrate that the option selection type effects on neural activity were significantly different from the presentation level effects, we tested the categorical differences and interactions of the two conditions. Figure 10 shows that the observed effects of OS differences (HOS - LOS) were significantly greater than the differences between Presentation Level (high - low) types in bilateral putamen and nucleus accumbens for the first presentation event.

Figure 11 shows that during the second presentation event, right parietal and MCC showed significant differences between OS and PL effects. It is important to note that the right parietal cortex showed significant effects due to OS and PL conditions. On the other hand, no PL effect was observed in MCC. Nevertheless, the observed effect of OS within the MCC proved to be significantly greater than the influences of high and low reward and effort level presented during the event. In addition, the opposite direction (high-low PL effect compared to HOS-LOS effect) was observed in the right LOFC and adACC. Since both of these regions show significant results for OS and PL contrasts, this 2x2 analysis just demonstrates that these effects were significantly different.

No significant interactions were observed for the first presentation event. Figure 12 shows that the second presentation event produced significant interactions given high and low presentation levels and high and low option selection for that trial. The right nucleus accumbens, bilateral parietal and motor cortices, and pdACC revealed significant condition interactions. All of these regions showed

Activity during Presentation B: high > low				
Region	X	Y	Z	Mean Z Score
Left Caudate				
Right Caudate*	14	14	4	5.0625
Left Putamen				
Right Putamen				
Left Nucleus Accumbens				
Right Nucleus Accumbens				
Left Insula				
Right Insula				
Left LOFC				
Right LOFC**	32	22	-8	9.3636
Left Middle Frontal Gyrus^	-48	12	36	3.7249
Right Middle Frontal Gyrus***	48	30	30	11.0889
Left Parietal Cortex**	-36	-52	52	10.8241
Right Parietal Cortex*	36	-52	50	6.2001
Left Primary Motor Cortex^	-46	2	34	3.9601
	-52	4	36	
Right Primary Motor Cortex^	50	4	38	3.3856
	30	4	50	
Middle Cingulate Cortex				
posterior dorsal ACC**	0	22	44	9.1809
anterior dorsal ACC**	0	32	32	8.3521
pregenual ACC				

Figure 9: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. ROI BOLD effects comparing second presentation events (PresB) for which the high reward and effort cues were presented to second presentation events for which the low reward and effort cues were presented. There were no significant effects for the presentation level condition during the first presentation event.

OST and PL effect differences: PresA

Region	X	Y	Z	Mean Z Score
Left Caudate				
Right Caudate				
Left Putamen*	-32	-6	-6	4.7524
Right Putamen*	30	4	2	5.1529
Left Nucleus Accumbens*	-6	12	-8	7.9524
Right Nucleus Accumbens*	8	14	-8	6.76
Left Insula				
Right Insula				
Left LOFC				
Right LOFC				
Left Middle Frontal Gyrus				
Right Middle Frontal Gyrus				
Left Parietal Cortex*	-16	-48	60	3.1329
Right Parietal Cortex*	24	-48	60	3.2041
Left Primary Motor Cortex				
Right Primary Motor Cortex				
Middle Cingulate Cortex^	8	-4	44	3.7636
posterior dorsal ACC				
anterior dorsal ACC				
pregenual ACC^	10	44	14	3.3489
	-10	44	18	

Figure 10: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. OS and PL effect differences during Presentation A.

OST and PL effect differences: PresB

Region	X	Y	Z	Mean Z Score
Left Caudate				
Right Caudate				
Left Putamen				
Right Putamen				
Left Nucleus Accumbens				
Right Nucleus Accumbens				
Left Insula				
Right Insula				
Left LOFC				
Right LOFC*	**38**	**20**	**-8**	**-8.3521**
Left Middle Frontal Gyrus				
Right Middle Frontal Gyrus				
Left Parietal Cortex^	-20	-50	62	3.5721
Right Parietal Cortex*	26	-48	68	5.29
Left Primary Motor Cortex^	-24	-10	66	4.4521
Right Primary Motor Cortex^	26	-10	62	3.4969
Middle Cingulate Cortex*	2	-2	50	7.3984
posterior dorsal ACC				
anterior dorsal ACC*	**-2**	**36**	**24**	**-5.1076**
pregenual ACC				

Figure 11: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. OS and PL effect differences during Presentation B.

OST and PL Interaction: PresB

Region	X	Y	Z	Mean Z Score
Left Caudate				
Right Caudate				
Left Putamen				
Right Putamen				
Left Nucleus Accumbens				
Right Nucleus Accumbens*	4	14	-6	6.0516
Left Insula^	-40	2	-6	4.2849
Right Insula				
Left LOFC				
Right LOFC				
Left Middle Frontal Gyrus^	-32	32	40	3.3124
Right Middle Frontal Gyrus				
Left Parietal Cortex***	-34	-54	58	12.8881
Right Parietal Cortex*	38	-48	54	6.5025
Left Primary Motor Cortex*	-28	0	66	5.9049
Right Primary Motor Cortex*	44	2	36	8.0089
Middle Cingulate Cortex^	0	2	34	4.1209
posterior dorsal ACC*	0	10	38	6.76
anterior dorsal ACC				
pregenual ACC				

Figure 12: ^= $p < 0.1$; *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.005$. OS and PL effect interactions during Presentation B.

similar activity patterns across the 2x2 categories. Each region showed high BOLD activity during the combination of HOS intention of the subject and a presented high level task cue for the second event.

0.4 Discussion

The results for presentation events grouped by reward/effort level show that significantly more activity was present in the right middle frontal gyrus and bilateral parietal cortex during the second presentation for high levels compared to low. Many previous studies show that the frontoparietal network is prominent in attention [10], especially with reward present [25]. The DLPFC, parts of which were included in the MFG ROI, has been shown to increase activity when engaging in working memory updating for rewarding cues [12]. Since the high option cue represents the task that leads to greater reward, it follows that the subject engages higher attention in order to properly consider the salient option.

The second presentation phase also showed higher right lateral orbital frontal cortex activity for high level of reward and effort. Much research has demonstrated that the lateral OFC is responsible for representing high levels of reward when present [19, 13, 14]. It seems logical that activity in this limbic region would be present in this contrast.

In addition, the anterior and posterior divisions of the dorsal ACC showed higher activity for high reward/effort level presentation cues. This has been shown previously in human imaging experiments where subjects are presented cues representing varying levels of effortful engagement [9, 7]. We reproduced this finding here by showing adACC and pdACC activity during PresB for high level cues, as the second presentation event carries a larger preparation weight since it precedes the moment of decision. However, the current finding does not separate the function of this area with respect to representing effort or reward.

On the other hand, the contrast between option selection types showed significant effects for both presentation events. The first presentation event showed significant bilateral activity in all three of the striatal regions (putamen, nucleus accumbens, and right caudate) for trials that ulti-

mately resulted in a high option selection compared to the trials with a low option choice. Research has shown that the nucleus accumbens and striatum exhibit increased activity for anticipation of reward [23] and effort [9, 26]. Studies in decision-making have also demonstrated that the striatum is important in gating information that may be important for motor plans [8] or for switching or initiating attention to cues associated with reward or goals [11, 3]. Given the observed significant effects between HOS and LOS trials, and the predictable pattern of consecutive choices for each subject, the significant striatal activity for trials ending in high option selection compared to low option selection during the first presentation phase suggest the activation of a possible gating mechanism. It is likely that this signal represents the initiation of an intent to exert effortful grip force on the device.

This first presentation event also showed significant activity in the aforementioned frontoparietal circuit, although only in the bilateral parietal cortex. The high activity in this circuit persisted until at least the decision phase, suggesting a general heightened attention to the screen and task during the progression of high option selected trials.

As research has shown the anterior cingulate cortex to be implicated in effort representation and motivation, it does not seem surprising to see significantly increased BOLD signal in this area leading up to the effortful task. The middle cingulate cortex ROI as well as bilateral motor regions showed heightened activity for the first presentation event prior to physically effortful engagement. Vogt (2009) suggests that this middle zone of the cingulate gyrus is responsible for motivating simple motor movements [32]. Kremer et al. showed that electrical stimulation of the cingulate motor region in pre-surgical patients resulted in the self-report feeling of having the urge to reach out and grab [18]. Therefore, it seems likely that the MCC signal is responsible for recruiting the necessary muscular drive to complete the physically demanding task in this experiment.

During the second presentation event, high option selection trials showed continuing significant activity in bilateral motor and parietal cortex as well as middle cingulate cortex. On the other hand, trials resulting in low option selection showed higher activity in more rostral ACC regions, with significant signal observed in adACC and a trend of activity in pgACC ($p<0.1$). Significant higher

activity for LOS trials was also observed in right LOFC. Rostral cingulate areas have been tied to pain or loss expectation [29] as well as conflict [6]. While strong attention and motor recruitment is probable in high option trials, low option trials may involve a conflict of primary goals (achieving points) and bodily state (pain of muscle exertion or glucose depletion). As participants showed persistence in working for high points accumulation, decision of taking the low point option may conflict with their main strategy of making money in the task. It is possible that the fatigue from previous trials may have built up so much that it conflicted with the motivation to take on the effortful task.

Following with the conflict detection story [6], the approaching moment of decision with a strong signal of physical fatigue/weakness or worry of failure may be represented in this more rostral cingulate area, adACC (and trending pgACC) which could potentially drive a NoGo/Stop signal to impede ongoing motivation for points. Then, an alternate strategy may be spurred up in LOFC which could represent the goal to relax or select low effort related cues. O'Doherty et al. (2003) have shown that human subjects show increase in LOFC activity that is related to detecting a change in reward contingencies [22] [28]. This increase in BOLD signal may be due to the ramp up of a new goal representation and/or the inhibitory interneuron activity that quenches the recent, no long relevant goal activity pattern.

In order to demonstrate the strength of the results for each contrast (option selection type and presentation level) (OS and PL), we ran a 2x2 effect differences and 2x2 interaction test. The significant effect we observed for HOS trials over LOS trials during the first presentation event in bilateral putamen and nucleus accumbens proved to be significantly greater than any difference between high and low presentation level events. However, no other significant OS region proved to have a significant difference from the PL contrast for the first presentation. Nevertheless, this significant difference for the OS contrast in the striatum suggests that participants did indeed make task decisions by Presentation A. Furthermore, as discussed above, this activity may represent a gating signal necessary to update an attention or motor plan to engage in the high effortful task once the decision moment arrives.

Moreover, OS and PL effect differences were significant in the right LOFC, right parietal, MCC, and adACC for the second presentation. It is expected to see effect differences in the right LOFC and adACC as the effects for PL were positive and for OS negative. Right parietal had a significant positive result in both OS and PL contrast. However, the effect was very strong across option selection type. In addition, the MCC effect was very strong for the OS contrast. This suggests that participants show more activity in MCC for all trials that result in choosing to execute a highly effortful task compared to choosing the easy task relative to what is being presented on the screen.

It is also important to account for the interactions of event categories. Right parietal, as well as left parietal, right nucleus accumbens, pdACC, and bilateral motor cortices showed a significant interaction. All of these regions showed the highest activity for the event where the high option cue was presented and was also ultimately selected. Based on previous discussion, higher attention and motor recruitment seems likely during this presentation category. Higher nucleus accumbens activity might suggest a strong gating signal occurring to promote an action plan to carry out the currently presented high reward/effort cue. Also, high pdACC activity for this condition would suggest a significant recruitment in attention for the salient cue, as well as potential motor recruitment. However, pdACC activity was not significant for the OS contrast.

Of the significant effects observed between the simple OS contrasts and PL contrasts, a good story about goal, attention, and behavioral recruitment in effort-related decision-making emerges. When we divide the presentation events to highlight the difference of ultimate decision, we see high activity in the MCC and motor regions. Therefore, the middle cingulate cortex, which has also been described as the cingulate motor area [33, 32], is responsible for recruiting activity in the supplementary and primary motor cortex for preparation of high physically effortful action. This recruitment appears to last several seconds as the signal was present for both presentation events prior to the decision.

As the subjects showed a great drive for accumulating points, it can be assumed that the reward cues (mostly filled dollar signs) during the presentation events that signified the high option should represent a salient, reward-predicting piece of information. Therefore, it is reasonable to

conclude that the anterior and posterior dACC coactivation we observed with the fronto-parietal network is due to recruiting attention towards salient, reward-related information that can greatly influence decision-making.

Beckmann et al. (2009) parcellated the cingulate cortex into 9 separate subregions [4]. Their study showed very strong white matter connectivity (using DTI imaging) between the DLPFC and clusters in the ACC that would overlay the pdACC and adACC ROIs in the present study. Beckmann also showed high connectivity between the premotor cortex and ACC clusters that correspond to the MCC and pdACC ROIs here. This anatomical relationship strongly supports the observation of coactivity between MCC and premotor and between dACC and MFG, as well as the behavioral contrasts with which they corresponded.

Finally, assuming the subjects were acting to maximize their point total, it seems likely that deciding to avoid full effort exertion and accept the lower point option did not fit their prominent goal or motivation. Therefore, we conclude that the adACC and right LOFC coactivation for LOS events compared to HOS events suggests a detection of cost while quenching original goal representations and/or actively recruiting a new goal representation. As mentioned, O'Doherty et al. (2003) showed that LOFC is active for a change in reward contingencies due to unexpected loss of reward [22]. The activity seen in right LOFC prior to low option selection may be due to a goal update due to realization of a lack of resources to successfully exert effort.

However, Beckmann et al. (2009) showed that there is little to no white matter connection between adACC and pgACC regions with LOFC [4]. Rather, only the sgACC (BA 25) has interconnections to the orbital zones. While we did not include vmPFC or sgACC regions in our ACC ROI gradient, we still did not see significant activity there for this experiment (may be due to signal dropout for present fMRI imaging protocol). Nevertheless, the LOS>HOS contrast proved to be our most rostral significant signal in the ACC. Sallet et al. (2011) showed that rostral areas of the ACC brain project to the frontal pole (BA 10) in the macaque [30]. We speculate that the rostral activity of the ACC (adACC specifically) for LOS presentation events could potentially be sending recruitment-related activity to frontal pole regions. Boorman et al. (2009) showed that

heightened activity in the frontopolar cortex precedes and is present during the decision to switch to an alternative plan of action [5]. While we did not see reliable significant activity in our aPFC ROIs, it is possible that adACC activity could recruit abstract regions of the PFC until a new goal representation is formed in LOFC areas. Alternatively, adACC activity for LOS presentation events may instead send information down to the dorsal or ventral striatum [4] to influence the canceling or updating of goal representations in LOFC.

Overall, in this study, we demonstrated that we could successfully break apart the decision-making process regarding effort by presenting pieces of information for the decision as two distinct options. We showed that presenting these two options separately as a cue for a highly motivating (high points) yet highly difficult (high effort) task and as a cue for a less motivating and easy task, subjects could choose between them over many repetitions and show significant differences in PFC activity compared across behavioral contrasts.

Secondly, we demonstrated that the anterior cingulate cortex has varying roles in processing strategy progress. Specifically, this region has a rostral-caudal gradient along which a function of strategy updating, evaluation, and preparation behavior is dependent. Azuar et al. (2014), Badre et al. (2009), and O'Reilly (2010) have demonstrated a hierarchy of abstraction in cognitive functioning across the lateral PFC [1, 2, 24]. Maintenance or attention to abstract concepts requires very anterior LPFC regions, while concrete simple rules are represented in more posterior LPFC. In addition, Beckmann et al. (2009) and Sallet et al. (2011) have shown anatomical connectivity of the ACC and PFC that follows this rostral-caudal axis [4, 30]. We have extended the knowledge of the ACC connective and functional gradient to decisions involving exerting high levels of effort to achieve reward, specifically by MCC recruitment of premotor areas for action preparation, by pdACC recruitment of MFG for attentive evaluation, and finally by adACC recruitment of LOFC for strategy updating.

This study has shown that negative events, or challenges, can be represented in the ACC (overcoming fatigue and still exerting a strong physical force in MCC, or giving in to fatigue and switching strategies to avoid overexertion in adACC). It also shows that the appropriate response

to these challenges are, in some way, recruited by this mPFC signal and represented in the lPFC. Previous research has suggested that the ACC plays a role in representing a 'cost' value that is then subtracted into a 'benefit' value to produce a 'utility' value [7, 9]. Thus, each option that could be considered in a decision has its own 'benefit' and 'cost' value that forms a final 'utility'. The option with the highest utility value is the option that is ultimately selected. However, if decision-making is a settling process that is carried out by the excitatory glutamatergic activations in the neocortex, how can a 'cost' representation provide a negative weight to the utility calculation?

The answer may have something more to do with how the 'cost' (or any negative signal) drives a response than it does with bringing down a scalar value of utility. Shenhav et al. (2013) have proposed a theory of cognitive control in the ACC. They suggest that the ACC monitors ongoing context and behavior. When conflict, error, or uncertainty is predicted, a signal in the ACC then specifies a response in the LPFC. Here, a representation then acts to regulate current behavior and attention in order to drive an appropriate response in a chaotic environment [31].

This monitor-specification-regulation theory for ACC-LPFC interaction may have a role outside cognitive control. We have proposed the rostral-caudal gradient of the ACC has functional range between responding to concrete and abstract goals, as well as representing 'what' characteristics and 'how'/'where' relationships of motor behavior. The ACC-LPFC interaction may apply to any coordinate of the full rostral-caudal ACC topography (from MCC to subgenual (sg) ACC). This would suggest that ACC could pick up any flavor of 'what'/'how' and concrete/abstract representation linked to online goals and recruit the corresponding rostral-caudal LPFC region that could regulate appropriate behavior. Instead of the ACC representing a 'cost' factor that subtracts value from a generic utility measure, the ACC predicts negative events (e.g. cost) and drives a response that has been learned to produce the best (most rewarding, satisfying, etc) behavior for that situation.

Future work involves teasing apart the causal directionality of rostral ACC regions and goal contingency switching in the lateral OFC regions. Also, it may be of interest to elucidate the specific effects of varying levels of reward and effort on mPFC activity. How does ACC activity vary along

this recruitment gradient as a function of available reward separately from required effort?

In addition to further experimental dissection, neural network models can be designed to capture the motivational processing functions of the ACC and its recruitment interactions with lateral PFC regions. Personal future work will involve modeling motivation processing and behavioral recruitment.

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