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Research report

# The neural signature of escalating frustration in humans

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ABSTRACT

Mammalian studies show that frustration is experienced when goal-directed activity is blocked. Despite frustration's strongly negative role in health, aggression and social relationships, the neural mechanisms are not well understood. To address this we developed a task in which participants were blocked from obtaining a reward, an established method of producing frustration. Levels of experienced frustration were parametrically varied by manipulating the participants' motivation to obtain the reward prior to blocking. This was achieved by varying the participants' proximity to a reward and the amount of effort expended in attempting to acquire it. In experiment 1, we confirmed that proximity and expended effort independently enhanced participants' self-reported desire to obtain the reward, and their self-reported frustration and response vigor (key-press force) following blocking. In experiment 2, we used functional magnetic resonance imaging (fMRI) to show that both proximity and expended effort modulated brain responses to blocked reward in regions implicated in animal models of reactive aggression, including the amygdala, midbrain periaqueductal grey (PAG), insula and prefrontal cortex. Our findings suggest that frustration may serve an energizing function, translating unfulfilled motivation into aggressive-like surges via a cortical, amygdala and PAG network.



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From running and missing the bus to helplessly observing someone commandeer our taxi, daily life throws numerous obstacles in the path of our desired goals. Such events evoke frustration, which can escalate into aggression, in alignment with theories positing that frustrating barriers to the attainment of expected gratification instigate aggressive behavior (Berkowitz, 1989; Dollard, Doob, Miller, Mowrer, & Sears, 1939). Yet despite frustration's putative role in this process, its underlying neural systems remain unspecified. One proposal is that frustration reflects mild engagement of the reactive aggression system which increases in proportion to the intensity of the desire that is thwarted (Panksepp, 2005); however, this remains to be demonstrated.

Knowledge of the neural basis of reactive aggression comes largely from comparative research. Electrical and chemical stimulation studies and lesion studies in animals have identified a core aggression circuit comprising the amygdala, hypothalamus, and periaqueductal grey (PAG) (Nelson & Trainor, 2007; Panksepp, 2005). The area of PAG involved in aggression receives direct inputs from the hypothalamus, and from the medial prefrontal and insular cortices which have been proposed to have a role in evaluating the emotional content of frustrating events (Bandle, 1988; Panksepp, 2005). The prefrontal cortex has inhibitory connections to aggression-relevant regions of the amygdala, and both regions have been implicated in aggression-related psychiatric disorders (Blair, 2010; Davidson, Putnam, & Larson, 2000). Following the hypothesis that frustration induces reactive aggression, we predicted that the areas implicated in reactive aggression would be associated with frustration in humans.

Motivation or desire to attain a goal has been shown to affect the level of frustration and aggression when thwarted (Amsel, 1992; Dollard et al., 1939). We therefore used a parametric design that varied participants' motivation prior to blocking using two established strategies — the goal gradient principal, which shows an animal's desire to achieve a goal increases with increasing goal proximity (Hull, 1932; Shidara & Richmond, 2002), and the effort expended in reaching the goal (Pompilio, Kacelnik, & Behmer, 2006; Staw, 1976). Manipulations of goal gradient are frequently confounded with expended effort (Hull, 1932; La Camera & Richmond, 2008; Shidara & Richmond, 2002). Therefore, it is important to separate contributions of these prospective (proximity) and retrospective (expended effort) variables.

Human research shows that people's frustration is often displaced towards innocent bystanders or inanimate objects, for example, slamming a door or forcefully pressing the keys of a computer keyboard (Haner & Brown, 1955; Kapoor, Burleson, & Picard, 2007). Similarly, comparative research shows that a frustrating event has an invigorating effect on behaviors that immediately follow it (Amsel, 1992). Consequently, we used participants' key-press force to confirm the outcome (blocked or win) as an objective index of frustration in response to blocking (Kapoor et al., 2007). In addition, participants were also asked to rate their level of frustration after being blocked. Experiments 1a & b verified that our paradigm was effective in eliciting frustration, and that the level of frustration was related to the participants' motivation to attain the goal at the point of blocking. Experiment 2 used functional magnetic resonance imaging (fMRI) to address the neural basis of human frustration. We predicted that frustration would engage similar brain areas to those implicated in animal models of reactive aggression, and that mirroring the behavioral data, the level of engagement should be related to participants goal-directed motivation when blocked.

## 1. Experiment 1a (behavioral study)

### 1.1. *Materials and methods*

#### 1.1.1. *Participants*

Twenty-seven healthy male volunteers (mean age and SD 23.4 ± 2.5) participated in Experiment 1a. All were right-handed and fluent English speakers. The study was authorized by the Hertfordshire Research Ethics Committee and informed written consent was obtained from each participant.

#### 1.1.2. *Apparatus*

A specially designed pressure button box was used to record the force participants applied to the buttons and their reaction times (Magconcept® Sunnyvale, CA). The digitized force signal was recorded with a resolution of ~.3 N (Newton). The sampling rate was 500 Hz. This allowed RTs to be measured to the nearest 2 msec. RTs were computed as the time at which the force first exceeded 2 N. This value is well within the range used by standard all-or-none response keys for recording RTs.

#### 1.1.3. *Paradigm*

The multi-trial reward schedule task was composed of separate schedules comprising four (1/4, 2/4, 3/4, 4/4), three (1/3, 2/3, 3/3), two (1/2, 2/2) or one (1/1) trial(s). Participants were required to complete all trials in each schedule to obtain two pounds reward. Each trial was preceded by a two second presentation of a schedule cue indicating the number of trials that were left to complete (e.g., two filled boxes and two blank boxes represented two trials left to complete) (Fig. 1). Progress towards winning the reward was also indicated by the proportion of a two-pound coin that was visible.

After each schedule cue, participants were presented with an array of 3 arrows (i.e., ">>>" or "<<<") for 1 sec and were required to indicate the direction of the arrows as quickly and accurately as possible to advance through the schedule. Participants were told that the response criterion for each trial was set by the computer in an unpredictable fashion. If their RT was slower than the criterion or they responded incorrectly, the appropriate feedback ("Blocked") would be presented for 2 sec, and they would fail to win the reward. However, if they completed all trials in a schedule successfully they would win the reward and the feedback "Win" would be presented. In fact, the response criteria were predetermined so that participants lost about 14 times at each schedule state and won on about 33% of trials within each schedule (Fig. 2). Thus, if the feedback was predetermined to be negative, participants would be presented "Blocked" regardless of their actual RT. If the feedback was predetermined to be positive, participants would advance to the next trial in the schedule or

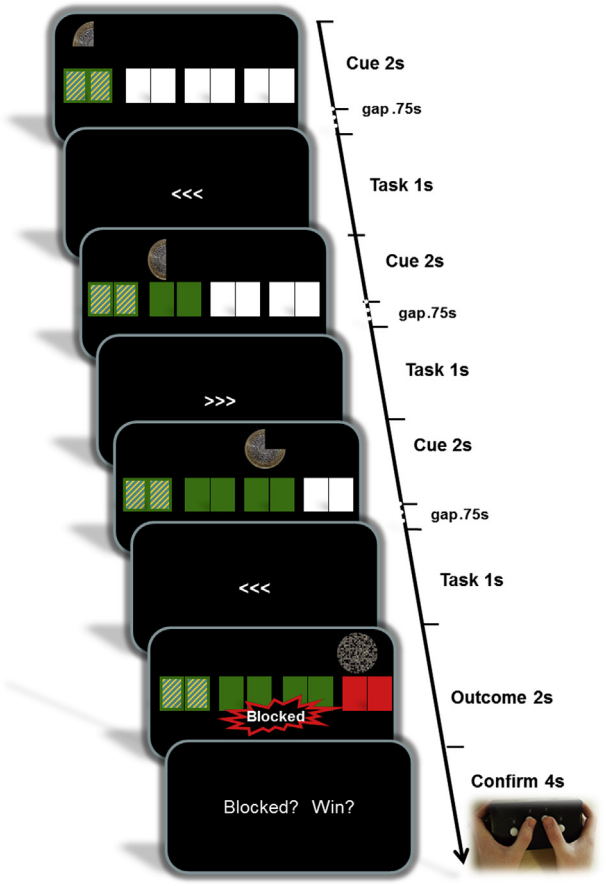


**Fig. 1 – The multi-trial reward schedule task in Experiment 1a. Illustration of a 3-trial schedule in which the participant has been blocked on the last trial.**

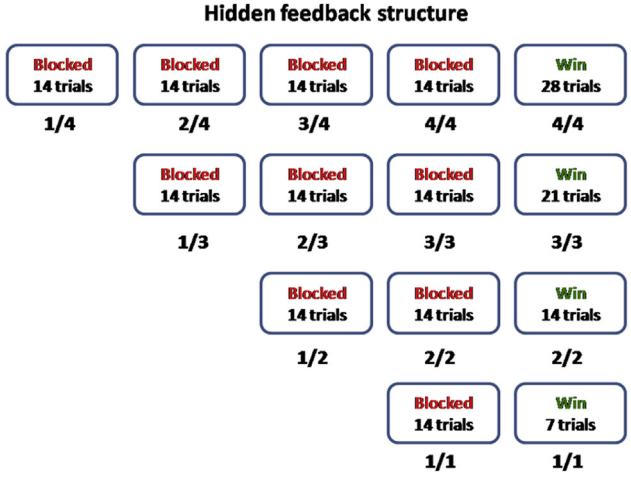


**Fig. 2 – The predetermined feedback structure of Experiment 1a. The number of trials for blocked and win outcomes in each schedule state. The outcomes were predetermined such that the percentage of schedules rewarded was 33% and participants were blocked the same number of times at each schedule state.**

be presented "win" if it is the last trial, unless they pressed the wrong button or their RT was slower than 500 msec. Note that these probabilistic contingencies result in different expected values across the trials within each schedule, such that the expected value generally increases as a function of goal proximity and effort expenditure. The task was designed in this way to reinforce the impact of proximity, on the basis that such probabilistic contingencies are common in ecological situations (Pompilio et al., 2006), and have been used in previous animal research (Shidara & Richmond, 2002). Participants were encouraged to respond as fast as possible and post-experiment debriefing did not identify any performance strategies deliberately.

After the feedback, participants were presented with words "Win? Blocked?" (or "Blocked? Win?") on the screen and were required to press the corresponding key to confirm the schedule's outcome within 4 sec. In order to dissociate the force with speed in confirmation stage, we deliberately asked participants to take their time to indicate the outcome valence. Participants were not required to confirm outcomes as fast as possible. They were told that "Confirming the outcome is not a speeded task, and that you have plenty of time (4 sec) to make this response". Thus response force is unlikely to be confounded by response speed and the two measures were not significantly correlated ($p = .72$). The stimulus presentation and response recording was controlled by E-prime (Psychology Software Tools, Inc. Pittsburgh, PA, USA, www.pstnet.com/eprime). The whole experiment comprised 210 trials and lasted about 52 min.

At the end of the experiment, participants were asked to indicate how motivated they felt at different schedule stages using a 10-point analogue Likert scale (1 = not at all, 10 = very intensely). They were also asked to indicate how frustrated and surprised they felt after being blocked at each schedule state. After completing the experiment, all participants were rewarded ten pounds bonus in addition to a nine pounds payment for participating.

#### 1.1.4. *Behavioural data analysis*

To test the proximity effect, we carried out three separate ANOVAs: one comparing performance on the first trial of the four schedules (1/4, 1/3, 1/2 and 1/1) for which proximity varied from 1 to 4, while the expended effort level was kept constant (effort level = 1), one for the second trials (2/4, 2/3, 2/2; proximity 1 to 3, effort level = 2), and another for the third trials (3/4 and 3/3; proximity 1 to 2; effort level = 3). Stouffer's combined $p$ was calculated as an overall index of the significance of the proximity effect. This method combines $p$-values from several different analyses to test whether collectively they can reject a common null hypothesis (Stouffer, Suchman, DeVinney, Star, & Williams, 1949; Whitlock, 2005). Similarly, we carried out three separate ANOVAs to test the effort effect: one comparing performance on the final trials (4/4, 3/3, 2/2, 1/1) for which expended effort varied from 4 to 1, while proximity was constant (proximity = 4), one for the penultimate trials (3/4, 2/3, 1/2; effort 3 to 1, proximity = 3), and another for the antepenultimate trials (2/4, 1/3; effort 2 to 1, proximity = 2). Again, Stouffer's combined $p$ was calculated as an index of the significance of the overall expended effort effect.

## 2. Results & discussion

Subjective emotion ratings completed after Experiment 1a showed that participants' motivation increased as a function of increasing goal proximity (Stouffer's combined $p < .001$), and as a function of increasing expended effort (Stouffer's combined $p < .001$; see Fig. 3a and Table 1). Similarly, RTs decreased as a function of both goal proximity (Stouffer's combined $p < .001$) and expended effort (Stouffer's combined $p < .001$, Fig. 3b and Table 1). Mean RTs in 10 schedule states were significantly correlated with mean self-reported motivation across subjects ($r = -.90$, $p < .001$), indicating good consistency between these measures.

Consistent with our hypothesis that frustration would be influenced by factors affecting motivation, we found that both self-reported frustration (Fig. 3c) and response force to confirm blocking (Fig. 3d) increased as a function of proximity (Frustration: Stouffer's combined $p < .001$; Response force: Stouffer's combined $p < .005$) and expended effort (Frustration: Stouffer's combined $p < .001$; Response force: Stouffer's

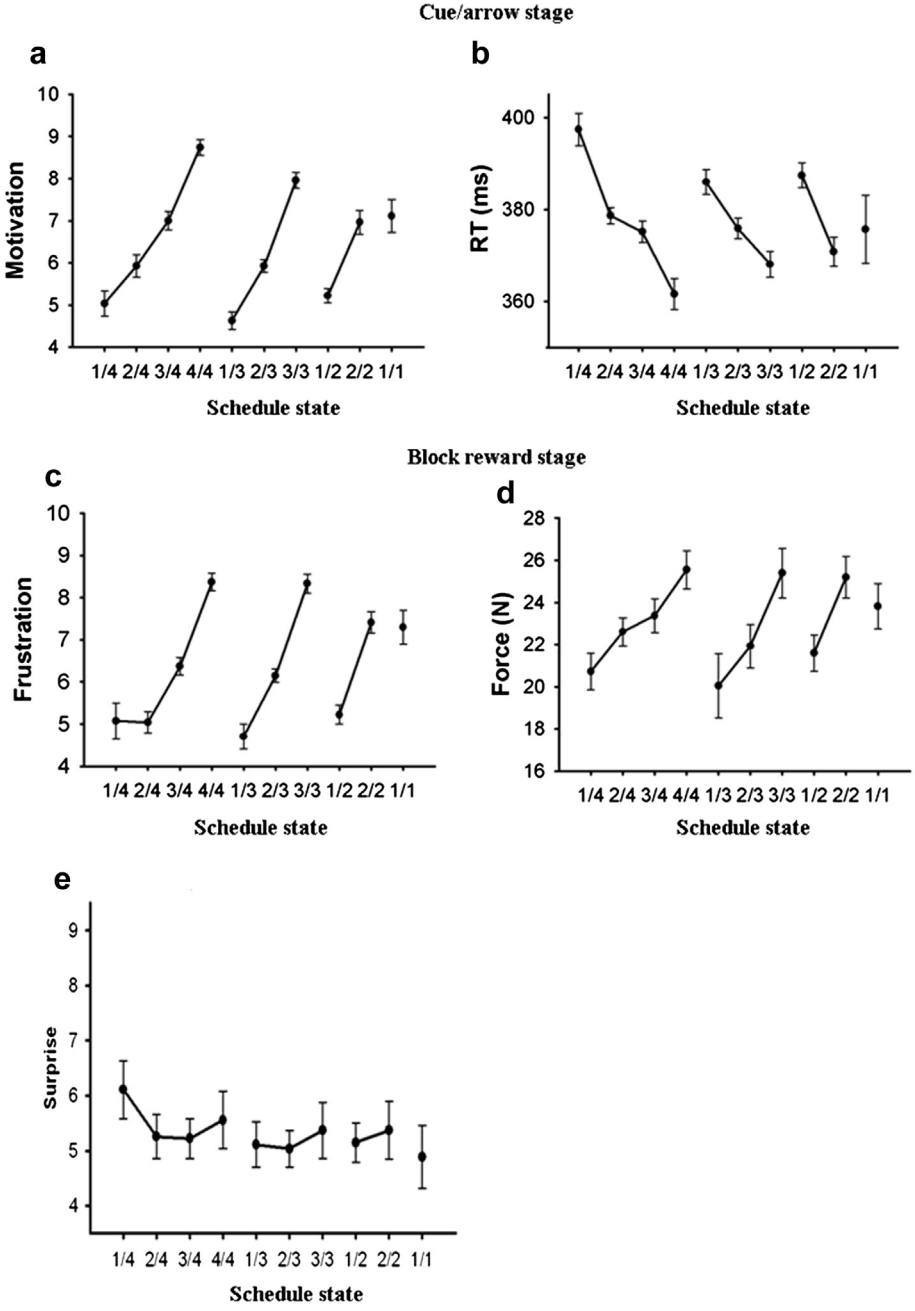


**Fig. 3 – Behavioral data from Experiment 1a (behavioral study). Self-reported motivation (a) to obtain the reward and RTs (b) to arrows at each of the different schedule states; Self-reported frustration (c), applied response force to confirm blocked outcome (d), and self-reported surprise (e) at being blocked. Error bars indicate standard error of the mean, after between-subject variability has been removed, which is appropriate for repeated-measures comparisons (Loftus and Masson, 1994). This applies to all error bars shown in this paper.**

**Table 1 – The *F* values and *p* values from the ANOVAs in Experiment 1a examining the linear effects of proximity and expended effort across 4, 3, and 2 trials. *Stouffer's combined *p* values are also reported as an index of the significance of combined effects of proximity or expended effort across the three ANOVAs.**

| Conditions | Motivation | RT to arrows | Frustration | Force | Surprise |
|---|---|---|---|---|---|
| *Proximity effect* | | | | | |
| 1/4, 1/3, 1/2, 1/1 | 10.76 ($p = .003$) | 5.93 ($p = .022$) | 9.40 ($p = .005$) | 2.89 ($p = .101$) | 3.85 ($p = .051$) |
| 2/4, 2/3, 2/2 | 4.00 ($p = .056$) | 6.12 ($p = .02$) | 24.91 ($p < .001$) | 4.72 ($p = .039$) | .37 ($p = .592$) |
| 3/4, 3/3 | 7.17 ($p = .013$) | 5.16 ($p = .032$) | 51.07 ($p < .001$) | 2.21 ($p = .149$) | .15 ($p = .886$) |
| Combined effect* | $p < .001$ | $p < .001$ | $p < .001$ | $p < .005$ | $p = .455$ |
| *Expended effort effect* | | | | | |
| 4/4, 3/3, 2/2, 1/1 | 16.69 ($p < .001$) | 2.34 ($p = .139$) | 9.20 ($p = .005$) | 1.85 ($p = .186$) | 2.87 ($p = .072$) |
| 3/4, 2/3, 1/2 | 27.50 ($p < .001$) | 9.26 ($p = .005$) | 10.35 ($p = .003$) | 1.68 ($p = .207$) | .811 ($p = .421$) |
| 2/4, 1/3 | 20.47 ($p < .001$) | 3.97 ($p = .057$) | 1.56 ($p = .223$) | 1.65 ($p = .210$) | .47 ($p = .644$) |
| Combined effect* | $p < .001$ | $p < .001$ | $p < .001$ | $p = .07$ | $p = .227$ |

combined $p = .07$). Furthermore, motivation prior to blocking in 10 schedule states was significantly correlated with mean frustration ($r = .95$, $p < .001$) and mean response force ($r = .66$, $p < .05$) when blocked across subjects, consistent with the hypothesis that motivation would enhance each, and mean response force was significantly correlated with mean self-reported frustration across subjects ($r = .85$, $p < .005$), supporting the hypothesized relationship between these latter dimensions. Importantly, self-report ratings of surprise at being blocked did not increase as a function of proximity or expended effort (Stouffer's combined *p* values >.1, see Fig. 3e). This demonstrates that the behavioral and neural indices of blocking are unlikely to reflect any unexpected or startling property of these events. Moreover, it challenges the view that blocking needs to be unexpected or surprising in order to produce an aggressive reaction (Kregarman & Worchel, 1961).

Participants made an incorrect response on 7.0% (SD = 5.1%) of trials in Experiment 1a. Since the number of errors for each condition was small and the data contained a number of cells for which performance was at floor (0%), the error rates were not analyzed further. RTs for outcome confirmations were 886 msec (SD = 212). There was no main effect of proximity or expended effort on outcome RTs ($p > .1$). Thus, the effects of proximity or expended effort on response force following block outcomes are unlikely to reflect differences in RTs. Indeed, mean RTs in 10 schedule states were not correlated with mean response force across subjects, $p = .72$. Thus, outcome RTs were slow and pressing buttons hard were not simply a result of pressing faster. For the error rates, participants made an incorrect response at outcome on 3.3% (SD = 2.7%). Since the number of error trials for each condition was small, error rates were not analyzed further.

The effects of proximity or expended effort on self-reported surprise following blocking were not significant (Stouffer's *p* values >.2). Thus, the effects on other measures (frustration, response force) cannot be accounted for by any alerting or arousing property of being blocked.

The findings demonstrate that our paradigm captures the effects of blocking goal-directed behavior on frustration and displaced aggression, and the facilitating effects of heightened motivation. In Experiment 1b we sought further confirmation of the accentuating effects of motivation by investigating whether rated frustration and response force were greater when blocked from obtaining a large (£2) relative to a small (20pence) reward.

## 3. Experiment 1b (behavioral study)

### 3.1. *Materials and methods*

#### 3.1.1. *Participants*

Twenty healthy male, right-handed subjects (mean age ± SD: 22.3 years ± 2.1) participated in Experiment 1b. Participants were instructed that they would have the opportunity to win money on the task and were rewarded four pounds bonus in addition to the nine pounds payment for participation. The study protocol was approved by the Hertfordshire Research Ethics committee and informed written consent was obtained from each participant.

#### 3.1.2. *Paradigm*

At the beginning of each trial, participants were presented with an image of a coin (e.g., £2 or 20p) indicating the reward they could win on this trial. In order to receive the reward, they were required to successfully perform a series of four arrow discrimination tasks. The rest of the procedure had the same format as the 4-trial schedules from Experiment 1a, except that the whole experiment comprised 192 trials (96 trials for £2 condition and 96 trials for 20p condition; for each magnitude condition, there were 16 blocked trials at each schedule state and 32 win trials). The experiment lasted approximately 43 min.

## 4. Results & discussion

In Experiment 1b, we found that as the final (rewarded) trial approached, participants' self-reported motivation increased and their RTs decreased, consistent with the results of Experiment 1a (Fig. 4 and Table 2). Participants also reported stronger motivation and were faster to categorize the direction of the arrows for high than low reward schedules. After being blocked, self-reported frustration and response force increased as a function of increasing proximity to the reward and increased reward magnitude (Fig. 4 and Table 2). Consistent with Experiment 1a, participants' self-reported frustration in 10 schedule states when blocked was significantly correlated with their response force to confirm blocked outcome ($r = .19$, $p = .031$). Also consistent with Experiment 1a, self-reported ratings of surprise at being blocked showed no significant

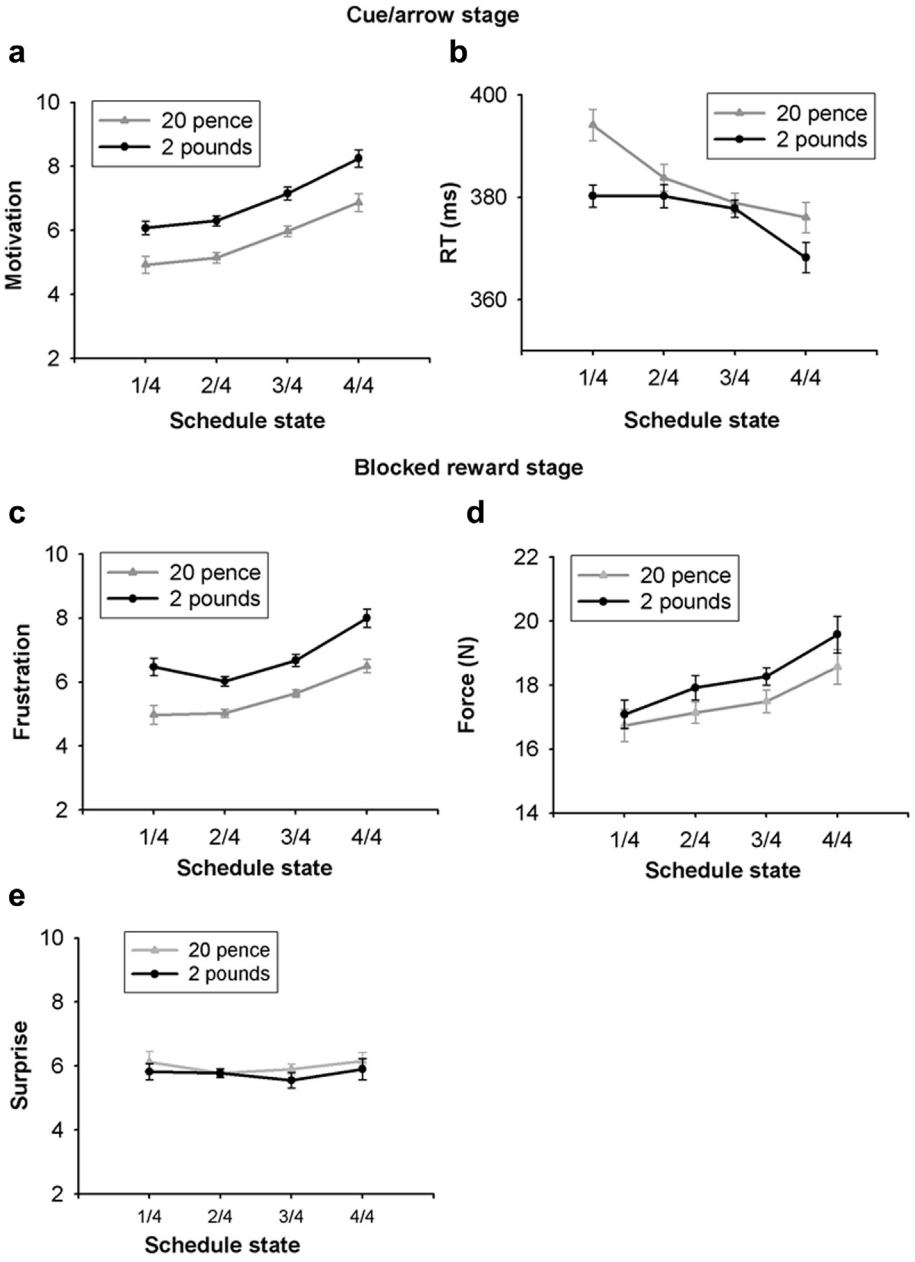


**Fig. 4 – Behavioral results from Experiment 1b (behavioral study). Self-reported motivation (a) to obtain a reward (20p or £2) and RTs (b) to arrows at the different schedule states (i.e., 1/4, 2/4, 3/4, and 4/4); Self-reported frustration (c), applied force response to confirm outcome (d), and self-reported surprise (e) at being blocked at the outcome stage.**

main effects of reward magnitude or proximity (*p*s > .2) (Fig. 4). Participants made an incorrect response to arrow cues on 5% (SD = 3.7%) of trials and an incorrect response to confirm outcome on 3.4% (SD = 4.2%) of trials in Experiment 1b. Since these data contained a number of cells for which performance was at floor (0%) and error rates were low, neither were submitted to a statistical analysis. Mean RTs to confirm outcomes were 954 msec (SD = 246), as for Experiment 1a RTs were not significantly related to response force ($p > .5$), and there was no main effect of proximity or magnitude on RTs to confirm blocked outcome (*p* values >.2). Hence, the effects of response force at outcome were not secondary to effects of RTs.

**Table 2 – The *F* values and *p* values from the ANOVA in Experiment 1b, examining the linear effects of proximity and the main effects of reward magnitude.**

| Conditions | Motivation | RT to arrows | Frustration | Force | Surprise |
|---|---|---|---|---|---|
| Proximity effect | 22.49 ($p < .001$) | 10.66 ($p = .004$) | 13.94 ($p < .001$) | 11.85 ($p = .003$) | 1.65 ($p = .212$) |
| Magnitude effect | 23.68 ($p < .001$) | 15.17 ($p = .001$) | 60.26 ($p < .001$) | 5.79 ($p = .026$) | .289 ($p = .597$) |
| Proximity × magnitude interaction effect | $F < 1$ | $F < 1$ | $F < 1$ | $p > 0.5$ | $F < 1$ |

**Table 3 – The *F* values and *p* values from the ANOVAs in Experiment 2 examining the linear effects of proximity and effort. *Stouffer's combined *p* values are also reported as an index of the significance of the combined proximity or expended effort effects of the three ANOVAs.**

| Conditions | Motivation | RT to arrows | Frustration | Surprise |
|---|---|---|---|---|
| *Proximity effect* | | | | |
| 1/4, 1/3, 1/2, 1/1 | 24.72 ($p < .001$) | 34.40 ($p < .001$) | 5.31 ($p = .032$) | 2.12 ($p = .161$) |
| 2/4, 2/3, 2/2 | 10.91 ($p = .004$) | 5.25 ($p = .033$) | 11.84 ($p = .003$) | .50 ($p = .486$) |
| 3/4, 3/3 | 11.67 ($p = .003$) | 2.75 ($p = .113$) | 9.78 ($p = .005$) | .274 ($p = .787$) |
| Combined effect* | $p < .001$ | $p < .001$ | $p < .001$ | $p = .447$ |
| *Expended effort effect* | | | | |
| 4/4,3/3, 2/2, 1/1 | .846 ($p = .369$) | .216 ($p = .647$) | 10.87 ($p = .004$) | .180 ($p = .676$) |
| 3/4, 2/3, 1/2 | 7.67 ($p = .012$) | 7.03 ($p = .015$) | 10.09 ($p = .005$) | .323 ($p = .701$) |
| 2/4, 1/3 | 13.67 ($p = .001$) | 7.92 ($p = .011$) | 1.41 ($p = .249$) | 1.205 ($p = .242$) |
| Combined effect* | $p < .001$ | $p < .001$ | $p < .001$ | $p = .565$ |

The accentuating effect of motivation is further underlined by this experiment in which rated frustration and response force were enhanced when blocked from obtaining a large (£2) versus a small (20 pence) reward. Next, we used the paradigm from Experiment 1a in conjunction with fMRI to study the neural mechanisms of frustration.

## 5. Experiment 2 (fMRI study)

### 5.1. *Materials and methods*

#### 5.1.1. *Participants*

Twenty-one healthy male volunteers (mean age and SD 24.6 ± 4.6) participated in Experiment 2. All participants were right-handed, fluent English speakers and screened for psychiatric or neurological problems. The study was authorized by the Hertfordshire Research Ethics Committee and informed written consent was obtained from each participant.

#### 5.1.2. *Paradigm*

The Experimental paradigm was identical to Experiment 1a, except that response force measures were not available.

#### 5.1.3. *fMRI acquisition*

MRI scanning was conducted at the Medical Research Council Cognition and Brain Sciences Unit on a 3-T Tim Trio Magnetic Resonance Imaging scanner (Siemens, Germany) using a 32-channel whole-head gradient coil. Whole-brain data were acquired with echoplanar T2*-weighted imaging (EPI), sensitive to BOLD signal contrast (48 sagittal slices acquired using a sequential descending sequence, 3-mm thickness; TR = 2400 msec; TE = 25 msec; flip angle = 90°; FOV = 224 mm; voxel size: 3 × 3 × 3 mm). To allow for equilibration effects the first 5 volumes were discarded. Participants also underwent high-resolution structural T1-weighted magnetization-prepared rapid acquisition gradient echo scans (MPRAGE; TR = 2250 msec; TE = 2.99 msec; flip angle = 90°; voxel size: 1 × 1 × 1 mm).

#### 5.1.4. *fMRI analysis*

SPM5 software (www.fil.ion.ucl.ac.uk/spm/) was used for data analysis. The EPI images were sinc interpolated in time for correction of slice-timing differences and realignment to the first scan by rigid body transformations to correct for head movements. Although there has been an ongoing debate about the effectiveness and applicability of slice-timing, recent evidence showed a benefit of slice-timing correction for parameter estimation on single-subject level particularly for event-related designs (Sladky et al., 2011). Given that subject movement was moderate, we performed slice-timing correction before realignment as suggested by Sladky et al. (Sladky et al., 2011). Field maps were estimated from the phase difference between the images acquired at the short and long TE and unwrapped, employing the FieldMap toolbox (Andersson, Hutton, Ashburner, Turner, & Friston, 2001). Field map and EPI imaging parameters were used to establish voxel displacements in the EPI image. Application of the inverse displacement to the EPI images served the correction of distortions. Utilizing linear and non-linear transformations, and smoothing with a Gaussian kernel of full-width-half-maximum (FWHM) 8-mm, EPI and structural images were coregistered and normalized to the T1 standard template in Montreal Neurological Institute (MNI) space (MNI – International Consortium for Brain Mapping). Global signal correction was not used due to the possibility that there is a significant risk of introducing anticorrelations by this method (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Weissenbacher et al., 2009). This preprocessing approach has been used for data acquired using this same scanner to image the amygdala and midbrain. We took a straightforward approach

**Table 4 – Experiment 2: Comparison of Schedule Cue and Block outcomes.**

| Brain regions | Z scores | MNI coordinates | | |
|---|---|---|---|---|
| | | X | Y | Z |
| Cue – block | | | | |
| L ventral striatum | 3.14* | −12 | 6 | −8 |
| R ventral striatum | 4.28* | 12 | 6 | −8 |
| R middle frontal gyrus | 3.89 | 36 | −4 | 50 |
| R inferior temporal gyrus | 4.67 | 42 | −68 | −2 |
| Block – cue | | | | |
| L anterior insula | 4.64* | −32 | 24 | 2 |
| L amygdala | 3.33* | −22 | 0 | −26 |
| R amygdala | 3.87* | 26 | 2 | −20 |
| L midbrain PAG | 3.30* | −8 | −34 | −10 |
| L culmen | 5.71 | −34 | −44 | −26 |
| L middle occipital gyrus | 6.56 | −32 | −92 | −2 |
| R middle occipital gyrus | 5.51 | 28 | −98 | −4 |
| R superior temporal gyrus | 4.18 | 48 | 14 | −24 |

*$p < .05$ FWE-corr svc, other values $p < .001$ uncorrected.

**Table 5 – Experiment 2: effects of increasing proximity and expended effort on brain responses to Cue.**

| Brain regions | Z scores | MNI coordinates | | |
|---|---|---|---|---|
| | | X | Y | Z |
| *Cue$^{increased\ proximity}$* | | | | |
| L caudate | 4.24* | −8 | 14 | 6 |
| R caudate | 3.65* | 4 | 10 | 6 |
| L putamen | 4.14* | −18 | 0 | 14 |
| R putamen | 3.26* | 20 | 6 | −8 |
| L ventral striatum | 3.59* | −14 | 12 | −4 |
| R ventral striatum | 3.26* | 20 | 6 | −8 |
| L anterior insula | 3.05* | −30 | 18 | 8 |
| R anterior insula | 4.04* | 34 | 24 | 2 |
| L premotor cortex | 4.06 | −48 | −36 | 44 |
| R premotor cortex | 3.53 | 50 | −46 | 54 |
| L visual cortex | 4.98 | −26 | −84 | −10 |
| R visual cortex | 4.93 | 34 | −86 | −10 |
| *Cue$^{increased\ expended\ effort}$* | | | | |
| L caudate | 3.51* | −14 | −2 | 20 |
| R caudate | 3.50* | 8 | 16 | 12 |
| L putamen | 3.69* | −28 | −4 | 10 |
| L anterior insula | 3.50* | −30 | 0 | 16 |
| L posterior insula | 4.07 | −48 | −26 | 22 |

*$p < .05$ FWE-corr svc, other values $p < .001$ uncorrected.

to preprocessing and analysis, using the same preprocessing pipeline used in other recent publications from our group (Mobbs et al., 2013, 2010; Yu, Calder, & Mobbs, in press). We have found that these sequences on our scanner are reliably effective for imaging of the amygdala and the midbrain.

For each participant we constructed an fMRI design matrix by modeling the following regressors: 'Schedule cue' (modeled as a 2-sec duration event at the onset of schedule cues indicating the progress); 'Cue modulated by proximity' (a parametric modulator of the cue regressor indicating the proximity level, i.e., 1, 2, 3, and 4); 'Cue modulated by expended effort' (a parametric modulator of the cue regressor indicating the expended effort level, i.e., 1, 2, 3, and 4); 'Blocked' (modeled as a 6-sec duration event at the onset of 'Blocked' feedback); 'Blocked modulated by proximity' (a parametric modulator of the block regressor indicating proximity level); 'Block modulated by expended effort' (a

**Table 6 – Experiment 2: effects of increasing proximity and expended effort on brain responses to Block outcomes.**

| Brain regions | Z scores | MNI coordinates | | |
|---|---|---|---|---|
| | | X | Y | Z |
| *Block$^{increased\ proximity}$* | | | | |
| L dACC | 3.42* | −2 | 26 | 36 |
| L anterior insula | 3.23* | −40 | 16 | 0 |
| L amygdala | 2.75* | −28 | −6 | −14 |
| L midbrain PAG | 2.97* | −10 | −28 | −14 |
| L middle frontal gyrus | 4.08 | −40 | 50 | 16 |
| L lingual gyrus | 3.98 | −10 | −86 | −16 |
| L posterior cingulate cortex | 4.00 | 2 | −16 | 32 |
| *Block$^{increased\ expended\ effort}$* | | | | |
| L dACC | 3.85* | −8 | 10 | 42 |
| L anterior insula | 4.35* | −34 | 6 | 10 |
| R anterior insula | 3.16* | 48 | 12 | −2 |
| L amygdala | 2.71* | −28 | 0 | −18 |
| R amygdala | 3.08* | 24 | −10 | −10 |
| L midbrain PAG | 3.37* | −6 | −30 | −14 |
| R midbrain PAG | 3.20* | 10 | −34 | −16 |
| R inferior occipital gyrus | 4.45 | 34 | −82 | −8 |
| R superior temporal gyrus | 3.98 | 54 | −38 | 14 |
| L culmen | 3.51 | −18 | −54 | −12 |

*$p < .05$ FWE-corr svc, other values $p < .001$ uncorrected.

**Table 7 – Experiment 2: effects of increasing proximity and expended effort on brain responses to Block outcomes after masking the corresponding proximity and expended effort effects in cue stage.**

| Brain regions | Z scores | MNI coordinates | | |
|---|---|---|---|---|
| | | X | Y | Z |
| *Block$^{increased\ proximity}$* | | | | |
| L dACC | 3.68* | −8 | 38 | 24 |
| L anterior insula | 3.23* | −40 | 16 | 0 |
| L amygdala | 2.75* | −28 | −6 | −14 |
| L midbrain PAG | 2.97* | −10 | −28 | −14 |
| L middle frontal gyrus | 4.09 | −40 | 50 | 16 |
| L lingual gyrus | 3.98 | −20 | −76 | −18 |
| L posterior cingulate cortex | 3.94 | −2 | −18 | 34 |
| *Block$^{increased\ expended\ effort}$* | | | | |
| L dACC | 3.85* | −8 | 10 | 42 |
| L anterior insula | 4.35* | −34 | 6 | 10 |
| R anterior insula | 3.16* | 48 | 12 | −2 |
| L amygdala | 2.71* | −28 | 0 | −18 |
| R amygdala | 3.08* | 24 | −10 | −10 |
| L midbrain PAG | 3.37* | −6 | −30 | −14 |
| R midbrain PAG | 3.20* | 10 | −34 | −16 |
| R inferior occipital gyrus | 4.45 | 34 | −82 | −8 |
| R superior temporal gyrus | 3.98 | 54 | −38 | 14 |
| L culmen | 3.51 | −18 | −54 | −12 |

*$p < .05$ FWE-corr svc, other values $p < .001$ uncorrected.

**Table 8 – Experiment 2 without orthogonalization: effects of increasing proximity and expended effort on brain responses to Block outcomes after masking the corresponding proximity and expended effort effects in cue stage.**

| Brain regions | Z scores | MNI coordinates | | |
|---|---|---|---|---|
| | | X | Y | Z |
| *Block$^{increased\ proximity}$* | | | | |
| L dACC | 3.71* | −6 | 32 | 38 |
| L anterior insula | 3.17* | −40 | 16 | −6 |
| L amygdala | 2.99* | −16 | −2 | −18 |
| L midbrain PAG | 3.10* | −10 | −28 | −14 |
| | 3.05* | −10 | −35 | −12 |
| L middle frontal gyrus | 4.04 | −40 | 50 | 16 |
| L lingual gyrus | 3.74 | −20 | −78 | −18 |
| R posterior cingulate cortex | 3.96 | 2 | −16 | 32 |
| *Block$^{increased\ expended\ effort}$* | | | | |
| L dACC | 3.75* | −8 | 6 | 48 |
| L anterior insula | 4.16* | −34 | 4 | 10 |
| R anterior insula | 3.30* | 46 | 14 | −2 |
| R amygdala | 2.74* | 26 | 2 | −16 |
| L midbrain PAG | 3.37* | −6 | −30 | −14 |
| R midbrain PAG | 3.20* | 10 | −34 | −16 |
| R inferior occipital gyrus | 4.45 | 34 | −82 | −8 |
| R superior temporal gyrus | 3.98 | 54 | −38 | 14 |
| L culmen | 3.51 | −18 | −54 | −12 |

*$p < .05$ FWE-corr svc, other values $p < .001$ uncorrected.

parametric modulator of the block regressor indicating the degree of expended effort); 'Win' (modeled as a 6-sec duration event at the onset of reward feedback). The two parametric modulators (proximity and effort) were orthogonalized using Gram-Schmidt orthogonalization procedure. We also did the analysis without using Gram-Schmidt orthogonalization and found similar findings (see Table 8 for the main results without orthogonalization). To take care of the concern that the proximity or expended effort effects in the outcome stage may be driven by the residual BOLD signals from the corresponding effects in the cue stage, we also used the contrast image of cue proximity effect (or cue expended effort effect) at $p < .05$ uncorrected as exclusive mask for the analysis of the proximity effect (expended effort effect) in the outcome stage (see Table 7).

We also included 6 motion parameters as effects of no interest to account for motion related variance, as well as a session constant. Global changes were removed by high-pass temporal filtering with a cut-off of 128 sec to remove low-frequency drifts in signal. A random effects analysis (second level one-sample t test) was performed to analyze data at a group level. Montreal Neurological Institute coordinates and statistical z-scores are reported in figure legends.

Activation in hypothesized regions of interest (ROIs) was corrected for multiple comparisons at the family-wise error (FWE $p < .05$) level using small-volume corrections (svc). ROIs comprised regions implicated in reward and aggression: (1) The ventral striatum was defined as a 6 mm sphere at ±14, 10, −10 (O'Doherty et al., 2004); (2) The dorsal cingulate cortex was defined as a combination of the anterior cingulate and mid-cingulate templates from the AAL (Tzourio-Mazoyer et al., 2002); (3) The anterior insula was defined by restricting the structural template for the insula derived from AAL to the region anterior to the AC plane; (4) The amygdala was defined with the corresponding AAL mask divided into left and right hemispheres; Using the independently defined probabilistic amygdala by combining superficial, latero-basal and centro-medial complex in SPM Anatomy Toolbox (Amunts, Schleicher, & Zilles, 2007) generated similar results. (5) Midbrain PAG was defined as a 6 mm sphere at ±6, −33, −14 (Mobbs et al., 2007). Activations in other areas are reported if they survived $p < .001$, uncorrected, cluster size $k > 10$.

## 6. Results

### 6.1. Behavioral results

The behavioral findings replicated Experiment 1a (Fig. 5 and Table 3). Participants made an incorrect response when indicating the arrow's direction on 4.6% (SD = 3.8%) of trials in Experiment 2. Since the number of errors for each condition was small and the data contained a number of cells for which

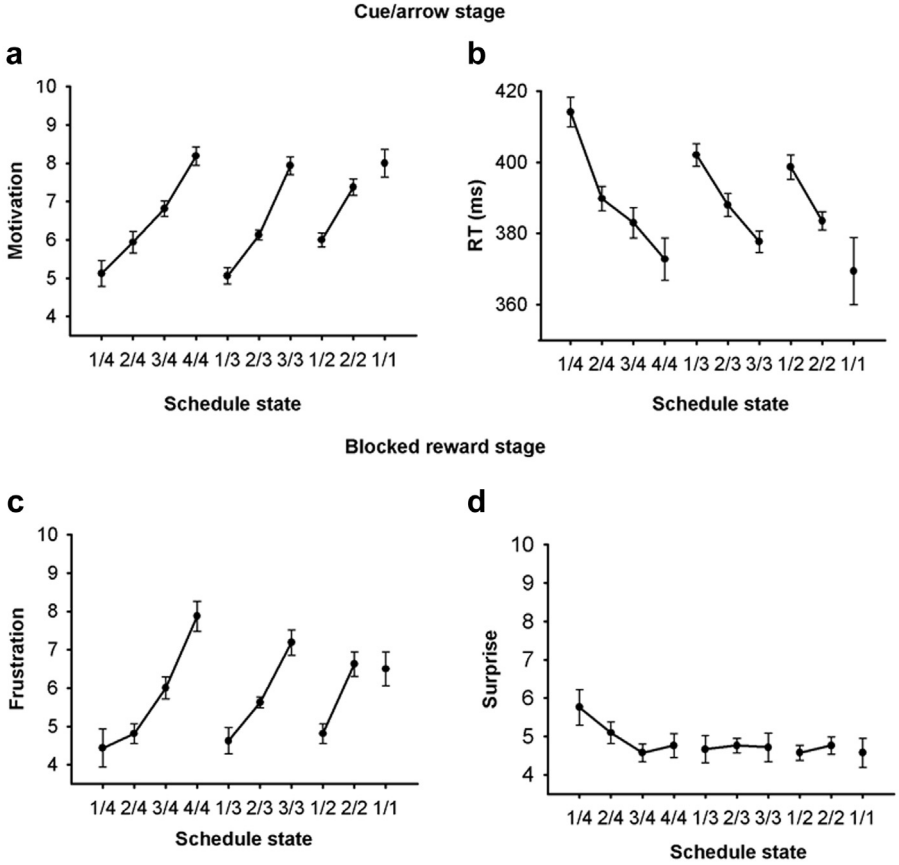


**Fig. 5 – Behavioral data from Experiment 2 (fMRI study). Self-reported motivation (a) to obtain the reward and RTs (b) to arrows at each of the different schedule states; Self-reported frustration (c) and self-reported surprise (d) at being blocked at the outcome stage.**

performance was at floor (0%), the error rates were not analyzed further.

RTs for outcome confirmations were 873 msec (SD = 200). There was no main effect of proximity or expended effort on RTs at outcome confirmation stage ($p > .1$). For the error rates, participants made an incorrect response at outcome on 2.8% (SD = 5.1%) of trials. Since the number of error trials for each condition was small, error rates were not analyzed further. The effects of proximity or expended effort on self-reported surprise following blocking were not significant (Stouffer's $p$ values $> .4$).

### 6.2. *fMRI results*

For the neuroimaging data, we first compared the brain responses to the schedule cues indicating successful progress (excluding block or win outcomes) relative to the response to block outcomes. This verified that our task schedule cues activated bilateral ventral striatum, consistent with previous studies demonstrating this region's role in anticipation of reward (O'Doherty et al., 2004). By contrast, the brain response to block outcomes (*vs* schedule cues) activated the bilateral amygdala, left midbrain PAG and left anterior insula (Table 4), regions that have been implicated in animal models of reactive aggression.

Next, we examined how reward proximity and expended effort modulate the brain responses to the blocked outcomes. This revealed that activation in key areas of animal models of aggression, including the left amygdala, left midbrain PAG, left anterior insula, and dorsal anterior cingulate cortex (dACC) increased as a function of increasing proximity when blocked (Fig. 6 and Table 6). Notably, the participants' expended effort at the point of blocking was positively correlated with activity in similar brain areas (bilateral amygdala, bilateral PAG, bilateral anterior insula, and dACC Fig. 6 and Table 6), no matter whether we orthogonalized expended effort with respect to proximity or not in our analysis. Direct comparison between block × expended effort and block × proximity contrasts yielded no significant differences in a priori regions of interest (ROIs), suggesting similar pathways were involved. Note also that brain activity for the proximity and expended effort effects in the blocked phase cannot simply be explained by the accumulative effect of the proximity and expended effort effects in the cue phase (see Table 5) since that the effects for the blocked phase remained significant after masking out the corresponding proximity and expended effort effects in the cue phase using a mask thresholded at $p < .05$ uncorrected (Table 7) (Friston, Penny, & Glaser, 2005). Hence, areas activated in the blocked phase are unlikely to reflect an accumulative effect from the cue phase.

## 7. General discussion

Given its central role in instigating aggression, understanding the principles that govern frustration and its neural substrates is a crucial step to understanding the mechanisms that cause aggression and violence. We have shown that blocking the attainment of a reward manifests as heightened levels of experienced frustration and more vigorous responding. In addition, we found that both of these outcomes were enhanced by factors that increase motivation (i.e., goal proximity, invested effort, and reward magnitude). The results of Experiment 1a were replicated by the behavioral data from Experiment 2, and both experiments showed that the effects

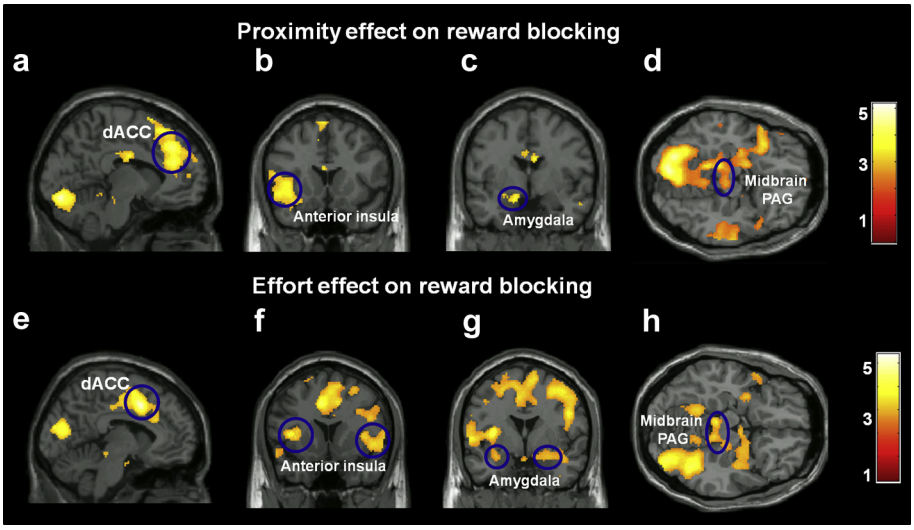


**Fig. 6 – Parametric increases in BOLD response to block outcomes associated with increasing proximity and increasing expended effort. Positive associations with increasing proximity were found in (a) Left dACC (−2, 26, 36, $z = 3.42$), (b) Left anterior insula (−40, 16, 0, $z = 3.23$), (c) Left amygdala (−28, −6, −14, $z = 2.75$), and (d) Left midbrain PAG (−10, −28, −14, $z = 2.97$). Positive associations with increasing expended effort were found in (e) Left dACC (−8, 10, 42, $z = 3.85$), (f) Bilateral anterior insula (left, −34, 6, 10, $z = 4.35$; right, 48, 12, −2, $z = 3.16$), (g) Bilateral amygdala (left, −28, 0, −18, $z = 2.71$; right, 24, −10, −10, $z = 3.08$), and (h) Bilateral midbrain PAG (left, −6, −30, −14, $z = 3.37$; right, 10, −34, −16, $z = 3.20$). All activations are significant at $p < .05$, small volume corrected. For display purposes, maps are thresholded at $p < .005$, uncorrected.**

of blocking were not due to any surprising or unexpected property of blocked outcomes.

These findings accord with work in rodents showing that frustrative non-reward has an invigorating effect on behaviors that immediately follow it (Amsel, 1992). For example, rats restrained near a food goal pulled their harness harder than those restrained farther away (Holton, 1961). Similarly, previous studies in humans have shown that response force is enhanced by frustrating events (Haner & Brown, 1955; Kapoor et al., 2007). The evolutionary significance of this relationship between frustration and response force might be to transfer unfulfilled motivation into subsequent behavioral vigor to overcome goal-blocking obstacles. The results of our fMRI experiment suggest this may operate by engaging a fronto-insula-amygdala-midbrain network.

Specifically, the fMRI experiment showed that the two factors that enhance appetitive motivation (i.e., goal proximity and expended effort) produced increased activation of similar brain circuits encompassing a dACC-insula-amygdala-midbrain network when progress towards a goal was blocked. Additional analyses showed no significant differences between the brain areas enhanced by proximity and expended effort, indicating that both factors modulate statistically indistinguishable networks when goal-directed activity is blocked. Note also, that brain areas modulated by proximity and effort at the blocked outcome phase were not attributable to residual activation from the cue stage, since the blocked-stage activation survived a conservative analysis in which any regions showing an effect of proximity and effort at the cue stage were masked at $p < .05$ uncorrected. Furthermore, given that goal proximity and expended effort were orthogonalized, therefore removing any correlation between the two, the results provide convergent evidence that different factors affecting appetitive motivation affect the level of engagement of the reactive aggression network when participants are confronted by a frustrating event.

The dACC-insula-amygdala-midbrain network engaged by blocking shows considerable overlap with the rage circuitry in rodents, which runs from forebrain through the amygdala and down into the dorsal PAG of the midbrain (Panksepp, 2005). This suggests a possible neural account of why frustration evokes aggression (Dollard et al., 1939). The amygdala is a critical part of the rage network. Stimulation of its medial section (i.e., corticomedial amygdala) in rodents results in increased aggression (Potegal, Hebert, DeCoster, & Meyerhoff, 1996). In humans, murderers and spousal abusers show hyper-responsivity of the amygdala (Lee, Chan, & Raine, 2008; Raine et al., 1998) and recent work suggests that the low expression variant of monoamine oxidase A (MAOA) gene — a variant associated with impulsive aggression in animals (Cases et al., 1995) — is linked to a hyper-responsive amygdala and impaired regulatory prefrontal function in humans (Meyer-Lindenberg et al., 2006), but also see (Molendijk et al., 2012). Our current study shows that the amygdala is also involved in frustration, and so future research should investigate in more detail the neural mechanisms by which frustration is transferred into aggression.

The PAG is a second critical component of the rage network. Animal research shows that this region is central to active coping, including fight behaviors (Bandler, Keay, Floyd, & Price, 2000), and its stimulation can elicit aggression (Potegal et al., 1996). In view of our observation that both proximity and expended effort also modulated the neural response to blocking in the insular cortex and dACC, it of interest that both of these regions project to PAG sites that support aggressive behavior (Panksepp, 2005). Inputs to PAG from the orbito insular cortex, are thought to relate to the role of these cortical regions in processing irritations (e.g., pain or aggressive displays of others) (Panksepp, 2005), whereas projections from dACC to PAG in rodents have been associated with fight-or-flight responses (An, Bandler, Ongur, & Price, 1998). The dACC also shows decreased gray matter in boys with aggressive and defiant traits (Boes, Tranel, Anderson, & Nopoulos, 2008), decreased BOLD-signal in adolescents with conduct disorder (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005) and both decreased gray matter and BOLD-signal reactivity in subjects carrying the low expression variant of MAOA gene (Meyer-Lindenberg et al., 2006).

The exact role of the dACC is still unknown. Theories of dACC emphasize a role in performance monitoring and action selection in cognitive domain (Botvinick, Braver, Barch, Carter, & Cohen, 2001). However adaptive control theory proposes that this region is involved in negative affect and executive control, and it may act as a hub where the expression of affect and execution of goal-directed behavior are linked (Shackman et al., 2011). Recent studies have shown that the dACC is involved in appraisal and expression of negative emotion, such as anxiety and fear (Etkin, Egner, & Kalisch, 2011). Thus, the dACC may be involved in goal-directed components such as the increased vigor to acquire a goal and the control of aggressive behavior evoked by increasing levels of frustration. It is worth noting that the dACC also projects to the ventral striatum, suggesting a possible role in motivation (Kunishio & Haber, 1994), and to the amygdala (Morecraft et al., 2007).

As discussed earlier, inputs from the hypothalamus to PAG are thought to be instrumental in aggression and sham rage (Panksepp, 2005; Siegel, Roeling, Gregg, & Kruk, 1999), however, no hypothalamic activity was found in this study. One reason may be that we did not explicitly evoke aggression, or at least sufficiently extreme aggression to engage the hypothalamus. Alternatively, a more likely explanation is that signal in this region is generally poor, due to its limited spatial extent, heterogeneous structure, and proximity to the nasal cavity (Karlsson et al., 2010).

Another concern is that amygdala activation might be driven by flow changes in nearby large vascular (Hutton et al., 2011). While image distortions are more severe in the amygdala region as compared with other commonly examined brain regions, the draining vein problem can be assumed to be less pronounced in the amygdala (Ball et al., 2007). The amygdala is relatively small and is drained by several veins, whereas the braining vein problem is more pronounced for large areas and for areas being drained by a single vein (Turner, 2002). Empirical findings also suggest that there are no sizable draining vein artifacts in the amygdala region (Robinson, Windischberger, Rauscher, & Moser, 2004). Nevertheless, future studies may use high-resolution neuroimaging and physiological noise correction to minimize the influence of blood vessels on the amygdala responses.

Although we have noted the similarity between dACC-insula-amygdala-midbrain network engaged by blocking and

the rage/reactive aggression circuit identified in lower mammalian species, the limited spatial resolution of fMRI makes it difficult to be certain that these are homologous circuits. Moreover, the neural correlates of rage/aggression in humans are still unclear (Gregory et al., 2012; Payer, Lieberman, & London, 2011) and thus cross-species comparisons are inevitable. Future studies are needed to directly compare the neural correlates of frustration identified in the present study and the rage circuit in humans. The rage circuit interdigitates with the fear circuit and although the two are segregated within the amygdala, with the rage circuit involving the medial nucleus and fear circuit the lateral and central nuclei, this is beyond the spatial resolution of our current fMRI study (Panksepp, 2005). The close proximity of the circuits for aggression and fear is an outstanding issue for neuroimaging studies of emotion, and is not unique to this study. However, there are good reasons to think that our task is unlikely to evoke fear. Earlier behavioral work has shown that blocking goal-directed behavior evokes frustration/aggression rather than fear (Berkowitz, 1989). Consistent with this, our current study showed that ratings of frustration and response vigor were similarly enhanced by blocking. It therefore seems unlikely that the areas we have identified reflect increased fear.

The exact psychological process underlying proximity and effort modulated frustration is still unclear. One possibility is that counterfactual thinking might contribute to the observed enhanced frustration. Previous studies have shown that participants are more ready to be engaged in counterfactual thinking when a goal is close because counterfactual thinking might be easier if the possible outcome is easier to imagine (i.e., closer). Indeed, this analysis in terms of counterfactuals has been applied to near misses – for example the relatively aversive state of winning a silver compared to a bronze medal (Clark, Lawrence, Astley-Jones, & Gray, 2009; Medvec, Madey, & Gilovich, 1995). In addition, the anticipation of regret or disappointment might build with successive wins (goal proximity). This is important because the surprising absence of reward following a 'blocking' event might re-engage executive control processes over previous automatic processes. Although our experiment cannot rule out the possibility that a Pearce–Hall like learning process may be engaged in the frustration task (Pearce & Hall, 1980), self-reported surprise ratings data suggest that the absence of reward following a 'blocking' event at different stages did not elicit different levels of surprise in participants. Future studies may further investigate the psychological processes underlying the proximity and effort effects.

Our data provide both behavioral and neurophysiological evidence that the negative affect and behavioral vigor (response force) induced by frustrating events are modified by the motivating effects of both prospective reward proximity and retrospective investment of effort. The results of our fMRI experiment showed that this may occur via a dACC-insula-amygdala-midbrain network, and that this network may transfer frustration resulting from unfulfilled motivation into response vigor. The network may well correspond to the rage/reactive aggression system identified in rodents (Panksepp, 2005), however, it is important that this is verified by future research, including high-resolution fMRI to identify the nuclei of the amygdala involved. Our findings provide new insights into the psychological and neural mechanisms of frustration, relevant not only to the pathophysiology of psychiatric disorders of aggression, but also to the milder frustrations of everyday life.

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