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The motivational determinants of human action, their neural bases and functional impact in adolescents with OCD

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Abstract

Background
Establishing the motivational influences on human action is essential for understanding choice and decision-making in health and disease. Here we used tests of value-based decision-making, manipulating both predicted and experienced reward values to assess the motivational control of goal-directed action in healthy adolescents and those with obsessive-compulsive disorder (OCD).

Methods
After instrumental training on a two action-two outcome probabilistic task, adolescents (n=21) underwent Pavlovian conditioning using distinct stimuli predicting either the instrumental outcomes, a third outcome or nothing. We then assessed fMRI during choice tests in which we varied predicted value, using specific and general Pavlovian-instrumental transfer (PIT), and experienced value, using outcome devaluation. To establish functional significance, we tested a matched cohort of adolescents with OCD (n=20).

Results
In healthy adolescents both predicted and experienced values influenced the performance of goal-directed actions, mediated by distinct orbitofrontal (OFC)-striatal circuits involving the lateral-OFC and medial-OFC respectively. In adolescents with OCD, however, choice was insensitive to changes in either predicted or experienced values. These impairments were related to hypoactivity in the lateral OFC and hyperactivity in medial OFC during specific PIT and hypoactivity in anterior prefrontal cortex, caudate nucleus and their connectivity in the devaluation test.

Discussion
We found, therefore, that predicted and experienced values exerted a potent influence on the performance of goal-directed actions in adolescents via distinct orbitofrontal- and prefrontal-striatal circuits. Furthermore, the influence of these motivational processes was severely blunted in OCD as was the functional segregation of circuits involving medial and lateral OFC, producing dysregulated action control.

Keywords: obsessive-compulsive disorder; Pavlovian-instrumental transfer; outcome devaluation; orbitofrontal cortex; anterior prefrontal cortex, caudate nucleus; adolescents
Introduction

The capacity for goal-directed action allows us and other animals to control the environment in the service of our basic needs and desires (1,2). Such actions constitute, therefore, an adaptive and flexible form of behavioral control that depends on encoding the relationship between actions and their consequences, or outcome, during learning and on the value of the outcome for performance (3). Despite the functional significance of this capacity, the processes that generate the outcome values determining human action remain unclear (4,5). In contrast, considerable evidence from rodents suggests that value-based control involves two forms of incentive learning; one generated by stimuli that predict reward — called predicted values (2,6,7) — and a second induced by the direct experience of the emotional response evoked by contact with the specific goals or outcomes of goal-directed actions — called experienced values (6,8). These values influence instrumental performance in humans (9,10), and the broader circuitry that mediates this influence appears to be well conserved across species (11). Nevertheless, the way that these values are integrated with action-outcome retrieval during performance and the neural substrates that support that integrative process are underexplored in humans, as is their causal role in action control (12,13).

To examine these sources of motivational control, we developed behavioral tests that probe the influence of predicted and experienced values on human action (14–16). These forms of incentive learning have distinct psychological and behavioral determinants (17,18). However, recent evidence from rodents suggests that their influence on performance, which requires outcome-specific recall, may be modulated by a common ideomotor process (19,20) mediated by orbitofrontal cortex (OFC) (21) and its projections to the striatum (22). In evaluating the neural bases of these incentive processes, therefore, we focused on this orbito-striatal circuit. Importantly, converging evidence from people with various psychiatric conditions suggests that aberrant orbitofrontal activity is associated with a range of symptoms, particularly those observed in obsessive-compulsive disorder (OCD) (16,23–26).

Therefore, to establish the functional significance of these incentive processes we compared their influence in healthy participants to a matched cohort diagnosed with OCD. Because longer duration of illness and its consequences often interferes with establishing the functional effects of psychiatric conditions (27), we focussed on a period early in the course of illness, i.e., during adolescence, using a sample of healthy adolescents as controls. If the OFC is critical for the motivational control of goal-directed action, then activity in the orbito-striatal circuit should relate to performance in healthy people whereas abnormal activity and connectivity should be predicted to attenuate value-based control of goal-directed action in people with OCD.

Methods

NOTE: The full methods are provided in the Supplementary Material.

Participants

21 healthy adolescents (control group) and 20 adolescents with OCD (OCD group) were recruited based on a power analysis drawn from a similar study (14) that stipulated a minimum sample size of n=16 to achieve 80% statistical power at an alpha of 0.05. There
were no group age, gender, handedness, education, or intelligence differences (all ts < 1; Table 1). Participants with OCD were a representative sample; the mean OCD symptom score (17; SD=9) was moderate (n=3 ≤ 7, lifetime OCD, and n=18 ≥ 8, current OCD), psychotropic medications were used by 70%, and 75% had a comorbid (lifetime) psychiatric diagnosis.

This study was approved by The University of Sydney Human Research Ethics Committee (2012/2284).

**Behavioral Methods.**

The learning and performance tasks used here were based on tests developed and validated in rodents (Figure 1)(2,14). Outcomes consisted of five different foods, rated in pleasantness by participants on a 7-point Likert scale. Stimulus presentation and response recording was controlled by PsychoPy© software (v1.82.00) with responses recorded on a two-button response pad (Cedrus©, California).

**Instrumental conditioning.** Left (A1) and right (A2) button presses were reinforced on a variable-ratio schedule (VR5) with a specific food, counterbalanced, dependent upon each participant’s three highest rated foods (Figure 1; Supplementary Material). As each outcome was earned, an image of that food appeared on the screen for 1-s and participants were invited to eat one piece of the relevant food from two plates positioned in front of them on the desk. Participants were asked verbally which outcome was associated with which action and training ceased when a participant registered six consecutive correct answers.

**Pavlovian conditioning.** Prior to the start of conditioning the button box was removed. Three plates holding the three food rewards (O1, O2, O3) used in Pavlovian conditioning were placed on the desk. Four stimuli (S1, S2, S3, S4) were paired with four outcomes (O1, O2, O3, Ø) (Figure 1). Two stimuli (S1, S2) were paired with two outcomes from instrumental conditioning, another stimulus (S3) was paired with an outcome (O3) not used in instrumental training and a fourth stimulus (S4) was paired with the word ‘EMPTY’ indicating no food was available. Stimuli were presented for 5-s, after which the image of the food outcome appeared beneath the stimuli for 1-s. The inter-trial-interval (ITI) was 10-s (+/-5) during which neither stimuli nor outcomes were shown. After every block of four stimulus-outcome trials a multiple-choice question “Which snack will fall out?” appeared on the screen with a stimulus (coloured vending machine). If participants answered this question correctly, they were invited to eat one piece of the relevant outcome. Pavlovian conditioning ceased after a participant registered six consecutive correct answers.

The next two phases were conducted in scanner using an MRI-safe button box.

**Pavlovian-instrumental transfer test (Figure 1).** There were 12 blocks during which each of the four stimuli were presented in random order for 6-s every 18-s (0-4-s random jitter). Participants were able to tilt the vending machine during stimulus presentation and when the vending machine was unlit during the ITI, providing an active baseline measure. This test was conducted in extinction, i.e., no outcomes were delivered, to ensure that responding was not influenced by the incidence of outcome delivery. PIT data for one participant per group was lost, leaving OCD n=19 and controls n=20.

**Outcome devaluation procedure and test (Figure 2).** Participants were shown a 4-minute
video of cockroaches crawling on one of the foods they had earned during instrumental conditioning (counterbalanced). The blank vending machine then appeared for 30 trials of 12 seconds each. Before each trial, a fixation cross was presented for 18(±6)-s. Participants could tilt the machine at any time. No outcomes were presented during the devaluation test. After the devaluation test, whilst still in the scanner, participants rated the desirability of O1 and O2 on a scale of Likert scale 1 to 7.

After exiting the scanner participants re-completed the self-report hunger and food pleasantness scales presented at the start of behavioral training. They also completed a self-report six-item multiple-choice test of recall of the instrumental (e.g., ‘What snack was associated with the LEFT key?’) and Pavlovian (e.g., ‘What snack was associated with the BLUE light?’) contingencies.

Imaging methods.

Scanning occurred in a 3T GE Discovery with a 32-channel head coil (GE Healthcare, UK). A T1-weighted high-resolution was acquired for each participant for registration and anatomical screening: 7200-msec repetition time; 2700-msec echo time; 176 slices in the sagittal plane; 1-mm slice thickness (no gap); 256-mm field of view; and 256 x 256 matrix. We acquired 300 T2* -weighted whole-brain echo planar images with a 2910-msec repetition time (TR); 20-msec echo time; 90-degree flip angle; 240-mm field of view; and 128 x 128 matrix with SENSE (Sensitivity Encoding). Each volume consisted of 52 axial slices (2-mm thick) with a 0.2-mm gap. Whole brain diffusion-weighted images were acquired using an echo planar imaging sequence with the following parameters: TR=8250ms; TE=85ms; number of slices=55 thickness=2mm-thick axial slices; matrix size, 128x128; in-plane resolution, 1.8x1.8mm²; 69 gradient directions. Eight images without gradient loading (B0 s.mm-2) were acquired prior to the acquisition of 69 images with uniform gradient loading (B0=1000s.mm-2).

Data Analysis.

Statistical analysis methods are detailed in Supplementary Materials.

Results

Predicted values influence choice in healthy adolescents but not in those with OCD

There were no significant group differences in hunger rating (HA=5.9, OCD=6.2; t<1) or number of outcomes earned during instrumental conditioning (HA=18.5, OCD=18.7; t<1). Groups also did not have an action selection bias and showed a similar relationship between response rate and rating for preferred reward (Pearson r for cases and controls was 0.33 and 0.38, respectively). There were also no differences in Pavlovian conditioning. Healthy adolescents and those with OCD could recall these associations during training (HA=98%; OCD=91%; t=1.39, p=0.1) after the choice tests and MRI scans. Mean group percentage correct was 98 and 93 percent, respectively (p=.40) (see Supplemental Materials for additional group comparisons).

In the specific PIT test (Figure 1) the stimuli had different effects depending on the outcome they predicted (Figure 2A). Action rate was comparable between groups during the pre-stimulus (baseline) period (t<1) – see the peri-stimulus periods prior to stimulus onset.
in Figure 2A. However, in healthy adolescents, the specific stimuli (i.e., S1 and S2) elicited an immediate and potent elevation in the performance of the action that, during instrumental conditioning, resulted in the ‘same’ outcome as predicted by the stimulus, and a concomitant reduction in the performance of the action associated with the ‘different’ outcome. In contrast, the effect of predicted outcome values on choice was markedly impaired in adolescents with OCD who showed a mild but undifferentiated, that is general, increase above baseline for both the ‘same’ and ‘different’ actions during the specific stimuli (S1, S2). There was, therefore, clear evidence of significantly impaired specific transfer in OCD (planned group by action interaction $F_{1,37}=6.26$, $p=.017$, $\eta^2_p=.15$).

We also tested the general arousing effect of predictive stimuli – i.e., General PIT(7) – by comparing responding during the generally rewarding (S3) and null (S4) predictors. Importantly, the general value prediction induced by S3 increased the performance of both actions (A1 and A2) relative to the null value prediction of S4 (Figure 3A) and, unlike the specific value predictions in the specific PIT test, this effect did not appear to differ between participant groups. The planned group-by-stimulus interaction conducted on action rates during the S3 and S4 stimuli was not significant ($p=.47$). There was, however, a significant main effect of stimulus ($F_{1,37}=7.22$, $p=.01$, $\eta^2_p=.17$).

**The influence of predicted values on choice is associated with orbitofrontal activation**

BOLD activity was parametrically modulated by the rate of specific transfer during each trial of S1 and S2 (i.e., the rate on the ‘same’ minus ‘different’ action), revealed by the planned SPM t-test of healthy adolescents. The global peak voxels occurred in: (i) the bilateral OFC (right lateral OFC, BA47, MNI:36,34,-18; $t=7.35$, $k=122$, $pFDR=.025$; left lateral OFC, BA47, MNI:-30,34,-20; $t=6.05$, $k=14$, $pFDR=.026$) (Figure 2C); (ii) left dorsal caudate (Cd) (MNI: -18,4,24; $t=6.41$, $k=20$, $pFDR=.026$); (iii) right putamen, fundus region (FPu) (MNI:18,16,-2; $t=6.14$, $k=20$, $pFDR=.026$); (iv) the superior frontal gyrus (BA9, MNI:8,56,34; $t=5.84$, $k=12$, $pFDR=.032$) and (v) the left supramarginal gyrus (SMG) in the inferior parietal cortex (BA40: MNI:-46,-30,36; $t=7.26$, $k=138$, $pFDR=.025$) – refer Table 2 – suggesting that a corticostriatial network involving these structures modulated predicted value in healthy adolescents.

In contrast, adolescents with OCD showed localised hyperactive neural responses associated with outcome-specific predictions compared with healthy adolescents in the planned whole-brain SPM t-test. The greatest hyperactivity occurred in the left medial orbital gyrus (MOG)/medial OFC (BA11: MNI:-4,50,-20; $F_{2,31}=31.33$, $k=582$, $pFDR<.001$) (Figure 2D). Examination of the BOLD parameter estimates for each group confirmed that this difference was due to larger BOLD estimates in adolescents with OCD rather than negative BOLD estimates in those without (Figure 2D inset). No between-group differences in activity in the caudate was found; however there were significant differences in the right lateral OFC (BA47, MNI:44,32,-8; $F=29.69$, $k=516$, $pFDR<.001$), left and right middle temporal gyri (e.g., BA21, MNI:-58,-26,-18; $F=22.95$, $k=693$, $pFDR<.001$; BA21, MNI:58,-18,-24, $F=22.91$, $k=259$, $pFDR<.001$) – Table 2. To explore the potential source of the BOLD hyperactivity in OCD, we conducted follow-up ROI analyses centred on the global peak voxels from the specific transfer test of the healthy adults using a 4 x 4 x 4 mm search space in each case. Hypoactivity (relative to HA) was found in the dorsal caudate (MNI:-18,2,26, t=4.44, pFWE<.001), right lateral OFC (BA47, MNI: 34,34,-20; $t=2.18$, pFWE=.048), but not the left lateral OFC (pFWE=.35) – refer Figure 2F. Posthoc ROI tests also revealed hypoactivity in the right putamen (MNI: 20,18,0; $t=2.45$, pFWE=.028), and superior frontal gyrus (BA9: MNI: 6,58,32; $t=2.8$, pFWE=.01) (See Supplementary Results for covariate analyses for age, WRAT
or handedness. See Supplementary Results and Figures S1A, S1B & S1C for tractography results).

Finally, we assessed the relationship between OCD symptoms and the largest hyperactive BOLD response in the medial OFC in the adolescents with OCD in the follow-up ROI correlation analysis (Figure 2B). This analysis included obsession and compulsion severity as SPM covariates-of-interest and revealed a significant positive correlation between compulsion severity and hyperactive BOLD responses in the left medial orbital gyrus (MOrg)/medial OFC (BA11: MNI: -8, 54, -16; t=2.79, pFWE=.047, svc) suggesting medial OFC hyperactivity and compulsion severity in OCD may be the source of the deficit in specific PIT.

**General PIT produced activity in a posterior region of medial OFC**

In General PIT no significant differences between groups in action rate during the general reward stimulus (S3) and the null reward stimulus (S4) were found (Figure 3A) and so we collapsed this measure across groups and examined the effect of incentive motivation on neural activity in a whole-brain analysis. A posterior region of medial OFC activity tracked changes in the predicted values across presentations of the general predictive stimuli (S3 vs. S4) in this overall groups analysis (Figure 3B: BA11: MNI:12,38,–6; t_{38}=4.71, k=67, pFDR=.044), indicating that S3 exerted a general effect of reward arousal on medial OFC activity. There were no significant group differences in the follow-up ROI comparison (pFWE=.19), indicating that the influence of the general reward predictions on this region of medial OFC did not differ between groups.

**The effect of experienced value on choice.**

Next, we manipulated experienced value to test its influence on choice in an outcome devaluation test. To induce devaluation, participants watched a short video showing cockroach infestation of one of the two outcomes (O1 or O2) used in instrumental conditioning. They were then given a choice test on the vending machine in nominal extinction, i.e., no coloured lights were shown and no snacks seen or consumed – Figure 4.

After viewing the video, healthy adolescents preferred the action previously associated with the ‘valued’ outcome, i.e., the outcome that had not been ‘devalued’. In contrast, people with OCD showed no behavioral preference between A1 and A2 responding similarly on the valued and devalued actions (Figure 5A). 3-way ANOVA (group x devaluation x time) confirmed the interaction between group and devaluation was significant (F(1,185)=8.028, p=.005, η²_p=.04): healthy adolescents responded significantly more on valued than the devalued action (t=2.84; df=37, p=.007) whereas OCD participants did not (t=1.14; df=35, p=.26) (Figure 5A inset). To satisfy fMRI protocols the outcome devaluation test was 15 minutes duration and there was a main effect of time as responding decreased across the test (F(4,140)=3.45, p<.001, η²_p=.085) but no group x action x time interaction (F(4,185)=0.11, p=.979, η²_p=.002). Simple effects analysis of the significant two-way interaction revealed a difference in performance between groups on the valued action (t=1.41, df=36, p=.005) but not devalued action (t=0.68, df=34, p=0.49). As participants were instructed to use one finger during the training and tests, this reduced performance on the valued action likely reflects response competition.

Interestingly, food desirability ratings showed no inter-group differences in the change in outcome desirability ratings (post–pre) for the food outcomes – Figure 5B. Two-way ANOVA revealed a significant main effect of devaluation on food ratings (F(1,39)=24.38, p<.001,
\( \eta_p^2 = .397 \) but neither a main effect of group nor a significant interaction (interaction \( F_{1,39} = 0.15, p = .903, \eta_p^2 < .001 \)). Despite the difference in choice performance, the correlation between outcome rating and action rate for the valued vs. devalued outcome was significant in both groups (\( r = .604 \) and \( .628, p < .05; \) OCD and HA, respectively). Linear regression confirmed there was no significant difference in slope between groups (\( p = .96 \)). Therefore, although choice performance after outcome devaluation clearly differed between groups, there was no difference in sensitivity to the devaluation treatment per se.

**Anterior PFC and dorsal caudate activity tracked the effect of experienced value on choice**

BOLD activity that tracked choice driven by experienced value was determined by the planned SPM t-test in healthy adolescents: significant effects occurred in the left medial caudate (MNI: -14,6,18; \( t_{19} = 17.75, \text{pFDR} < .001 \)), an anterior region of left middle frontopolar gyrus (MFPF)/anterior prefrontal cortex (BA10, MNI: -22,60,2; \( t_{19} = 16.44, \text{pFDR} < .001 \)), medial orbital gyrus (MOrG)/centrolateral OFC (BA13, MNI: -18,30,-2; \( t_{19} = 14.76, \text{pFDR} < .001 \)) and an anterior region in the right middle frontopolar gyrus (MFPF)/medial OFC (BA10: MNI: 14,54,-2; \( t_{19} = 13.19, \text{pFDR} < .001 \)) shown in **Figure 5C**—refer **Table 2**. Group differences were detected within the follow-up ROI analysis of this cluster within the anterior orbitomedial PFC region (OMPFC)(29,30) and revealed a significant deficit in activity in the right anterior prefrontal cortex (AntPFC; BA10) extending into right dorsal anterior cingulate (dACC; BA32) of the adolescents with OCD (**Figure 5D**, BA32: MNI: 2,50,10; \( F_{2,39} = 10.64, k = 29, \text{pFWE} = .028, \text{svc} \)).

Parameter estimates from the peak voxel in this OMPFC ROI were extracted per participant and correlated with a devaluation score calculated for each participant, i.e., the average response rate on the valued action minus the average rate on the devalued action. The correlation between BOLD activity and this devaluation difference score was \( r = -.51 \) and +.17 in people with and without OCD, respectively, and these associations differed between groups, \( p = .046 \) (**Figure 5D inset**). Taken together, these findings suggest that, in adolescents with OCD, hypoactivity in this anterior PFC/dorsal ACC region resulted in a deficit in the choice between goal-directed actions after a change in experienced value.

**Anterior PFC-caudate tract strength is weaker in adolescents with OCD.** Using the anterior PFC/dorsal ACC region identified above as a seed region, tractography analysis compared afferent and efferent tracts between groups to investigate neural disconnection as a contributing factor to task performance. This analysis revealed a lower tract strength in the projection to the caudate nucleus (peak MNI coordinates: 6,18,-6; cluster size: 56 voxels) in adolescents with OCD relative to healthy controls (pFWE=.008; **Supplementary Figure S2A**). **Supplementary Figure S2B** shows the average connectivity, across all participants, of the anterior PFC/dorsal ACC seed mask (top 0.02% of tracts sent from this seed mask).

**Discussion**

We provide here a first assessment of the motivational control of goal-directed action in adolescents; i.e., the effect of reward values derived from Pavlovian predictions, or **predicted values**, and those derived from direct, largely consummatory, contact with the outcome of goal-directed actions, or **experienced values**(2,6,17) on goal-directed performance. Importantly, replicating findings in adults, we confirmed in healthy
adolescents that: (i) stimuli generating specific reward predictions biased choice towards actions earning the outcome predicted by the stimulus (specific PIT), (ii) general reward predictions elevated the performance of actions regardless of outcome (general PIT) and (iii) changes in experienced value biased choice of action away from the devalued action and towards that associated with the still-valued outcome (outcome devaluation).

The neural bases of motivational control in healthy adolescents.
We established that specific reward predictions in the specific-PIT test induced increased activity bilaterally in the lateral OFC, right dorsolateral PFC, right putamen, left medial OFC, left lateral caudate, and left inferior parietal lobe. These effects suggest considerable commonality with those documented in rodents, particularly those in the lateral OFC, medial OFC and both dorsomedial and dorsolateral striatum(31–34), and are consistent with evidence that specific PIT is driven by stimulus-mediated retrieval of the instrumental outcome and, subsequently, the action via an outcome-response (O-R or ideomotor) association(28,35). Other research has, however, also implicated a more ventral circuit, likely engaged by specific stimulus-outcome predictions, including the ventrolateral putamen(36) and basolateral amygdala(37) in humans; although we did not see evidence of this involvement in the current study. Similarly, with regard to the general reward predictions in the general-PIT test we found increased activity in a posterior region of the right medial OFC, as we have found previously(14), whereas prior research has focused on a circuit involving central amygdala and accumbens core in both rodents and humans(7,36,37). The role of the medial OFC may be pivotal here; maintaining a relationship with dorsal and ventral striatum in a number of potentially related functions(22,38). Finally, the influence of expected reward values on instrumental performance following outcome devaluation engaged a circuit linking an anterior part of both the left and right OMPFC with the medial caudate – a circuit that previously implicated in value-based decision-making in humans(9,39,40).

The functional significance of this circuitry as revealed by OCD
In contrast to healthy adolescents, we found that, behaviorally, the influence of both forms of incentive process on choice performance was blunted or abolished in OCD. In specific-PIT performance, adolescents with OCD did not differ in their choice between actions regardless of the outcome predicted by the stimuli and, in the outcome devaluation test, participants with OCD appeared insensitive to the effects of devaluation, responding similarly on both the valued and devalued actions. Nevertheless, on other measures, OCD participants did not differ from controls: our assessment of their Pavlovian and instrumental conditioning suggested they learned the specific stimulus-outcome and action-outcome associations similarly and showed similar changes in outcome desirability ratings after the devaluation treatment. Nor could we find any change in the size of the deficits in those with OCD when we restricted our analyses to participants that overlapped with controls on our conditioning measures (see supplementary results). It is, of course, possible the measures of conditioning and of changes in value that we used were less sensitive than the specific transfer and devaluation tests in detecting group differences. It is also possible that the verbal assessment we used to check our participants’ ability to retrieve the associations interfered with or altered that learning is some way and, certainly, a non-verbal conditioned response would have been preferable. Nevertheless, the adolescents with OCD showed a significant general elevation in the general-PIT test similar to that observed in controls.

Importantly, these motivational deficits in OCD were associated with reduced functional
segregation between the neural circuits associated with predicted and experienced reward values in healthy adolescents. The most notable effects were patterns of hypoactivity in the lateral OFC (BA47) during the specific PIT test and in the anterior PFC (BA10), extending to the dorsal ACC (BA32) during the outcome devaluation test. This cortical hypoactivity was accompanied by hypoactivity in caudate and putamen, implicating orbito-striatal and prefronto-striatal disconnection in these effects. Interestingly, specific-PIT was also accompanied by hyperactivity in the medial OFC (BA11), an effect that was positively correlated with compulsion severity (see also (41)). Although in a more anterior region of BA11 to general PIT, this hyperactivity suggests that, in the absence of specific reward predictions, adolescents with OCD were responding to the general reward predictions of the specific stimuli. If true, this medial OFC activity was likely suppressed in healthy participants, implying that, in specific PIT, the lateral and medial OFC interact to release and to suppress action selection and its inhibition(42,43). The insensitivity of adolescents with OCD to changes in outcome value in the outcome devaluation test is likewise consistent with a failure to suppress inappropriate actions related, in this case, to hypoactivity in dorsal ACC (BA32), an area broadly implicated in executive functions including action conflict resolution(44,45).

These findings in adolescents with OCD resonate with evidence showing impaired cognitive flexibility in OCD: in adults, in their ability to report degradation-induced changes in the action-outcome relationship(46,47), and, in adolescents, in tests assessing learning and memory and the ability to use specific stimulus-outcome associations to guide go and no-go discrimination(48). However, the current tests go further in pointing to broader deficits in the emotional and motivational processes that control instrumental performance. Deficits in goal-directed control have been interpreted as suggesting the intrusive thoughts and behavioral compulsions in OCD reflect a shift to an automated or habitual process(24,49).

However, the pattern of deficits observed here appear to be more closely associated with dysregulated action control due to specific failures of inhibition during conflict, resulting in the intrusion of actions irrelevant to achieving currently adaptive goals. Previous research has linked anterior medial OFC, in particular, with the retrieval of specific outcomes for action selection and performance, and a deficit in this retrieval would necessarily reduce the influence of specific outcome predictions on choice (50). Lateral OFC hypoactivity with medial OFC hyperactivity during specific-PIT is broadly consistent with a failure to suppress alternative actions and, indeed, neural activity in people with OCD in inhibition and set-shifting tasks consistently shows a combination of hypo- and hyperactivity across the OMPFC(51). This has led to theoretical propositions regarding compulsions in OCD being associated with lateral OFC hypoactivity and medial hyperactivity (24) with circuit models hypothesizing these effects reflect aberrant activity in an afferent corticostriatal-thalamocortical circuit linking lateral and medial OFC via ventral striatum and mediodorsal thalamus (2,50,52–54). Converging with this, a number of the structures in this circuit are current targets for treatment in OCD using deep brain stimulation(55). Nevertheless, differences emerge between experimental and symptom provocation tasks in people with OCD — meta-analyses of the latter show uniformly increased BOLD across the medial and lateral OFC, ACC, caudolateral PFC, and the medial putamen(56). Disambiguation of these differences between task- and symptom-based activation patterns could enhance the precision of neurostimulation targets; for instance, the OFC as a whole has not yet proven to be an effective transcranial magnetic stimulation target(57).
Our focus on adolescents to advance an understanding of the causal role of OCD pathophysiology is important given OCD begins during childhood or adolescence in 80% of cases (58) and in that group has greater genetic contribution (45–65%) than adult-onset disorder (27–47%) (59). Moreover, premorbid ritualised behavior in early childhood occurs in probands and strong reactions to everyday sensory events are associated with high childhood ritualism (60,61). The current data suggest that these repetitive behaviors may be an early manifestation of an impairment in the motivational control of goal-directed action, presenting a behavioral marker that, combined with a family history of illness, might predict disease onset and indicate early intervention. This is particularly important given that meta-analysis of results from clinically developed tests does not show cognitive impairment in children or adolescents with OCD, something that questions whether these impairments are a consequence of the illness or its social and experiential sequelae (62,63). Certainly, in the current study we found performance on behavioral tests less reliant on verbal instructions and responses was sensitive to impairments in motivational control of decision-making in younger people with OCD.

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Author contributions:
Conception: IEP and BWB. Design: IEP, RWM, SQ, KG, FW, MO, PLH, and BWB. Data acquisition: IEP, RWM, SQ, FW, and MO. Data analysis: IEP, RWM, SQ, and KG. Data interpretation: IEP, RWM, SQ, KG, PLH, and BWB. Drafted or substantively revised the manuscript: IEP, RWM, KG, PLH, and BWB. All authors approved the submitted manuscript and agreed both to be personally accountable for the author’s own contributions and to questions related to the accuracy or integrity of any part of the work.

Conflict of interest statement
The authors report no biomedical financial interests or potential conflicts of interest.
References


### Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>OCD (n = 20)</th>
<th>Controls (n = 21)</th>
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<th>p-value</th>
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<td>15 (2)</td>
<td>0.48</td>
<td>0.63</td>
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<tr>
<td>Right handed (total)</td>
<td>17</td>
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<td>8</td>
<td>8</td>
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<td>English second language (total)</td>
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<td>5</td>
<td>1.73</td>
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<td>Years of education</td>
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<td>11 (1)</td>
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<td>0.51</td>
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<td>49 (5)</td>
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<td>Symptom dimensions: DASS-21</td>
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<tr>
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<td>3 (4)</td>
<td>2.53</td>
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<td>2.98</td>
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<td>Stress</td>
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<td>OCD diagnosis</td>
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<td>OCD symptoms: CY-BOCS</td>
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<tr>
<td>Obsessions</td>
<td>9 (5)</td>
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<tr>
<td>Compulsions</td>
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<tr>
<td>Total</td>
<td>17 (9)</td>
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<tr>
<td>Lifetime comorbid psychiatric diagnoses</td>
<td>15 (75%)</td>
<td>3 (14%)</td>
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<tr>
<td>anxiety disorder</td>
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<td>2*</td>
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<tr>
<td>tic disorder</td>
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<td>eating disorder</td>
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<td></td>
</tr>
<tr>
<td>elimination disorder</td>
<td>1 (5%)</td>
<td>1**</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>SSRI monotherapy</td>
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<td>SSRI and anti-psychotic</td>
<td>6 (30%)</td>
<td></td>
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</tr>
<tr>
<td>other</td>
<td>3 (15%)</td>
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</table>
Notes: Means (SD or percentages) or totals of each demographic variable, along with symptom severity scores. Obsessive-compulsive disorder (OCD) Children's Yale Brown Obsessive-Compulsive Scale (CYBOCS [score of 18 = moderate severity]), selective serotonin reuptake inhibitor (SSRI), Weschler Ranging Assessment Test (WRAT), Depression Anxiety Stres Scale 21-item version (DASS-21 [all means for cases in the moderate range; all means for controls in the normal range]), Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). *Adjustment disorder with depressed mood in full sustained remission. **Encopresis, in remission. None of the control group had a current psychiatric disorder.

Table 2. Summary of fMRI findings

<table>
<thead>
<tr>
<th>Task</th>
<th>Group</th>
<th>MNI</th>
<th>Area</th>
<th>Descriptor</th>
<th>BOLD</th>
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<tr>
<td>Specific transfer</td>
<td>HA</td>
<td>-22,34,-20</td>
<td>47</td>
<td>r. lateral OFC</td>
<td>↑</td>
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<tr>
<td>Specific transfer</td>
<td>HA</td>
<td>18,16,-2</td>
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<td>l. lateral OFC</td>
<td>↑</td>
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<tr>
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<td>HA</td>
<td>-18,4,24</td>
<td></td>
<td>r. Fundus of the putamen (FPu)</td>
<td>↑</td>
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<tr>
<td>Specific transfer</td>
<td>HA</td>
<td>8,56,34</td>
<td>9</td>
<td>r. dorsolateral prefrontal cortex (dIPFC)</td>
<td>↑</td>
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<tr>
<td>Specific transfer</td>
<td>OCD</td>
<td>-4,50,-20</td>
<td>11</td>
<td>l. inferior parietal lobe</td>
<td>↑</td>
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<tr>
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<td>OCD</td>
<td>-58,26,-18</td>
<td>21</td>
<td>l. middle temporal gyrus (MTG)</td>
<td>↑</td>
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<td>OCD</td>
<td>44,32,-8</td>
<td>47</td>
<td>r. lateral OFC</td>
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<td>-18,2,26</td>
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<td>34,34,-20</td>
<td>47</td>
<td>r. lateral OFC</td>
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<tr>
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<td>OCD</td>
<td>20,18,0</td>
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<td>r. putamen</td>
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<tr>
<td>Specific transfer</td>
<td>OCD</td>
<td>6,58,32</td>
<td>9</td>
<td>r. dorsolateral prefrontal cortex (dIPFC)</td>
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<tr>
<td>Specific transfer</td>
<td>OCD</td>
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<td>General transfer</td>
<td>BOTH</td>
<td>12,38,-6</td>
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<td>Outcome deval</td>
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<td>-22,60,2</td>
<td>10</td>
<td>l. anterior PFC</td>
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<tr>
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<td>13</td>
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<td>10</td>
<td>r. anterior OMPFC</td>
<td>↑</td>
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<td>2,50,10</td>
<td>10/32</td>
<td>r. anterior PFC/dorsal ACC</td>
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<tr>
<td>Outcome deval</td>
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<td>6,18,-6</td>
<td>14</td>
<td>r. anterior OMPFC-caudate tract</td>
<td>↓*</td>
</tr>
</tbody>
</table>

* Note: this is a change in tract strength
Figure captions

Figure 1. Experimental design for Pavlovian-instrumental transfer.

**Top panels:** Instrumental conditioning was conducted by participants tilting a virtual vending machine to the left (A1) or right (A2) (actions) to earn food reward outcomes (O1, O2; shown on monitor for 1-s) during blocks of learning on a variable-ratio schedule (VR5). The task was continuous, not trial based, and participants could respond freely on each action until the end of each block — see Supplementary Materials for full details.

**Middle panels:** Pavlovian conditioning involved four coloured lights (S1, S2, S3, S4) appearing on the machine for 6s in a random, non-replacing sequence within blocks which were followed by a multiple-choice question. The stimuli predicted the appearance of an outcome (O1, O2, O3, O4(empty) counterbalanced) that occurred during the final 1-s of that stimulus. There then followed an intertrial interval followed by the next (randomly selected trial) — see Supplementary Materials for full details.

**Lower panels:** During the Pavlovian-instrumental transfer test, the vending machine could again be freely tilted in either direct in a continuous manner both when it was unlit (i.e., during the 5-15-s inter-trial intervals to provide an active baseline measure), and when the coloured lights appeared on the machine. Four stimuli (S1, S2, S3, S4) appeared in a random, non-replacing sequence for 6-s per stimulus every 18 seconds (0-4-s random jitter). Each stimulus was presented 12 times in random order. This transfer phase was conducted in extinction, i.e., no outcomes were delivered, so as to ensure that responding was not influenced outcome exposure on test — see Supplementary Methods for full details.

Figure 2. Predicted value — Specific Pavlovian-instrumental transfer test results.

We tested whether participants could use outcome-specific predicted values, generated by stimuli S1 and S2, to direct choice toward actions associated with the ‘same’ outcomes as those predicted by the stimuli compared to actions associated with the outcome ‘different’ from that predicted (i.e., outcome-specific PIT).

(A) Mean (±SEM) rates of button pressing per second before and during the specific stimuli when the action predicted the ‘same’ food reward as the stimulus, or a ‘different’ food reward from the stimulus. Post-hoc t-tests confirmed the action rate for the same food reward was significantly greater than the other action in healthy adolescents (HA) (p < .01). However, performance in the OCD group did not differ (p>0.05). The inset shows the mean performance across the test and illustrates the significant group x stimulus interaction (p = .017). (B) Adolescents with OCD showed hyperactivity in medial OFC relative to controls and the degree of hyperactivity correlated with compulsion severity. (C) Bilateral BOLD activity in the lateral OFC (right lateral OFC, BA47, MNI: 36, 34, -18; left lateral OFC, BA47, MNI: -30, 34, -20) tracked the effect of same vs. different stimulus on choice performance during the specific transfer test in healthy adolescents. (D) In contrast, relative to HA controls, OCD participants showed hyperactivity in medial OFC (BA11: MNI: -4, 50, -20) during the test, due to larger BOLD estimates in adolescents with OCD than negative BOLD estimates in those without (inset). (E) OCD participants also showed generally increased activity in medial OFC (BA11, MNI: -4,50,-20); however, (F) OCD participants showed significant hypoactivity in right lateral OFC relative to HA (BA47, MNI: 34, 34, -20).
**Figure 3. Predicted value — General Pavlovian-instrumental transfer test results.**

(A) Mean (±SEM) response rates (per second) before and during the general excitatory stimulus, S3 associated with the reward that was not presented during instrumental training, and the neutral S4 stimulus associated with the ‘empty’ vending machine. Post hoc t-tests confirmed the response rate during S3 was significantly greater than S4 in both HA and OCD groups, ps<.05. (B) Activity in a posterior region in the medial OFC (BA11: MNI: 12,38,-6) tracked changes in the predicted values across presentations of the general predictive stimulus (S3) in both groups.

**Figure 4. Outcome devaluation**

After instrumental training (e.g., as in top panels) participants watched a video showing one of the outcomes infested with cockroaches as a devaluation treatment (middle panel). This treatment was effective (see Figure 5B). After the video we conducted a test in which all participants could tilt the vending machine to the left or right allowing us to assess their choice performance. Importantly, the devaluation test was conducted in extinction; i.e., no outcomes were delivered during the test.

**Figure 5. Experienced value — Devaluation test results.**

(A) Proportion of total button presses on the actions that previously delivered the ‘valued’ and the ‘devalued’ food rewards during each minute of the devaluation test in 3 min blocks. After viewing the outcome devaluation video, healthy adolescents (HA) preferred the action previously associated with the still ‘valued’ (non-contaminated) outcome vs. the now ‘devalued’ (contaminated) outcome. In contrast, people with OCD showed no behavioral preference responding similarly on the valued and devalued actions. Inset illustrates the significant interaction in the average performance across the session (p=0.005) (B) Mean (±SEM) change in the food ratings of the devalued (open bar) and non-devalued food (filled bar) after devaluation (pre – post). (C) BOLD activity tracked valued actions in the left dorsal caudate (MNI: -14,6,18), an anterior region of anterior prefrontal cortex (BA10, MNI: -22,60,2), medial orbital gyrus (MOOrG)/centrolateral OFC (BA13, MNI: -18,30,-2) and an anterior region of the medial OFC (BA10: MNI: 14,54,-2). (D) Group differences revealed hypoactivity in the right anterior prefrontal cortex (BA10) extending into the right dorsal anterior cingulate (BA32) of the adolescents with OCD (BA32: MNI: 2,50,10). (D - Inset) The inset shows the correlation between activity at the peak voxel per participant correlated with a devaluation score calculated as the average response rate on the valued action minus the average rate on the devalued action. OCD group in red (r=−.51), HA group in blue (r=+.17).
Instrumental

Pavlovian

'empty'

Transfer test (MRI)

choice
A. Responses per second

![Graph showing responses per second for OCD and HA.](image)

B. Posterior mOFC activity in OCD & HA

![Brain images showing activity at different z levels.](image)