Functional neuroimaging of avoidance habits in OCD

Claire M Gillan*, Annemieke M Apergis-Schoute, Sharon Morein-Zamir, Gonzalo P Urcelay, Akeem Sule, Naomi A Fineberg, Barbara J Sahakian, Trevor W Robbins

Location of Work: The Departments of Psychology and Psychiatry, and the Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge, Cambridge, UK; The Department of Psychology at New York University, New York, USA; South Essex Partnership Trust, Springhouse, Biggleswade Hospital, Bedfordshire, United Kingdom; The Department of Psychiatry, Queen Elizabeth II Hospital, Welwyn Garden City, Hertfordshire, UK; the Postgraduate Medical School, University of Hertfordshire, Hatfield, UK

*Corresponding Author: Dr Claire Gillan, Department of Psychology, New York University, 4 Washington Place, New York, NY 10003, USA. Email: claire.gillan@gmail.com

1

Abstract

Objective: The goal of this study was to determine the neural correlates of excessive habit formation in obsessive-compulsive disorder (OCD). We aimed to (i) test for neurobiological convergence with the known pathophysiology of OCD and (ii) infer, based on abnormalities in brain activation, whether these habits arise from dysfunction in the goal-directed or habit system.

Method: Thirty-seven OCD patients and 33 controls learned to avoid shocks while undergoing a functional Magnetic Resonance Imaging (fMRI) scan. Following 4 blocks of training, we tested if the avoidance response had become a habit by removing the threat of shock and measuring continued avoidance. We tested for task-related differences in brain activity in 3 ROIs, the caudate, putamen and medial orbitofrontal cortex at a statistical threshold of $p<.05$, family-wise error (FWE) corrected.

Results: We observed excessive habit formation in OCD patients, which was associated with hyper-activation in the caudate. Activation in this region was also associated with subjective ratings of increased urge to perform habits. The OCD group, as a whole, showed hyper-activation in the medial orbitofrontal cortex (mOFC) during the acquisition of avoidance, however this did not relate directly to habit formation.

Conclusions: OCD patients exhibited excessive habits that were associated with hyper-activation in a key region implicated in the pathophysiology of OCD, the caudate nucleus. Prior studies suggest that this region is important for goal-directed behavior, suggesting that habit-forming biases in OCD may be a result of impairments in this system, rather than differences in the build up of stimulus-response habits themselves.

Introduction

The habit hypothesis of obsessive-compulsive disorder (OCD) suggests that the disorder reflects dysfunction in the brain systems that support automatic habits and more purposeful, goal-directed control over action (1). Habits are automatic, stimulus-driven behaviors that can arise under many conditions, the most commonly accepted of which is the over-training of simple responses (2). However, habits can also arise from failures in goal-directed control, which can render behavior habitual even very early on in training (3, 4). These two systems, habit and goal-directed, therefore each contribute to the likelihood that a habit will be performed in a given situation. In OCD, it is currently unclear which of these putative systems drives the exaggerated tendency to display habits, which has been observed regardless of whether they are working to gain rewards (5) or avoid punishments (6). However, two recent studies found deficits in goal-directed behavior during trial-by-trial learning in OCD, using paradigms that did not involve repeating simple responses (7, 8). This suggests that excessive habits in OCD could arise due to disturbances in the goal-directed, rather than the habit system. The present study aimed to test for neurobiological convergence in support for this possibility, drawing on a rich cross-species neuroscience literature, which has identified dissociable neural substrates of these two systems (9).

The medial orbitofrontal cortex (mOFC) and the caudate nucleus each contribute to goal-directed control over our behavior. Specifically, the caudate and mOFC have both been shown to subserve learning involving action-outcome contingencies (4, 10, 11). Additionally, the mOFC plays a pivotal role in tracking the current value of outcomes (12-14). Another region in the basal ganglia, the putamen, is necessary for the formation of stimulus-response habits with practice (11, 15, 16). We tested if functional activation in these three regions was associated with habit-forming biases in OCD, and in doing so aimed to reveal if dysfunction in the goal-directed or habit-learning system accounted for excessive habits in OCD.

Generally, the habit hypothesis of OCD exhibits good face validity in that habits, like compulsions, continue in spite of awareness that these actions are not useful/wanted (i.e. ego-dystonic), and are associated with the experience of an urge to perform them (6). A secondary goal of this study was to test the neurobiological validity of the OCD habit hypothesis by assessing if activation associated with habit forming in OCD overlaps with that implicated in the disorder symptomatology. The literature has broadly converged on a model of OCD that involves hyperactivity within fronto-striatal circuits (17), with effects in the orbital gyri caudate nucleus head being among the most reliable (18-20). Evidence for this model comes primarily from (now rather dated) functional brain imaging studies examining brain activity at rest (21-23), during symptom provocation (24-26), and pre- and post-treatment with psychotherapy or pharmacotherapy (22, 27-29). A more widely distributed network of regions has also been implicated in OCD in recent studies employing task-related functional Magnetic Resonance Imaging (fMRI) analysis, including the nucleus accumbens, amygdala and other parts of the prefrontal cortex (30-32). However, given that fMRI activation patterns are entirely dependent on the task employed, the results have been unsurprisingly heterogeneous and have failed to confirm activation seen during earlier studies examining task-independent activity patterns that are characteristic of OCD. We hypothesized that, if excessive habits are an appropriate model of OCD, then brain-activation associated with habit-forming in these patients should overlap with those associated with the symptomatology, specifically in the mOFC and caudate. Although less consistently implicated, there is some suggestion that the putamen may be enlarged in OCD, an effect related to age, and plausibly the chronic performance of compulsive behavior (33). We

3

therefore also tested the possibility that aberrant activation in the putamen, perhaps reflecting over-active habit learning, would be associated with habits in OCD.

To investigate the neural basis of habit-forming biases in OCD, we used fMRI to examine changes in brain activation while patients acquired and later performed habits. To do this, we used an avoidance task that has previously been shown to be sensitive to differences in habit formation between OCD patients and controls (6). Only subjects who had not previously participated in the previously published behavioral study using this task were eligible to take part. This task was selected because avoidance rather than appetitive compulsions are characteristic of OCD. This approach therefore allowed us to model the disorder more closely, and secondarily to investigate how habit learning might relate to anxiety and explicit fears in OCD. To test for habits we used the so-called 'outcome devaluation' technique, where behavior is defined as a habit if it persists despite changes in the value that action produces (34), in other words, habits are behaviors that are driven by stimuli, not by motivation or 'goals'.

Method

Participants

Participants were 37 OCD patients and 33 controls matched at mean-level for age, handedness, smoking behavior, education and gender. A trend ($p=.092$) towards lower premorbid verbal IQ (using the National Adult Reading Test: NART, 35) was however observed in the OCD group, but analyses of covariance confirmed this did not drive any of the results. Participants in this study were excluded if they had participated in a previous study examining avoidance habits in OCD in our lab (6), i.e. all participants were task-naïve. Patients were free of co-morbid psychiatric diagnoses. Fourteen patients were free of psychotropic medication, the remaining 23 patients has been stabilized on medication for a minimum of six weeks prior to taking part in the study and the majority were taking selective serotonin reuptake inhibitors (SSRIs; see Supplement). For all of the results presented, there were no significant differences between medicated and unmedicated patients unless otherwise stated. Further details on participant characteristics and recruitment can be found in the Supplement.

Procedure

Avoidance Training and Habit Test

Participants completed a shock avoidance paradigm similar to one described in detail elsewhere (6) and in the supplementary materials. Participants were instructed that their goal was to avoid receiving shocks, which would be delivered to their right and left wrists following the presentation of a conditioned stimulus (CS+) (Figure 1). During fMRI scanning, we over-trained the avoidance response across 4 blocks each containing 30 trials (10 per CS), before testing for habits using outcome devaluation. Before the final block, the left shock outcome was 'devalued' by disconnecting the electrodes from participants' left wrists. The shock to the right wrist remained threatening or 'valued'. Importantly, up until this point, subjects had identical training with both left and right CSs that, in the final block,

were defined as devalued or valued by the connection status of wrist electrodes. Subjects were informed on-screen that they could no longer be shocked to the left wrist and their only goal was to avoid the remaining shock (which was on the right). The task proceeded for one block constituting the habit test. To prevent new learning during the test, shocks were no longer delivered to any CS.

Figure 1. Task Schematic
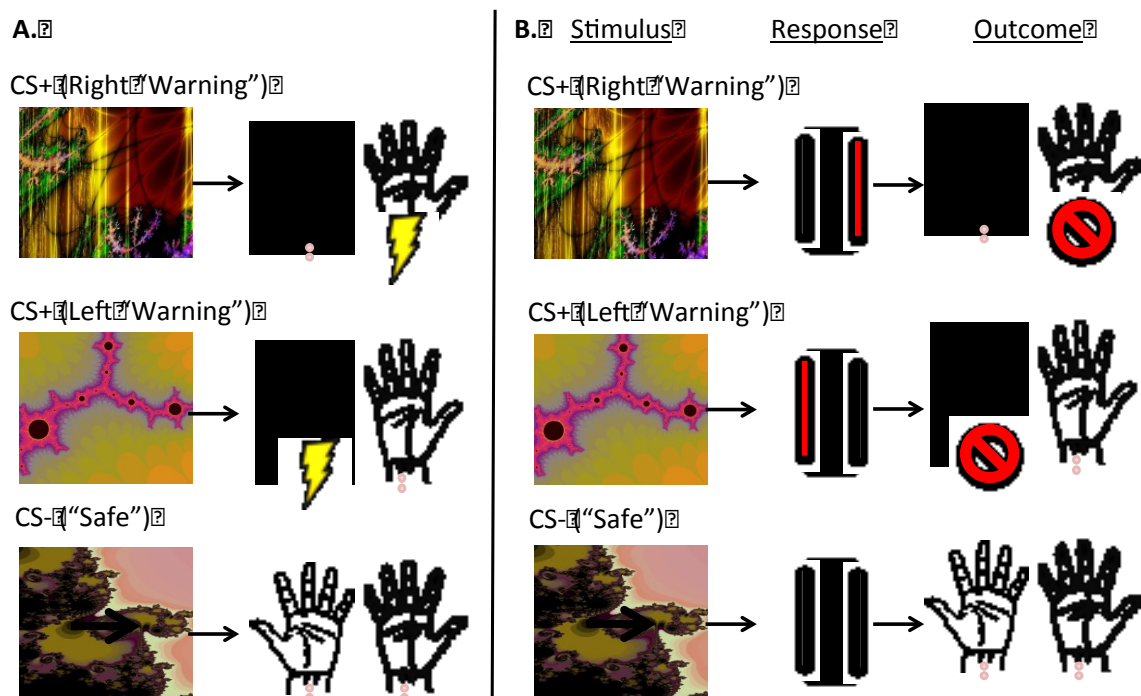
Panel A depicts the Pavlovian (stimulus-outcome) contingencies, which were 100% deterministic. There were two Warning CSs (CS+); one predicted a shock to the left wrist, and another predicted a shock to the right wrist. A Safe CS (CS-) never predicted shock.

Panel B depicts the avoidance contingencies, including stimuli, responses and outcomes. When top (right warning) predictive CS+ appears on screen, it indicates that a shock to the right wrist is imminent. If participants press on the right side of the foot-box (highlighted in red) while this CS+ is on-screen, they will avoid this shock. Likewise pressing on the left side of the foot-box when the middle (left warning) CS+ appears cancels an otherwise imminent shock to the left wrist. The safe stimulus always remained safe, regardless of responding.

To better clarify how habits in OCD relate to implicit and explicit fear and belief, we collected supporting data including skin conductance responses (SCRs), explicit contingency knowledge and subjective ratings of shock expectancy, shock unpleasantness, urge to perform habits and attempts to suppress habits. See also Supplement (Table S2). Participants completed an additional and unrelated experiment in the same session (after this task had been completed), the results of which will be published elsewhere.

Data Analysis

Behavior

Behavioral data were analyzed using ANOVA for parametric data and Mann-Whitney U, Chi-square and Spearman's rho correlations. In the habit test, which followed outcome devaluation, we compared the number of avoidance responses performed to the Devalued and Valued CSs. We also measured false alarms to the Safe CS. OCD patients were divided into two Habit Groups: "Habit" and "No Habit", determined by whether or not they made any response to the Devalued CS during the habit test. In subsequent analyses we compared the two groups defined by this distinction. During training, as left and right CSs each predicted an avoidable shock, we collapsed these into one factor, Warning (i.e. CS+). We analyzed accuracy during training in terms of percentage correct avoidance responses over each of the 4 experimental blocks. Results are presented as significant at $p<.05$ and trends are defined as $0.1>p>0.05$.

fMRI

Based on prior literature on habit learning in healthy humans, and the known neurobiological profile of OCD, we examined anatomically defined bilateral *a priori* regions of interest (ROI), the medial orbitofrontal cortex (mOFC) (11-13), caudate (10, 11) and putamen (11, 16). We used Pickatlas toolbox in SPM8 (36) to define ROIs according to the anatomical automatic labeling (AAL) atlas. Activation within these ROIs was deemed significant at $p<0.05$, corrected for family-wise error (FWE) at the voxel level, and for testing across multiple ROIs ($p<.05/3$). Results from whole brain exploratory analyses are presented at $p<.001$, uncorrected, with a minimum cluster size of 10 voxels. Whilst we discuss these results to some extent, we caution that replication is needed.

First level analyses of the habit test data from the final block, modeled the three CSs (Valued, Devalued and Safe) along with the six movement parameters produced during realignment (further details in supplement). The Habit Group was defined as patients who had formed habits and those who had not (No Habit Group), based on their responding to the devalued CS. Whilst behavioral responses to the devalued CS allow us to discern if a habit has formed, neural responses to this CS are confounded by the experience of the devaluation procedure, and the associated differences in behavioral responding, urge to respond and attempts to suppress responding. Therefore, to capture the neural signature of habits, we examined the contrast of Valued-Safe, which captures the neural activation associated with unperturbed habitual responding. This analysis therefore relies on the reasonable assumption that if avoidance responding to one CS+ (i.e. devalued) has become habitual, then so has responding to the other CS+ (i.e. valued), given the equivalence of contingencies and training duration.

In the first level analysis for training data from the first 4 blocks, we modeled the three CSs (Left, Right, and Safe), Block (1,2,3 and 4) and the six movement parameters for each block. To assess brain regions involved in the development of habits over time, we used a mixed factor generalized linear model, where we tested for an interaction between CS (Warning (collapsed Left + Right), Safe) and Block (1-4), where Block was a parametric modulator. We then tested for group differences at the second level. This allowed us to examine changes in activation that progressed with over-training, or the putative 'stamping in' of habits.

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Results

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Habit Test

OCD patients showed increased habits relative to healthy controls, replicating previous findings using both avoidance (6), and appetitive (5, 7) paradigms. There was a significant main effect of Group (OCD, Control) on the number of responses overall, $F(1,68)=10.691$, $p=.002$ and an interaction between group and CS (Valued, Devalued) during the devaluation test, $F(1,68)=5.408$, $p=.023$ (Figure 2A). Simple effects analyses revealed that OCD patients compared to controls responded at a significantly higher rate to the devalued CS, $F(1,69)=8.139$, $p=.006$, and to the valued CS, $F(1,69)=4.896$, $p=.030$. However, the significant interaction indicates that the group difference was greater for the devalued compared to the valued CS, and responding to the valued and devalued CSs were not significantly correlated Spearman's r=-.276, $p=.099$. The trend was in the opposite direction to what would be predicted by a disinhibition account, such that the greater the habits, the fewer the responses to the valued CS.

Figure 2. Habit Test: Behavioral Data
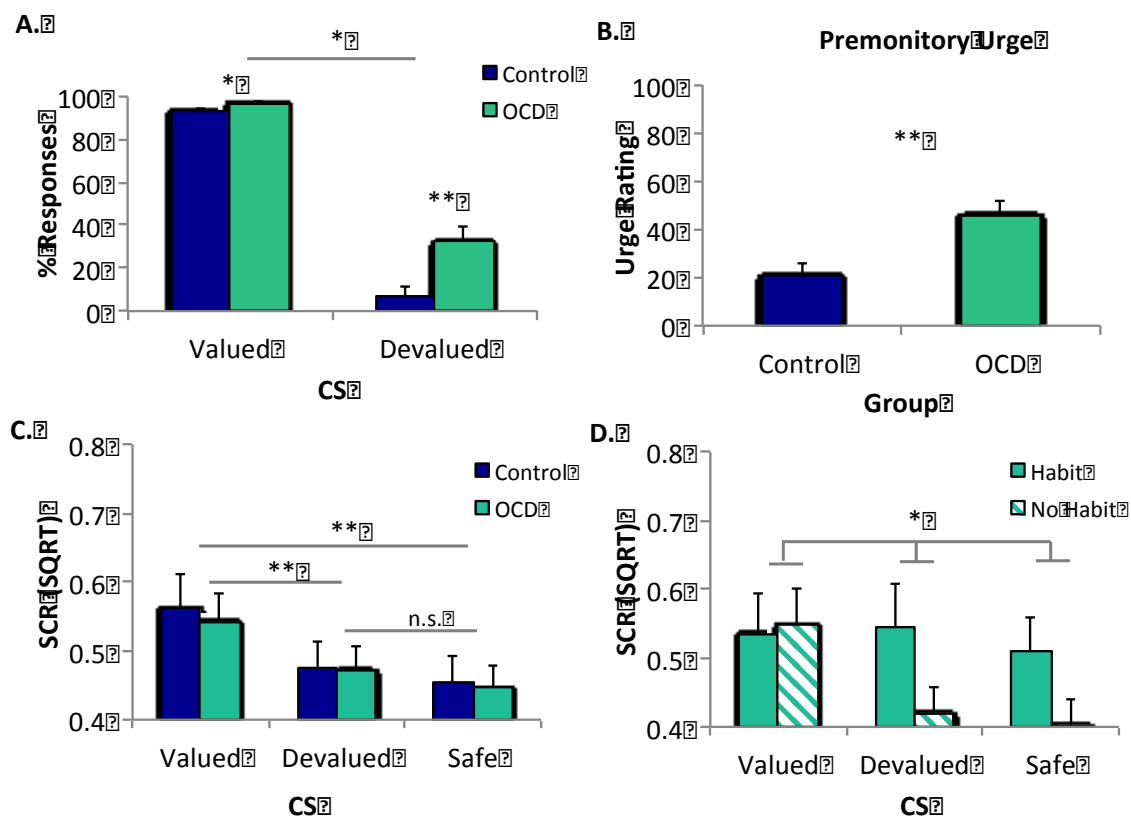
**** $p<.01$; *$p<.05$; n.s. non-significant**

Error bars denote standard error of the mean (SEM)

7

Panel A depicts the percentage of accurate avoidance responses made to the Devalued and Valued stimuli. In line with previous research, OCD patients developed more habits than Controls, evidenced by greater responding to the Devalued CS ($p<.006$). Overall, OCD patients (n=37) responded more to both the Devalued and Valued CSs relative to controls (n=33). However, a significant interaction between Group (OCD, Control) and CS (Valued, Devalued), $F(1,69)=5.335$, $p=.024$, indicated that the difference was greater for the Devalued compared to the Valued CS ($p<.037$).

Panel B depicts urge to respond ratings. OCD patients reported a greater urge to respond relative to healthy controls, $U=345$, $Z=-3.191$, $p=.001$.

Panel C depicts SCR data. There were no differences between OCD (n= 36) and Controls (n=31) in SCR (note 2 controls and 1 patient were excluded from this analysis due to insufficient SCR data). There was a main effect of CS, $F(2,130)=16.163$, $p<.001$. Conditioned fear responses extinguished to the Devalued CS to a level equivalent to the Safe CS, $p=.181$. Responses to the Valued CS remained elevated relative to the Devalued, $p<.002$ and Safe CSs, $p<.001$.

Panel D depicts SCR data between Habit (n=15) and No Habit (n=21; 1 subject excluded due to insufficient SCR data) groups from within the OCD group. There was a significant interaction between CS and Habit Group, $F(2,68)=4.818$, $p=.011$. While the No Habit group had a significant main effect of CS, $F(2,40)=9.934$, $p=.001$, the Habit group did not, $F<1$.

Supporting Data

Explicit contingency knowledge was equivalent across groups, $F<1$ (6). OCD patients and controls reported a greater urge to respond to the devalued CS relative to healthy controls, $U=345$, $Z=-3.191$, $p=.001$ (Figure 2B), and this urge correlated with the number of responses made to the Devalued CS by OCD patients, Spearman's $r(37)=.668$, $p<.001$. There were no differences in SCR between OCD patients and Controls ($F<1$), but those patients who formed habits showed inferior discrimination between the three CSs (devalued, valued and safe) compared to those who did not form habits during the habit test (CS by Group interaction: $p=.011$), but not during training ($F<1.8$). More detailed analyses are presented in the supplement along with expectancy and suppression data.

fMRI

Habit Test

Activation associated with habitual responding in OCD patients was captured using the contrast of Valued – Safe CSs, comparing Habit Groups (Habit n=15, No Habit n=22). OCD patients exhibiting habits during the test showed hyper-activation in the left caudate nucleus [-12,17,4] (extending to the right) relative to those who did not (Figure 3), $T(35)=4.68$, $p<.05$ FWE-corrected ROI. Using the urge to respond as a regressor in an independent analysis at the second level, replacing the binary Habit Group factor, we found that within the OCD

group, there was a positive relationship between activation in the right caudate [6,8,1] for this same contrast, $T(35)=3.81$, $p<.001$, uncorrected. This pattern was also observed in the left caudate at a more liberal threshold of $p<.005$. There was no such relationship in controls. Whilst there were no significant differences between Study Groups (OCD, Control) in activation to the Valued-Safe contrast, the OCD Habit group showed significantly greater activation of the right caudate [15,26,1] relative to controls ($p<.001$, uncorrected). Conversely, when comparing OCD No Habit to controls, we found hypo-activation in the right caudate ($p<.05$ FWE-corrected, ROI).

Figure 3. Comparison of OCD patients who did and did not develop habits
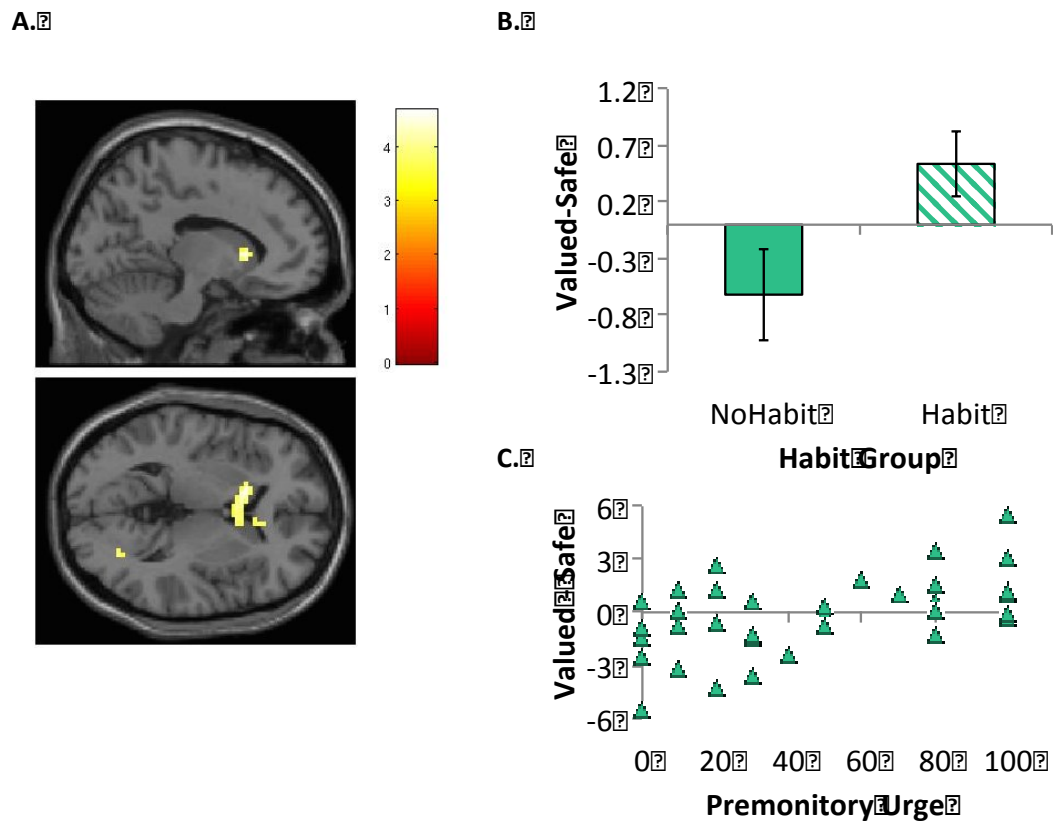
Panel A depicts the interaction between Group (Habit n=15, No Habit n=22), and CS (Valued, Safe) during the devaluation test in the left caudate at $T(35)=4.68$, FWE corrected level, $p<.05$ using a bilateral caudate ROI.

Panel B is a plot of the first eigenvariate of the Valued-Safe contrast extracted from left caudate cluster [-12,17,4] (pictured top right). Patients with habits show significant hyper-activation of the caudate relative to those who did not exhibit habits.

Panel C is a plot showing the parametric association between activity in the right caudate [6,8,1] and the self-reported urge to respond in OCD patients for the Valued-Safe contrast, $T(35)=3.81$, $p<.001$. This pattern was also observed in the left caudate at a more liberal threshold of $p<.005$.

Acquisition of Avoidance

We tested for differences between OCD and Controls in activity associated with the acquisition of avoidance (i.e. Block 1) using a contrast of CS (Warning, Safe). We found significant hyper-activation in the mOFC in OCD patients relative to controls, $T(68)=4.96$ [6,23,-11], (FWE $p<.05$ corrected ROI) (Figure 4A). A more extensive set of regions were hyper-active in OCD during this initial learning at $p<.001$, uncorrected (Table S2). Controls did not show greater activation than OCD patients in any region. There were no significant differences between Habit and No Habit patients.

Over-Training of Avoidance

To test if over-training was associated with changes in brain activation, we compared changes in BOLD activation between OCD patients and controls across blocks. There was a significant interaction with group in the mOFC, $T(68)=4.82$ (FWE $p<.05$ corrected ROI) (Figure 4B), such that OCD patients showed a decrease in activation over successive blocks, whereas controls showed an increasing pattern in this region (Figures 4C). The peak of this interaction was the same as that showing initial hyper-activation in OCD patients during block 1 [6,23,-11]. Other regions showing a similar pattern at $p<.001$ uncorrected are presented in the supplement (Table S3).

We compared Habit Groups on this contrast to test if differences in activation during training foreshadowed the expression of habits. There were no effects in our *a priori* ROIs. However, at $p<.001$ uncorrected, we found a significant interaction in the right precuneus, $T(1,35)=4.11$, $Z=3.68$ ([18,-49,34], cluster extent (Ke)=14) and right superior occipital gyrus $T(1,35)=4.42$, $Z=3.91$ ([27,-94,16], Ke=22). In both of these regions, patients in the No Habit group showed a decreasing pattern of activation, while those who later formed habits did not (Figure S2).

Psycho-Physiological Interaction (PPI) analysis

We conducted *post hoc* PPI analyses to interrogate if the caudate, which was hyperactive in OCD patients who formed habits and correlated with the self-reported urge to respond, showed abnormal neuronal connectivity during the acquisition of avoidance. To do this, we tested for functional connectivity between activation in the bilateral caudate (ROI) and the whole brain during Block 1 (Warning-Safe). There was a significant difference in neural coupling between the Habit and No Habit groups, such that in the No Habit Group, there was positive coupling between the caudate and the right inferior frontal gyrus (rIFG) (cluster corrected at FWE, $p<.05$) and left pallidum ($p<.001$, uncorrected) (Figure 5) during the early acquisition of avoidance, and negative coupling with activation in the subgenual ACC/olfactory cortex (Brodmann Area 25) ($p<.001$, uncorrected). This cluster was rostral to the mOFC cluster observed to be hyperactive in OCD patients (relative to controls) during this stage, but overlapped in 2 voxels ($p<.05$, FWE-corrected ROI of mOFC cluster where OCD patients showed hyper-activity during avoidance acquisition). This pattern was reversed for patients in the habit group (Table S5, Figure 5), such that they exhibited negative coupling between caudate and the rIFG and pallidum, and positive coupling with subgenual ACC/olfactory cortex. There were no differences between patients overall and controls.

Figure 4. Group differences during avoidance acquisition and over-training
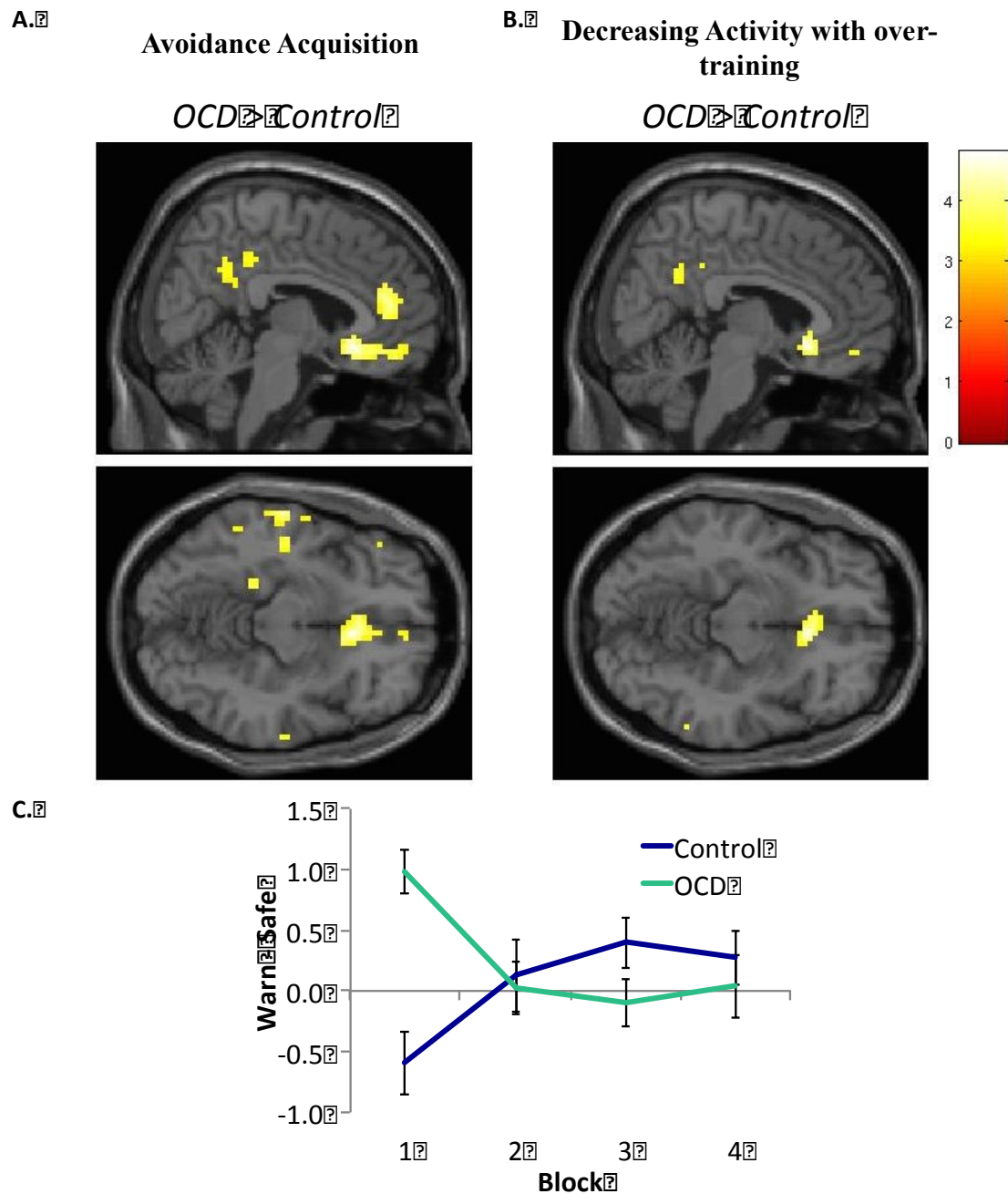
Panel A shows areas of hyper-activation in OCD patients relative to Controls during the initial acquisition of avoidance, i.e. Block 1. There was a significant difference in the medial OFC, $T(1,68)=4.96$ [6,23,-11], (FWE $p<.05$ corrected mOFC ROI).

Panel B depicts a significant interaction between Group (OCD, Control) and Stimulus (Warning, Safe) and Block (1,2,3,4) in the medial OFC $T(68)=4.82$, [(FWE $p<.05$ corrected mOFC ROI). The peak voxel was also at [6,23,-11].

Panel C is a plot of the mean eigenvariate for the contrast of Warn – Safe plotted across time for each of the groups using the mOFC cluster displayed above at $p<.001$ uncorrected. This graph reveals a pattern of hyper-activation in OCD patients during initial acquisition that decreases over time. Control participants show initial hypo-activation, which increases with extended training.

**Results are displayed at $p<.001$ uncorrected. Error bars denote SEM.**

Discussion

Habits in OCD were associated with hyper-activation in the caudate nucleus. During the performance of habits by those patients who displayed them there was greater caudate activation, than in controls and in OCD patients not forming habits. Independent analysis revealed that, across the entire OCD group, greater activation in this region was correlated with the self-reported urge to perform these habits; there was no such relationship in controls.

Translational work in rodents and humans has previously revealed that the caudate is necessary for goal-directed control over action. Lesions to this region in rodents render behavior habitual after only moderate training (4), cocaine-induced habitual responding is associated with increased excitability in the rodent homologue of the caudate (37), and in humans white matter connectivity between the caudate and the mOFC is predictive of improved goal-directed control over action (11) on a task that reveals habit biases in OCD (5). Studies examining dynamic mechanisms of associative learning (rather than devaluation) suggest an important role for the caudate in linking outcomes to actions, i.e. contingency learning (10, 38, 39). However, in the present study, as explicit contingency knowledge was matched across groups we would not expect the direction of activity in our study to mirror these results. Rather, our results may reflect difficulties in translating explicit contingency knowledge into action preferences, similar to a recent study by Corbit and colleagues (37). Hyper-activation in the caudate is one of the most consistent neurobiological markers of OCD symptomatology (with mOFC hyper-activation being the other) (18, 19), and our data therefore lend strong support to a model of OCD centered on failures in goal-directed control over actions, resulting in compulsive habits.

OCD patients showed initial hyper-activation in the mOFC during avoidance learning, which reduced with extended training, whereas control subjects showed the opposite pattern. A *post hoc* PPI analysis revealed that during the acquisition of avoidance, positive coupling between the caudate and the subgenual ACC (partially overlapping with the mOFC cluster) was observed in patients who later demonstrated habits, but a negative coupling was observed in those who did not. The role of the subgenual ACC in habit forming has been sparsely studied, but two studies have shown that its likely homologue, the infralimbic cortex, must be intact for habits to persist in rodents (40, 41), suggesting that excessive connectivity between this region and the caudate may be one possible way that goal-directed control is compromised in OCD. Other differences in BOLD activity associated with habit formation within the OCD group were observed in the precuneus and superior occipital gyrus, which were sensitive to extended training, and functional connectivity between the caudate and the rIFG and pallidum during early learning. These results require replication, but suggest the possibility that a more distributed network may be involved in habit-forming biases in OCD.

Figure 5. Regions where neural coupling between the caudate differed between Habit and No Habit groups
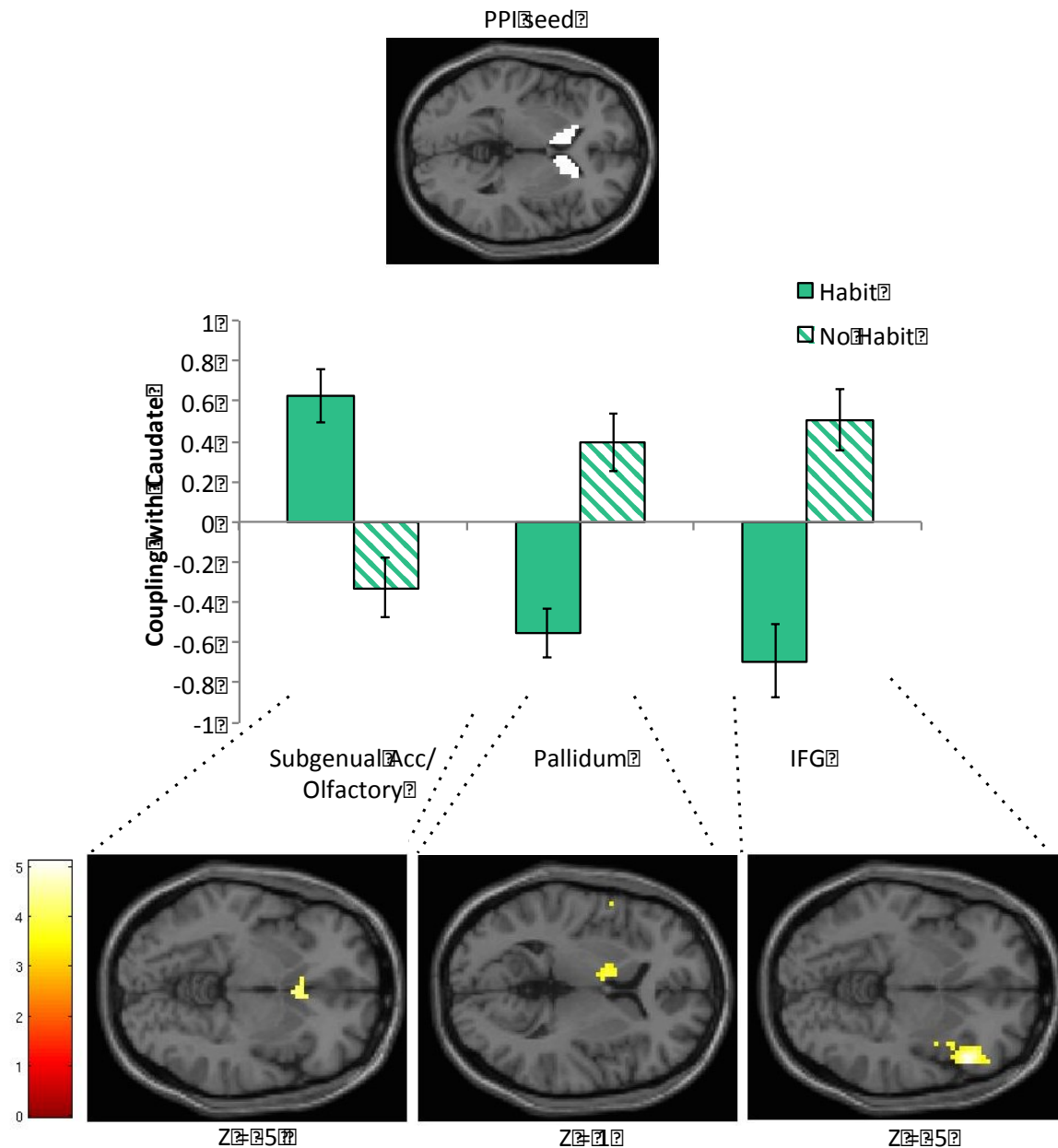
PPI analysis results at *p*<.001 uncorrected. The psychological variable was CS (Warning – Safe) during acquisition of avoidance, i.e. Block 1, and the physiological variable (PPI seed) was activity for this contrast in an anatomical caudate ROI. Eigenvariates from clusters showing interaction effects (between PPI and Habit group) are plotted below. The panel below displays the clusters showing significant psychophysiological interactions in olfactory/subgenual ACC (*T*(35)=4.4), pallidum (*T*(35)=3.91), and rIFG (*T*(35)=5.11), at *p*<.001 uncorrected.

Excessive habit formation in OCD was not related to differences in activation in the putamen. This region is critical for habit formation in rodents, such that lesions to the homologous dorsolateral striatum allow animals to remain goal-directed despite overtraining (15). Moreover, a similar dependency has been observed in healthy humans, such that the formation of habits is associated with white matter connectivity strength between the putamen and premotor cortex (11), and changes in putamen activity over time (16) (although directionality of the latter association has been inconsistent and may not relate to cue-evoked responses, but rather responses in general (42-44)). Although applying the usual caveat when interpreting null effects, the present data suggest that acquisition of automatic action tendencies may not be affected in OCD. Rather, habit biases in OCD appear to emerge as a result of failures in goal-directed control, associated with caudate (and possibly mOFC) hyper-activity. This conclusion dovetails with recent data showing that model-based instrumental learning, which is a constituent of goal-directed control, is impaired in OCD, and reliant on the structural integrity of the mOFC and caudate, but not the putamen (8).

The present study investigated avoidance, rather than appetitive, habits in order to determine how conditioned and explicit fear relates to habit formation in OCD. As this is the first study to have examined the neural correlates of avoidance habits, whether these results can be generalized to appetitive habit forming, which is similarly over-active in OCD (5), is an open question. The study of avoidance is critical in OCD, however, as prior studies have shown that aberrant fear conditioning processes are characteristic of OCD. For example, patients exhibit a pattern of hypo-activation in the ventromedial PFC (partially subsuming mOFC) and caudate during fear conditioning (45). The results of the present study converge with these finding in terms of localization, but diverge with respect to directionality, a difference presumably associated with passive fear learning vs. avoidance (46).

Whilst we observed no differences in SCR between OCD and controls, those patients who formed habits did not show differential SCRs to the stimuli (valued, devalued and safe) during the habit test (results presented in the Supplement). This could reflect overgeneralization of fear, which has been shown to relate to maladaptive instrumental avoidance (47). However, as these patients were able to discriminate during learning, this effect is likely a consequence rather than a cause of habitual responding. Taken together with the findings of Milad and colleagues (45), and studies suggesting that stress and anxiety contribute to habit biases in healthy people (48, 49), it is likely that a complex interaction between fear learning and habits may be critical to understanding the pathogenesis of OCD.

The findings in the caudate pertain primarily to patients who have formed habits versus those who have not, rather than representing a difference between patients and controls. As such, it is possible that with further training, for example, a similar pattern might be observed in control subjects who form habits. This is a question for future research. If this is the case, our results suggest that habit forming and associated caudate hyperactivity is hastened in OCD, rather than this process being qualitatively different.

The majority of our medicated patients were taking serotonergic medication (mainly SSRIs), which previous work has shown affects avoidance responding and inhibition in healthy humans (50). However, we found no evidence for differences between medicated and unmedicated patients (matched for symptom severity) in terms of behavior and almost all brain activation contrasts, indicating that medication effects did not drive our results.

Conclusions

These data implicate dysfunction in regions that support goal-directed control over action in excessive habit formation in OCD. These data also add convergent support to the habit hypothesis of OCD, such that it exhibits excellent neurobiological convergence with the known pathophysiology of OCD.

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