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Neuronal responses support a role for orbitofrontal cortex in cognitive set reconfiguration

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Abstract

We are often faced with the need to abandon no-longer beneficial rules and adopt new ones. This process, known as cognitive set reconfiguration, is a hallmark of executive control. Although cognitive functions like reconfiguration are most often associated with dorsal prefrontal structures, recent evidence suggests that the orbitofrontal cortex (OFC) may play an important role as well. We recorded the activity of OFC neurons while rhesus macaques performed an analogue of the Wisconsin Card Sorting Task that involved a trial and error stage. The OFC neurons demonstrated two types of switch-related activity, an early (switch-away) signal and a late (switch-to) signal, when the new task set was established. We also found a pattern of *match modulation*: a significant change in activity for the stimulus that matched the current perceptual rule (and would therefore be selected). These results extend our understanding of the executive functions of the OFC. They also allow us to directly compare the OFC with the complementary datasets we previously collected in the ventral (VS) and dorsal (DS) striatum. Although both effects are observed in all three areas, the timing of responses aligns the OFC more closely with DS than with VS.

Introduction

The orbitofrontal cortex (OFC) is a critical site for decision-making and adaptive behaviour. Its contributions to the evaluation and comparison of rewards are well-established (Padoa-Schioppa & Assad, 2006; Wallis, 2007). Perhaps less well-known are its executive roles. The OFC is critical for linking stimuli to values, in monitoring consequences of actions, in detecting and resolving conflict, in metacognition, and encoding rules and storing sensory information in working memory (Schoenbaum *et al.*, 1999; Wallis *et al.*, 2001; Wallis & Miller, 2003; Kepecs *et al.*, 2008; Lara *et al.*, 2009; Tsujimoto *et al.*, 2009; Abe & Lee, 2011; Rushworth *et al.*, 2011; Mansouri *et al.*, 2014; Sleezer *et al.*, 2016; Strait *et al.*, 2016). Indeed, the list of executive functions of the OFC is almost as long as those associated with classical executive structures like dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC).

One executive function for which the role of OFC is not as well-understood is cognitive set reconfiguration. This term refers to the adjustment of cognitive strategies or mental representations in response to changing goals or environmental circumstances (Robbins, 2007). It is often called switching for short and is most closely associated with executive regions in the dorsal prefrontal cortex and parietal cortex (Alan *et al.*, 1994; Dias *et al.*, 1996a; Mansouri *et al.*, 2006; Kamigaki *et al.*, 2012). Specific evidence for this linkage comes, in part, from physiological studies showing systematic modulations of firing rate during switch trials relative to other trials.

Although a number of studies suggest that the OFC contributes to simpler types of flexible decision-making (Dias *et al.*, 1996a,b, 1997; McAlonan & Brown, 2003), there are several reasons to believe that the OFC may participate directly in switching, especially between rules. First, as noted above, recent evidence supports a role for the OFC in many executive functions. Second, we and others have delineated a role for the OFC in the maintenance of rules or in updating based on rules (Wallis *et al.*, 2001; Buckley *et al.*, 2009; Yamada *et al.*, 2010; Tsujimoto *et al.*, 2011; Sleezer *et al.*, 2016). Third, recent work indicates that the OFC lesions disrupt the ability to switch between behavioural rules in rodents (Birrell & Brown, 2000). Finally, we previously showed switching-related activity in two basal ganglia structures – the dorsal (DS) and ventral (VS) striatum. Specifically, we found that switch signals in VS were strongest when switching away from previously relevant rules, while switch signals in DS were strongest when switching toward newly relevant rules. Because the OFC has direct anatomical projections to both VS and DS, we hypothesized that it may have a direct role in switching as well.

In our earlier study on striatal contributions to switching, we also found that the appearance of switch signals in VS and DS was consistent with the appearance of associative learning signals (i.e. the systematic enhancement or suppression in firing rate for

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task-relevant targets when they appear in a sequence of stimuli) in both regions. We therefore wondered whether the OFC neurons would demonstrate similar patterns of activity. Such signals likely relate to executive function, as they correspond to a linkage between mental representations of rules and presentation of specific offers.

To examine the role of OFC in switching, we recorded the activity of single neurons as macaques performed an analogue of the Wisconsin Card Sorting Task developed by Moore *et al.* (2005), and known as the Conceptual Set-Shifting Task (CCST). In some set-shifting tasks, rules are abstract (e.g. *match shape*, Mansouri *et al.*, 2006; Buckley *et al.*, 2009; Kamigaki *et al.*, 2012) but in this task, rules are more concrete (e.g. *match triangle*). An important feature our task is that rules were never cued, so subjects had to go through a trial and error phase to determine the currently relevant rule (this normally took 3–4 trials). They could then take advantage of the newly learned rule and maintain responding until the rule changed again (blocks were 15 trials long). We found systematic changes in firing associated with both early (switch-away) and late (switch-to) switch trials – i.e. explicit switch signals – in the OFC neurons. We also found that switch signals in the OFC were consistent with the appearance of associative signals in this region; associative signals arose slowly and only became strong once the rule was established. Together, these results are consistent with the idea that switch signals are linked to associative learning, and may even serve to initiate learning processes during flexible rule updating. More generally, these findings endorse a broader executive role for the OFC and are consistent with a recent theory proposing that the OFC instantiates a cognitive map of task space (Wilson *et al.*, 2014; Schuck *et al.*, 2016).

Materials and methods

Surgical procedures

All animal procedures were approved by the University Committee on Animal Resources at the University of Rochester and were designed and conducted in compliance with the Public Health Service's Guide for the Care and Use of Animals. Two male rhesus macaques (*Macaca mulatta*) served as subjects. We used standard techniques as described previously (Strait *et al.*, 2014). Animals were habituated to laboratory conditions and then trained to perform oculomotor tasks for liquid reward. A Cilux recording chamber (Crist Instruments) was placed over the OFC and attached to the calvarium with ceramic screws. Appropriate anaesthesia was used at all times; induction was performed with ketamine and isoflurane was used for maintenance. For surgical induction, we used 10–15 mg/kg of ketamine, 0.25 mg/kg of midazolam, and 2–4 mg/kg of propofol. For maintenance, we used isoflurane, ad lib level, set depending on active monitoring procedure. For systemic antibiotics, we used cefazolin and for topical application, we used standard veterinary triple antibiotic. For analgesics, we used meloxicam, and, when judged necessary by veterinary staff, buprenorphine.

Post-operative care included close monitoring and restoration of fluid intake. Animals received appropriate analgesics and antibiotics after all procedures. Position was verified by magnetic resonance imaging with the aid of a Brainsight system (Rogue Research Inc.). Recording locations are shown in Fig. 1C. Throughout both behavioural and physiological recording sessions, the chamber was kept sterile with regular antibiotic washes and sealed with sterile caps.

Recording sites

We approached the OFC through a standard recording grid (Crist Instruments). We used the standard atlas for all area definitions (Paxinos *et al.*, 2000). We defined the OFC as the coronal planes situated between 29 and 36 mm rostral to the interaural plane, the horizontal planes situated between 0 and 9 mm from the ventral surface, and lateral to the medial orbital sulcus. We recorded from Area 13 m (Öngür & Price, 2000). We confirmed recording locations before each recording session using our Brainsight system with structural magnetic resonance images taken before the experiment. Neuroimaging was performed at the Rochester Center for Brain Imaging, on a Siemens 3T MAGNETOM Trio Tim using 0.5 mm voxels. We confirmed recording locations by listening for characteristic sounds of white and gray matter during recording, which in all cases matched the loci indicated by the Brainsight system. The Brainsight system typically offers an error of < 1 mm in the horizontal plane and < 2 mm in the z-direction.

Electrophysiological techniques

Single electrodes (Frederick Haer & Co., impedance range 0.8 to 4M Ω) were lowered using a microdrive (NAN Instruments) until waveforms between 1 and 3 neuron(s) were isolated. Individual action potentials were isolated on a Plexon system (Plexon Inc., Dallas, TX, USA). Neurons were selected for study solely on the basis of the quality of isolation; we never pre-selected based on task-related response properties.

Eye-tracking and reward delivery

Eye position was sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research). Stimuli were controlled by a computer running Matlab (Mathworks) with Psychtoolbox and Eyelink Toolbox. Visual stimuli were presented on a computer monitor placed 57 cm from the animal and centred on its eyes. A standard solenoid valve controlled the duration of juice delivery. The relationship between solenoid open time and juice volume was established and confirmed before, during, and after recording.

Behavioural task

The task described here is the same as that used in two previous papers (Sleezer & Hayden, 2016; Sleezer *et al.*, 2016). Subjects performed an analogue of the Wisconsin Card Sorting Task (WCST, Moore *et al.*, 2005). Our version of the task uses two dimensions (colour and shape) and six specific rules (three shapes: circle, star, and triangle, and three colours: cyan, magenta, and yellow, Fig. 1A). On each trial, three stimuli were presented asynchronously at the top, bottom left, and bottom right of the screen (1 s asynchrony). The colour, shape, position, and order of stimuli were fully randomized on each trial. Each stimulus was presented for 400 ms and was followed by a 600 ms blank period. Subjects were free to fixate upon the stimuli when they appeared. Then all three stimuli reappeared simultaneously with a central fixation spot. The subject fixated on the central spot for 100 ms and then indicated its choice by shifting gaze to its preferred stimulus and maintaining fixation on it for 250 ms. Failure to maintain gaze for 250 ms did not lead to the end of the trial, but instead returned the subject to a choice state; thus, subjects were free to change their mind if they did so within 250 ms (although in our observations, they almost never did so). Following a successful 250 ms fixation, visual feedback was

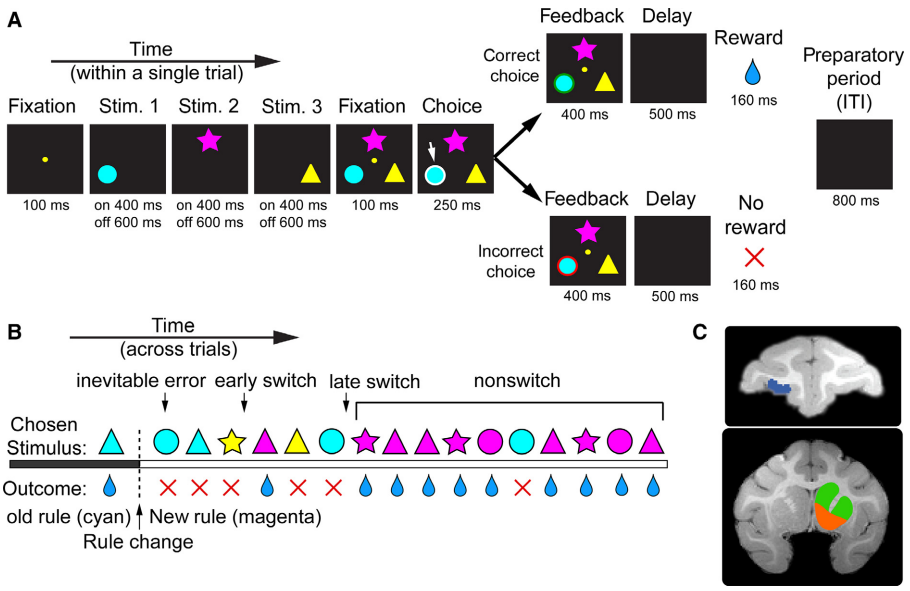

FIG. 1. Task and recording locations. (A) The inevitable error trial is the first trial after a rule change. The early switch is the post-feedback period following an incorrect choice and immediately before the start of the first correct trial. The late switch is the post-feedback period immediately before the first correct trial in a series of at least four consecutive correct trials. Non-switch trials include all trials after the late switch has occurred and before the start of the next block. (B) Example of one block illustrating the task. (C) Magnetic resonance image of subject C. Recordings were made in the orbitofrontal cortex (highlighted in blue). Comparison sites were in the ventral striatum (highlighted in orange), and dorsal striatum (highlighted in green). [Colour figure can be viewed at wileyonlinelibrary.com].

provided (a green/red outline around the chosen stimulus for correct/incorrect choices, respectively). After visual feedback, there was a 500 ms blank delay period; correct choices were followed by a liquid (water) reward. All trials were separated by an 800 ms inter-trial interval (ITI), which we refer to as the preparatory period. In each block, subjects responded according to one of the six rules. Subjects were required to use a trial and error learning process to determine the correct rule. Rule changes occurred after 15 correct trials and were not explicitly cued.

Analysis of behavioural performance across different types of rule changes

To determine whether subjects' performance differed depending on the type of rule change that occurred at the beginning of the block, we calculated the average number of trials monkeys completed prior to rule acquisition (i.e. the first trial in a series of four consecutive correct trials, Sleezer & Hayden, 2016) following intra-dimensional and extra-dimensional rule changes. Intra-dimensional rule changes refer to instances when the rule change occurs within one rule category (i.e. colour to colour or shape to shape), while extra-dimensional rule changes refer to instances when the rule change occurs across rule categories (i.e. colour to shape or shape to colour). To compare the number of trials monkeys completed before rule acquisition across intra-dimensional and extra-dimensional switches, we used a two-way repeated measures ANOVA with the between subjects factor subject (Monkey B, Monkey C) and the within subjects factor block type (intra-dimensional, extra-dimensional). We used *post-hoc* Fisher's LSD tests to compare specific differences across groups.

Analysis of switch-related neural activity

On the first trial of each block, subjects almost always chose according to the previously relevant rule. Because the block transition was not explicitly cued, we called this the 'inevitable error trial'. On blocks where the new rule happened to match the previous one by chance (1/6 of blocks), the first trial did not produce an error, and monkeys did not change strategy, so, for the purposes of analysis, we treated these blocks as 30 trial blocks. Moreover, because there were three stimuli on each trial, with two dimensions each, occasionally (1/3 of blocks), the correct stimulus on the first trial was consistent with the previously relevant rule. We therefore specified in our definition of the inevitable error trial that it referred to the first trial on which choosing according to the previous rule would produce an error.

We examined switch-related neural activity during the 1460 ms post-feedback period following feedback (that is, the combined duration of the 500 ms delay, 160 ms reward, and 800 ms preparatory periods) and before the start of switch and non-switch trials. The period of analysis included all time between the end of the feedback period and the start of the next trial. We analysed this period because monkeys likely reconfigured their cognitive rule set on switch trials during this period. Non-switch trials were defined as all trials other than switch trials. The two types of switch trials are defined below. This analysis period is long, but was chosen (before data analysis, and thus blind to possible results) because we reasoned that switching may occur slowly and may thus require a long analysis window to detect. Indeed, preliminary behavioural testing showed that animals performed best with inter-trial delays of this duration, suggesting that their performance required these long delays.

We identified two points in the block when monkeys likely reconfigured (i.e. switched) their cognitive rule set. The *early switch* was the post-feedback period following the first correct trial after the rule had changed. We chose this trial because subjects had switched away from the previously used rule (i.e. disengaged) but had not yet begun consistently responding according to the new rule. We excluded early switch points that were also identified as late switch points. The *late switch point* was the first correct in a series of at least four consecutive correct trials. We assumed that by this trial,

subjects had re-engaged with the new rule. (Note that we use the terms early and late switch to be as neutral as possible about the cognitive meaning of these events). We limited late switches by definition to one per block. This limit is important in cases where monkeys successfully switched to a new rule, then briefly erred, then returned to the new rule. We did not want to count these returns as late switches.

Task-related activity during the post-feedback period was determined using ANOVA with the factors trial type (switch or non-switch), block type (intra-dimensional or extra-dimensional), trial outcome (reward or no-reward), and next trial outcome (reward or no-reward). In these analyses, trial outcome refers to the outcome during the reward period during the post-feedback period, while next trial outcome refers to the outcome during the reward period on the following trial. Although we were interested in the effects of trial type, block type, and their interaction, we included trial outcome and next trial outcome in the ANOVA model to control for the potential influence of reward or error related activity. Adding outcome as a factor in the ANOVA controls for the presence of outcome, which occurred during the period of focus for these analyses.

Because current trial outcome and next trial outcome were not fully crossed with trial type in this model (that is, switch trials always consisted of a non-rewarded trial followed by a rewarded trial), we used a nested ANOVA in which current and next trial outcome were nested in trial type. A nested ANOVA measures the effects of a factor while partialling out the effects of a nesting factor. Thus, by utilizing a nested ANOVA in which current and next trial outcome were nested in trial type, this model includes an estimate of the effects of current and next trial outcome, which thus serves as control for reward outcome related effects. We conducted these analyses separately for early and late switch points. Based on the ANOVA results, we classified task-related activity into two types. The first type showed a significant main effect ($P < 0.05$) of trial type, the second showed a significant interaction ($P < 0.05$) between trial type and block type. *Post-hoc* comparisons (Fisher's LSD test) were conducted if the interaction was significant ($P < 0.05$). We refer to neurons with a main effect of trial type as *general switch signalling neurons* and neurons with an interaction between trial type and block type as *context-specific switch signalling neurons*.

To determine if the proportion of cells demonstrating a significant switch-related effect (a main effect of trial type or a significant interaction between trial type and block type) was significantly above chance, we conducted binomial tests, and adjusted the *P*-value using a Bonferroni correction for two comparisons. We corrected for two comparisons because we analysed activity at both early and late switch points. We chose to maintain an alpha of 0.05 and multiply the resultant *P*-values by two as a way of implementing the Bonferroni correction. Thus, the *P*-values reported for binomial tests in this paper have been adjusted for two comparisons, where appropriate. To determine if proportions of cells demonstrating an effect were significantly different across the OFC, VS and DS, we implemented a mixed model binary logistic regression procedure using the between subjects factor brain region (OFC, VS, DS) and the within subjects factors trial period (early, late) and modulation type (general switch, context-dependent switch). The model was fit using a generalized estimating equation (GEE) procedure, implemented in SPSS. In this analysis, 'within subjects' and 'between subjects' refer to neurons. In this procedure, an omnibus Wald Chi-Square test was applied to determine the significance of group effects, followed by pairwise comparisons using Fisher's LSD tests to examine specific group effects.

To examine the percent of variance explained by each switch-related effect across the populations of OFC, VS, and DS neurons, we calculated the average partial η^2. Partial η^2 is a measure of effect size in ANOVA, which measures the proportion of variance attributable to a factor after partialling out other factors from the non-error variance. Partial η^2 is calculated as:

$$\text{Partial } \eta^2 = \frac{SS_{factor}}{(SS_{factor} + SS_{error})}$$

where SS_{factor} is the variation attributable to the factor (sum of squares for the factor), and SS_{error} is the error variation (sum of squares error). To compare the average partial η^2 for switch-related effects at early and late switch points and in the OFC, VS, and DS, we used a two-way repeated measures ANOVA with the factors brain region (OFC, VS, and DS) and switch period (early and late), followed by *post-hoc* Fisher's LSD tests.

Analysis of associative learning-related activity

To examine the associative learning-related neural activity, we calculated the average firing rate during each of the three stimulus presentation epochs on all correct trials. We defined the stimulus presentation epoch as the 1000 ms period consisting of 400 ms when the stimulus was on the screen and the following 600 ms when the stimulus was off the screen. We then used two-way *t*-tests to compare the average firing rate during epochs in which the correct stimulus was presented to the average firing rate during epochs in which the correct stimulus was not presented.

To examine the magnitude of correct-stimulus selectivity, we calculated Hedge's g, a measure of effect size similar to Cohen's d. Hedge's g is recommended when groups have different sizes, and was also developed to remove a positive bias affecting Cohen's d (Hedges, 1981). As the sample sizes for the presentation of incorrect stimuli were always larger than the sample sizes for the presentation of correct stimuli (as each trial consisted of one correct stimulus and two incorrect stimuli), we chose to calculate effect size using Hedge's g, rather than Cohen's d. Hedge's g is calculated as:

$$\text{Hedges g} = \frac{M1 - M2}{SD_{pooled}}$$

where M1 and M2 are the means of each group, and SD_{pooled} is the pooled standard deviation, calculated as:

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

where n_1 and n_2 are the sample sizes for each group, and SD_1 and SD_2 are the standard deviations for each group.

To compare selectivity across brain regions, we first determined the average time of maximum selectivity within trials in each region (averaged across all correct trials) and analysed a 200 ms period surrounding that time (100 ms before and 100 ms after). We then used these analysis epochs to compare selectivity in the OFC, VS, and DS before and after late switch points. We compared selectivity across switch periods and brain regions using a 2-way repeated measures ANOVA with the factors switch period (pre-late switch and post-late switch) and brain region (OFC, VS, and DS), following by *post-hoc* Fisher's LSD tests.

Statistical analyses were carried out using MATLAB release 2012b (MathWorks Inc), SPSS Statistics version 24 (IBM Analytics),

and GraphPad Prism version 6 (GraphPad Software). In all cases, we verified that reported effects were similar for the two subjects.

Results

Behavioural performance

After a 2–3 month period of training, both subjects were able to reliably learn new rules and maintain a high level of accuracy once new rules were acquired (Fig. 2A). Once training was complete, we collected data during 78 individual OFC recording sessions (n = 35 sessions for subject B and n = 43 sessions for subject C). Subjects completed an average of 565.09 ± 12.57 (mean ± SEM) trials per session and an average of 30.92 ± 0.83 blocks per session.

On each block (besides the first block of each session), subjects completed either an intra-dimensional (ID) or extra-dimensional (ED) switch to the new rule. To determine whether subjects' performance differed following intra-dimensional and extra-dimensional rule changes, we examined the number of trials monkeys completed before rule acquisition following intra-dimensional and extra-dimensional rule changes using a two-way repeated measures ANOVA with the between subjects factor subject (Monkey B, Monkey C) and the within subjects factor block type (intra-dimensional, extra-dimensional). This analysis revealed a significant main effect of subject ($F_{1,\text{error in d.f. = 267}}$ = 75.70; P < 0.0001) and of block type ($F_{1,267}$ = 136.2; P < 0.0001), but no interaction between the two ($F_{1,267}$ = 0.7783; P = 0.3785). The results of our *post-hoc* comparisons are shown in Fig. 2B. We found that both subjects completed more trials prior to rule acquisition following extra-dimensional rule changes compared with intra-dimensional rule changes (Fig. 2B, P < 0.0001 for both subjects, Fisher's LSD Tests). (Note that in this case, there were only two subjects, thus limiting the interpretability of any observed main effect of subject). Figure 2B illustrates the summary statistics for two subjects in two conditions. The four relevant distributions were all well fit by a Gaussian distribution (Shapiro–Wilk test, P < 0.001 in all four cases). Not surprisingly, they were not found to be multimodal, as determined by a Hartigan's dip test (P > 0.05 in all four cases).

On average, subjects completed 14.94 ± 5.79 early switches and 27.62 ± 9.53 late switches per session. Before early switch trials, monkeys completed 3.12 ± 0.66 trials (3.34 ± 0.77 for monkey B and 2.97 ± 0.52 for monkey C), and before late switch trials, monkeys completed an average of 6.69 ± 2.31 (8.04 ± 2.74 for monkey B and 5.74 ± 1.29 for monkey C). These numbers include the inevitable error trial.

Neurons in the orbitofrontal cortex demonstrate switch-related activity

We collected responses of 115 neurons in the OFC (49 from Subject B and 66 from Subject C). We first characterized neural responses associated with switch trials. To do this, we compared firing rates on non-switch trials (all trials besides early- and late switch trials) with those obtained on early switch trials (that is, the first correct trial after a switch). Then, in a separate analysis, we compared non-switch trials with late switch trials (the first correct trial in a series of at least four consecutive correct trials). We analysed firing rate activity during the post-feedback period separately for each cell using ANOVA (see Methods).

Figure 3A shows an example of an OFC neuron demonstrating general switch-related activity at both early and late switch points. The average firing rate response for this neuron was significantly greater on early switch trials than early non-switch trials for both ID switches (red line and black dotted line, P < 0.0001, Fisher's LSD test) and ED switches (pink line and gray dotted line, P = 0.0015, Fisher's LSD test), and also significantly greater on late switch trials than non-switch trials for ID switches (dark blue line and black dotted line, P < 0.0001, Fisher's LSD test) and ED switches (light blue line and gray dotted line, P < 0.0001, Fisher's LSD test). This neuron showed no response difference for ID vs. ED switches, whether looking at early switch points (red line and pink line, P = 0.9263, Fisher's LSD test), or late switch points (dark blue line and light blue line, P = 0.6720, Fisher's LSD test).

To determine whether the proportion of the OFC cells demonstrating general switch modulation was above chance, we calculated the average proportion of cells demonstrating a significant effect across the 1460 ms post-feedback epoch and performed binomial tests. The period of interest included the combined duration of the 500 ms delay, 160 ms reward, and 800 ms preparatory periods, or the whole time between the end of the feedback period and the start of the next trial. We corrected for two comparisons (because we

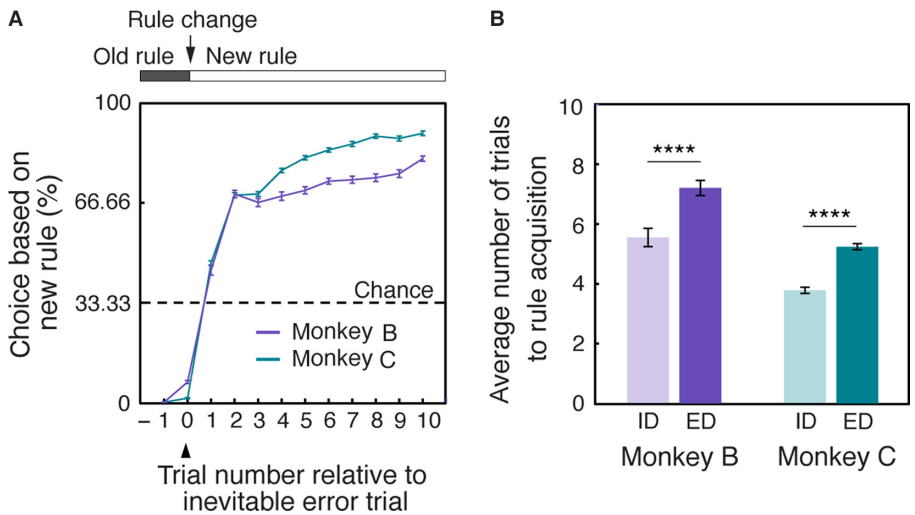

FIG. 2. Behavioural performanc. (A) Average choice accuracy on trials surrounding rule changes. (B) Average number of trials to rule acquisition following intra-dimensional (ID) and extra-dimensional (ED) rule changes. [Colour figure can be viewed at wileyonlinelibrary.com].

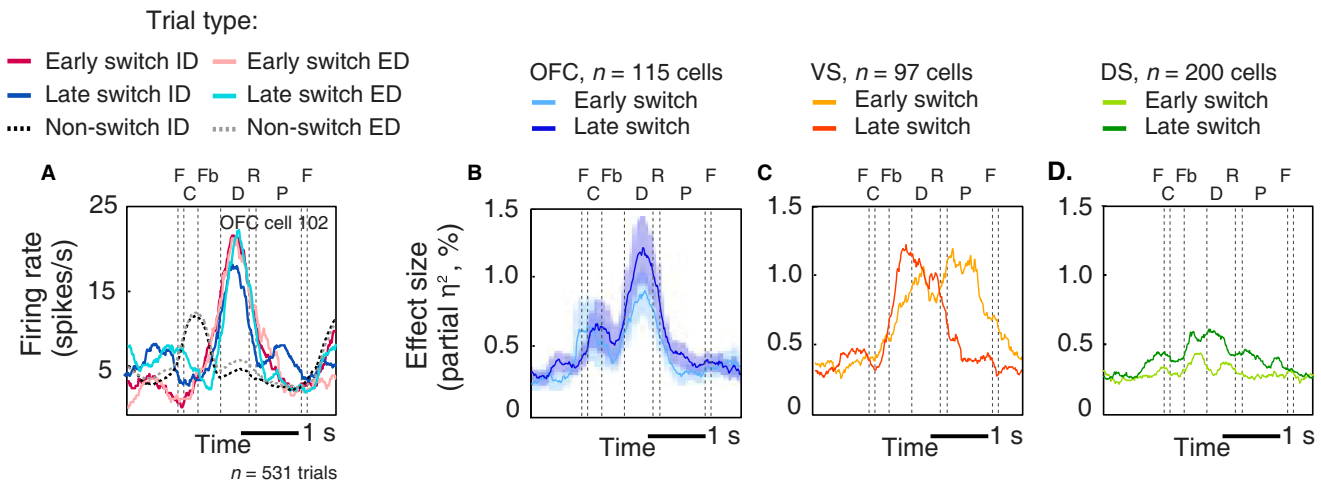

FIG. 3. General switch modulation. (A) Average response of a single OFC neuron demonstrating general switch-related activity [i.e. a main effect of trial type (switch or non-switch)] at early and late switch points. Red and pink lines indicate intra-dimensional (ID) and extra-dimensional (ED) switch trials at early switch points. Blue and light blue lines indicate ID and ED switch trials at late switch points. Black and gray dotted lines indicate ID and ED non-switch trials. C, choice; Fb, feedback; D, delay; R, reward; P, preparatory period (ITI); F, fixation. (B–D) Proportion of variance explained (partial η^2) across the populations of OFC (B), VS (C), and DS (D) neurons. Effect size measures reflect averages across all neurons (excluding six from VS and four from DS that were excluded because of an insufficient number of trials). [Colour figure can be viewed at wileyonlinelibrary.com].

looked at early and late switch points) using a Bonferroni correction. These results are shown in Fig. 4A. We found that the proportion of cells demonstrating general switch modulation was significantly above chance at early switch points (n = 20/115 cells) and at late switch points (n = 30/115 cells, $P < 0.0001$ in both cases).

In a previously published report, we examined the same effects in two striatal regions, ventral (VS) and dorsal (DS) striatum (Sleezer & Hayden, 2016). Data for VS and DS are shown as well, for comparison (Fig. 4A). We found that the number of cells demonstrating switch modulation in these areas was significant at early switch points (VS: n = 29/97 cells; DS: n = 24/200 cells, Bonferroni adjusted $P < 0.0001$ for all three regions, corrected for two comparisons, binomial test) and at late switch points (VS: n = 24/97 cells; DS: n = 41/200 cells, Bonferroni adjusted $P < 0.0001$ for all three regions, corrected for two comparisons).

We conducted additional analyses to determine whether our results were biased based on our choice of a nested model. Specifically, we re-examined the proportion of cells demonstrating a significant effect of trial type and/or a significant interaction between block type and trial type using a reduced ANOVA model with the following terms: trial type; block type; trial outcome; next trial outcome; trial type by block type; block type by trial outcome; block type by next trial outcome; and block type by trial outcome by next trial outcome. This model yielded nearly identical results compared with our original model. Specifically, in our original nested ANOVA model, we found the following proportions of cells modulated in the OFC: 17.39% (early switch, main effect of trial type), 26.08% (late switch, main effect of trial type). For VS, those numbers were: 29.90% (early switch, main effect of trial type), 24.74% (late switch, main effect of trial type), Using the new reduced ANOVA model, we found similar proportions: 18.10%, 25.51%, 26.80%, and 25.78% respectively. For DS, those numbers were 12.00% (early switch, main effect of trial type), 20.50% (late switch, main effect of trial type), and using the reduced ANOVA: 12.50% (early switch, main effect of trial type), 23.00% (late switch, main effect of trial type).

We wondered whether the cells involved in coding early switches were the same ones involved in coding late switches. To do this, we computed an index of selectivity (the F-statistic) for the z-scored

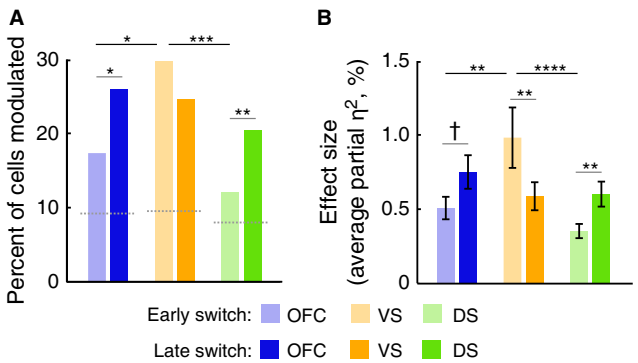

FIG. 4. General switch modulation at early and late switch points. (A) Proportion of cells demonstrating a significant main effect of trial type at early and late switch points. (B) Proportion of variance explained (partial η2) by the main effect of trial type at early and late switch points.The OFC (light blue and dark blue bars), VS (light orange and dark orange bars), and DS (light green and dark green bars). Bar graph shows the mean partial η2 (±SEM) during the post-feedback period. Gray lines and asterisks indicate significant effects across time (i.e. early and late switch points). Black lines and asterisks indicate significant effects across brain regions. †P = 0.0502, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. [Colour figure can be viewed at wileyonlinelibrary.com].

firing rates. (Z-scoring ensured that mean and variance were preserved across cells, thus controlling for the main effects of firing rate.) We found a positive correlation between these variables for all three brain regions (OFC: r = 0.21; VS: r = 0.28; DS: r = 0.27, $P < 0.0001$ in all cases). These positive correlations indicate that tuning strength for the two variables was positively correlated, and imply that coding for the two variables was drawn from a single set of relevant cells, rather than from separate classes of cells. We also wondered whether the set of cells encoding trial history (previous correct-incorrect) were the same as the ones that encoded switches. We observed a strong overlap between the population of cells that encoded trial history and the cells that showed shift-related activity. Specifically, a correlation between the regression coefficients of the two variables reveals a positive value (r = 0.24, P = 0.005). This positive correlation indicates that neurons in one set were

more likely than not to be in the other, and argues against the idea that there are two separate populations of cells for the two variables.

To compare the proportions of cells demonstrating each type of modulation across brain regions and across early and late switch points, we implemented a mixed model binary logistic regression procedure using the between subjects factor brain region (OFC, VS, DS) and the within subjects factors trial period (early, late) and modulation type (general switch, context-dependent switch). In this analysis, the terms 'within subjects' and 'between subjects' refer to neurons, which were the unit of analysis in this study. In this procedure, an omnibus Wald Chi-Square test was applied to determine the significance of group effects, followed by Fisher's LSD tests to examine specific group differences. This analysis revealed a significant main effect of brain region ($\chi^2 = 6.4922$, $P = 0.0389$), a significant main effect of modulation type ($\chi^2 = 68.3523$, $P < 0.0001$), and a significant interaction between brain region and trial period ($\chi^2 = 8.1057$, $P = 0.0174$).

Pairwise comparisons are shown in Fig. 4A. These analyses revealed a significantly greater proportion of cells demonstrating general switch modulation at late switch points compared with early switch points in both OFC and DS (OFC: $P = 0.0461$, DS: $P = 0.0090$, Fisher's LSD tests). In contrast, we found no difference in the proportion of cells demonstrating general switch modulation at early and late switch points in VS ($P = 0.3672$). However, we found that the proportion of cells demonstrating general switch modulation at early switch points was significantly greater in VS compared with both OFC and DS at the same time point (VS vs. OFC: $P = 0.0322$; VS vs. DS: $P = 0.0006$).

Figure 3B shows the average proportion of variance explained (partial η^2) by the main effect of trial type in the OFC across time within trials. Figures 3C, and D show the corresponding data in VS, and DS for comparison. To compare the average partial η^2 across OFC, VS, and DS, we calculated the average partial η^2 across the 1460 s post-feedback epoch and used a mixed-model ANOVA with the between subjects factors brain region (OFC, VS, and DS), and the within subjects factors trial period (early, late), and modulation type (general switch, context-dependent switch). As above, in this analysis, 'within subjects' and 'between subjects' refer to neurons. This analysis revealed a main effect of brain region ($F_{2,409} = 4.6948$, $P = 0.0096$), a main effect of modulation type ($F_{1,409} = 62.4911$, $P < 0.0001$), and an interaction between brain region and trial period ($F_{2,409} = 9.9800$, $P = < 0.0001$). *Post-hoc* comparisons are shown in Fig. 4B.

We found a greater modulation in the OFC at late switch points compared with early switch points, although this effect was not significant ($P = 0.0502$, Fisher's LSD test). At early switch points, we found a greater magnitude of general switch modulation in VS compared with both OFC and DS ($P = 0.0029$ and $P < 0.0001$), but no difference between OFC and DS at the same time point ($P = 0.2482$). At late switch points, we found no difference between any of the three regions (OFC vs. VS: $P = 0.3027$; OFC vs. DS: $P = 0.2694$; VS vs. DS: $P = 0.9174$).

These results indicate that VS neurons demonstrate greater switch-related modulation during early periods of trial-and-error learning compared with the later periods of rule acquisition and compared with the OFC and DS neurons at the same time point. In addition, OFC, VS, and DS appear to demonstrate equal levels of switch-related modulation at later points of rule acquisition, while OFC and DS neurons demonstrate greater switch-related modulation during later periods of rule acquisition compared with the early periods of trial-and-error learning.

We then performed an analysis to see whether putative switching effects were a by-product of changes in expected value associated with learning. We estimate the expected likelihood of correct performance of each trial-in-block based on performance so far in block. So, for example, if the first two choices in the block happen to be correct, the likelihood that the third one will be correct is higher than if the first was correct and the second was incorrect. We then estimate the value of the upcoming choice from that probability. To do this, we used the entire dataset to explicitly compute the probability of correct performance conditionally given current within-block performance. Thus, for example, we found that the average likelihood of correct performance on the second trial after the inevitable error trial (68.1%) was greater if the first post-inevitable error trial was correct (74.5%) than if it was incorrect (62.2%, $P < 0.0001$). We computed these probabilities, and others like them, from the large dataset of behaviour we collected. On each trial, then, we multiplied the expected probability by the standard reward size to compute an expected value for each trial. This approach automatically controls for expectational effects associated with erroneously perceived runs of correct and/or incorrect trials (Blanchard *et al.*, 2014).

Next, we estimate the tuning parameter for expected value of choice using a binomial regression procedure. We then correlate these tuning parameters with the tuning parameters for switch (separately for early and late switch) across the population. If these values are correlated, it would suggest that they are, to some extent, measuring the same thing. Instead, we find that they are uncorrelated, both for early and for late switches (early: $r = -0.003$, $P = 0.85$; late: $r = 0.024$, $P = 0.66$). In other words, the decrease in reward expectation associated with switch trials did drive responses in the OFC neurons, but those changes were orthogonal and, therefore could not explain, the effects of switching. So for example, if a neuron showed activation (enhanced firing rates) during the inter-trial interval for switch trials, then it was just as likely to show suppression as activation for rewards. The orthogonality of these two effects means that reward/learning effects were not sufficient to explain the switching effects we observe.

It is possible that our lack of measured effect reflects the fact that we did not have enough data to detect one; we assessed this possibility with a cross-validation procedure: in separate analyses we correlated early switch activity with itself using even and odd trials separated. We found positive effects in both cases, and the measured correlation effects were outside the 95% confidence intervals in both cases (early: $r = 0.29$, CI: 0.16–42; late: $r = 0.31$, CI = 0.22–0.40). These results suggest that we had sufficient statistical power to detect a correlation.

Latencies of switching signals

We next examined the latency of general switch signal appearance in the OFC, VS, and DS at early and late switch points. None of these analyses were reported in our earlier study (Sleezer *et al.*, 2016). To estimate latency, we calculated the average partial η^2 for the main effect of trial type (switch or non-switch) across time within trials using a 50 ms sliding window slid in 10 ms steps across the 1460 ms post-feedback period. To determine whether these latencies were significantly different across populations of neurons, we calculated the time of maximum selectivity across neurons and performed a one-way ANOVA using the factor brain region (OFC, VS, DS), separately at early and late switch points. This analysis revealed no significant differences in group latencies across brain regions at early ($P = 0.1027$) or late switch points ($P = 0.5793$).

Context-specific switch signals arise during the early trial-and-error period in VS, but not OFC or DS

We next investigated context-specific switching activity (i.e. encoding of switches specific to either extra- or intra-dimensional switches, but not both). These results are similar to those reported in our previous paper (Sleezer & Hayden, 2016), however, the analysis technique used here is more sensitive and the OFC data were not reported in the previous paper. We found that the proportion of cells demonstrating context-dependent switch modulation at early switch points was significantly above chance in VS (n = 11/97 cells, Bonferroni adjusted P = 0.0067, corrected for two comparisons, binomial test), but not OFC or DS (OFC: n = 3/115 cells, Bonferroni adjusted P = 1.6642; DS: n = 9/200 cells, Bonferroni adjusted P = 1.0906, corrected for two comparisons). At late switch points, the proportion of cells demonstrating a significant effect was not significant in the OFC, VS, or DS (OFC: n = 6/115 cells, Bonferroni adjusted P = 0.7051; VS: n = 5/97 cells, Bonferroni adjusted P = 0.7410; DS: n = 15/200 cells, Bonferroni adjusted P = 0.0887, corrected for two comparisons). In comparing proportions across brain regions at early switch points, we found a significantly greater proportion of cells demonstrating context-dependent switch modulation in VS compared with the OFC (P = 0.0138) and a greater proportion of cells in VS compared with DS, which was marginally significant (P = 0.0542). We found no difference between OFC and DS at early switch points (P = 0.2033), or between any of the three regions at late switch points (OFC vs. VS: P = 0.9836; OFC vs. DS: P = 0.4128; VS vs. DS: P = 0.4241).

In comparing the strength of context-dependent switch modulation across early and late switch points, we found significantly greater modulation in VS at early switch points compared with the late switch points (P = 0.0004, Fisher's LSD test), but no difference between the two time points in the OFC or DS (P = 0.7328, P = 0.3469). In comparing the strength of modulation across brain regions at early switch points, we found significantly greater modulation in VS compared with both OFC and DS (P < 0.0001 for both comparisons). We found no difference between the OFC and DS at early switch points (P = 0.8194), nor did we find any differences between the three regions at late switch points (OFC: P = 0.9855, VS: P = 0.5200, DS: P = 0.5564).

Taken together with our findings regarding general switch-related activity, the above results suggest that VS neurons demonstrate greater switch modulation during the early trial-and-error period of the block compared with the later point of rule acquisition, and that a portion of these cells carry information about the rule context (i.e. whether the switch is intra-dimensional or extra-dimensional). In contrast, the OFC and DS neurons demonstrate greater switch modulation during the later period of the block, and these signals carry no information regarding the switch context.

Neurons in the OFC demonstrate associative activity

We next wanted to know how the OFC responses reflect learning of associations between stimuli and outcomes (i.e. reward or no-reward), and how these responses relate to switch modulation. To do this, we examined the neural response to the three probe stimuli at the beginning of each trial (Fig. 1A).

Figure 5A shows the responses of an example OFC neuron with these effects. This neuron responded weakly to options as they appeared in sequence, but responded strongly when the correct option appeared. To assess this response statistically, we calculated the average firing rate during each of the three stimulus presentation epochs on all correct trials. We then used two-way t-tests to compare the average firing rate during epochs in which the correct stimulus was presented to the average firing rate during epochs in which the correct stimulus was not presented, separately for each of the three presentation epochs. This cell demonstrated a significantly greater firing rate when the correct stimulus was presented compared with when the correct stimulus was not presented during all three presentation epochs (first epoch: P < 0.0001, second epoch: P = 0.0048, third epoch: P < 0.0001, two-way t-tests).

A significant proportion of cells in the OFC demonstrated the modulation associated with the presentation of the correct stimulus during all three presentation epochs (first epoch: 35.65%, n = 41/115 cells; second epoch: 46.96%, n = 54/115 cells; third epoch: 49.57%, n = 57/115 cells, P < 0.0001 for all comparisons, binomial tests). Significant percentages were also observed in VS (first epoch: 45.63%, n = 47/103 cells; second epoch: 47.57%, n = 49/103 cells; third epoch: 50.49%, n = 52/103 cells, P < 0.0001 for all comparisons) and DS (first epoch: 35.47%, n = 72/204 cells; second epoch: 36.95%, n = 75/204 cells; third epoch: 41.87%, n = 85/204 cells, P < 0.0001 for all comparisons). Note that the significant encoding in the first epoch is itself significant, even when correcting for multiple comparisons. This fact is important because expectation of a rewarding cue is always 1/3 on the first of the three offers, but can potentially vary with learning on subsequent ones.

Associative activity increases after rule acquisition in the OFC and DS, but arises early in learning and remains constant across the block in VS

We next examined the average magnitude of correct-stimulus selectivity using Hedge's g (a bi-directional effect size measure similar to Cohen's d, see methods). The average selectivity across time within trials for the population of OFC cells is shown in Fig. 5B. Data for VS and DS are shown as well, for comparison (Fig. 5C and D). Within trials, we observed that the timing of neural responses in the OFC and VS appeared to arise sooner after the presentation of stimuli compared with DS, which is consistent to the general pattern we observed for single neurons. Thus, to directly assess the timing of correct-stimulus selectivity, we first determined the average time of maximum selectivity within trials in each region (averaged across all correct trials and all three presentation epochs). We found that correct-stimulus selectivity peaked 370 ms after the start of the stimulus presentation period in the OFC, 340 ms after the start of the stimulus presentation period in VS, and 520 ms after the start of the stimulus presentation period in DS. To determine whether these latencies were significantly different across populations of neurons, we calculated the time of maximum selectivity across neurons and performed a one-way ANOVA using the factor brain region (OFC, VS, DS). This analysis revealed a significant effect of brain region (P = 0.0478), which occurred because of a significantly greater latency across the population of DS neurons compared with the populations of the OFC neurons (P = 0.0442, Fisher's LSD Test) and VS neurons (P = 0.0466, Fisher's LSD Test).

We then examined correct-stimulus selectivity before and after late switch points (Fig. 5E). Because the populations of OFC, VS, and DS neurons demonstrated significantly different latencies for correct-stimulus selectivity, we calculated the average selectivity in a 200 ms window surrounding the average time of maximum selectivity for each population of neurons. We calculated this measure for all correct trials before late switch points and all correct trials after late switch points, averaged across all three presentation epochs. We found no difference in the magnitude of selectivity before or after late switch points in the VS (P = 0.5145, Fisher's LSD Test), but found a significantly greater magnitude of selectivity after late switch points compared with the before late switch points

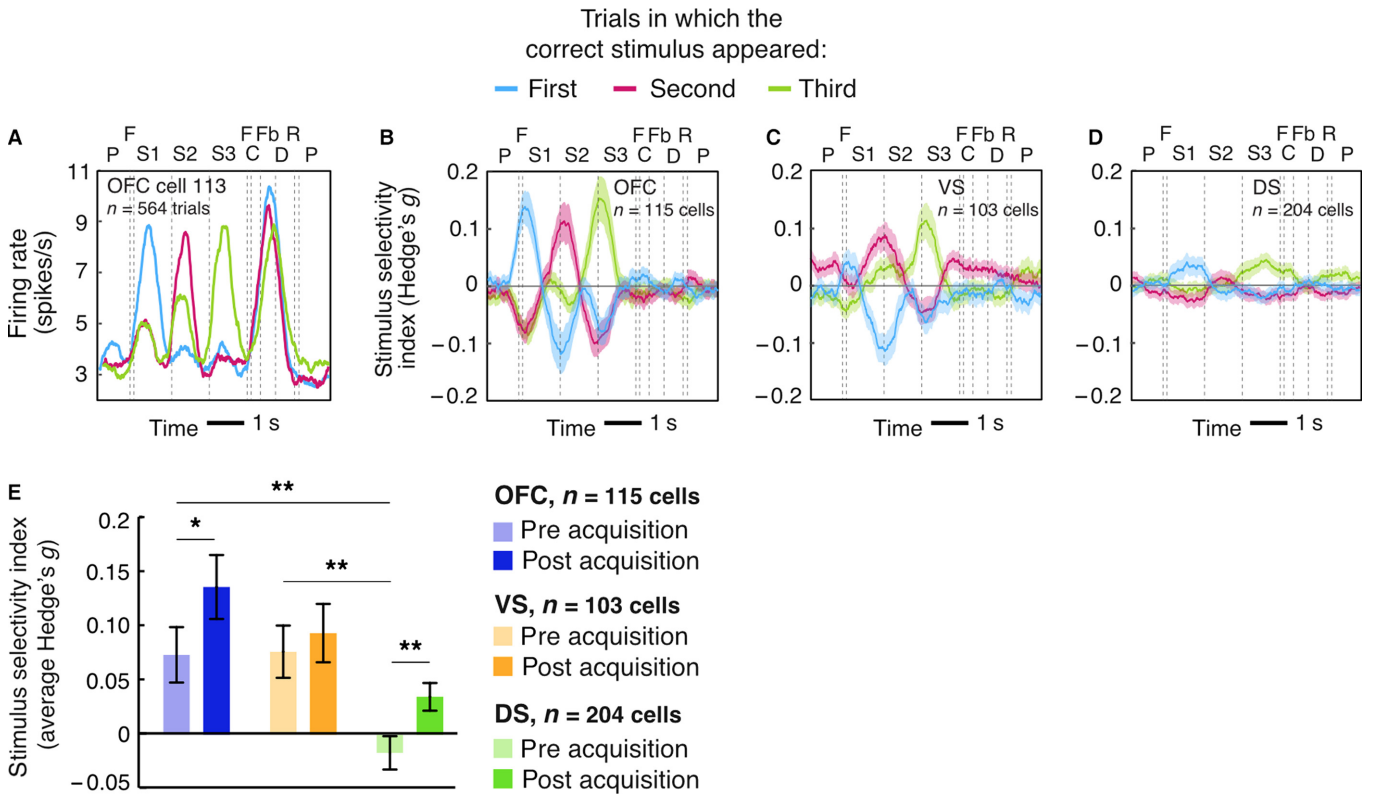

FIG. 5. Correct stimulus selectivity (A) Average response of a single OFC neuron demonstrating selectivity for the presentation of the correct stimulus during the first (blue line), second (red line), and third (green line) presentation epochs. C, choice; Fb, feedback; D, delay; R, reward; P, preparatory period (ITI); F, fixation; S1, first stimulus appearance; S2, second stimulus appearance; S3, third stimulus appearance. (B–D) Correct-stimulus selectivity (Hedges g) across the populations of OFC (B), VS (C), and DS (D) neurons. (E) Average proportion of variance explained (Hedge's g) by the presentation of the correct stimulus before late switch points and after late switch points for the populations of OFC (light blue and dark blue bars), VS (light orange and dark orange bars), and DS (light green and dark green bars) neurons. The analysis epoch for each region consists of a 200 ms period surrounding the average time of maximum selectivity. Bar graph shows the average Hedge's g (±SEM) during these epochs. Selectivity measures reflect averages across all neurons. *$P < 0.05$, **$P < 0.01$. [Colour figure can be viewed at wileyonlinelibrary.com].

in the OFC ($P = 0.0171$, Fisher's LSD Test) and DS ($P = 0.0072$, Fisher's LSD Test). We also found a significantly greater magnitude of selectivity in the OFC compared with DS before late switch points ($P = 0.0016$, Fisher's LSD Test) and after late switch points ($P = 0.0005$, Fisher's LSD Test), and a significantly greater magnitude of selectivity in VS compared with DS before late switch points ($P = 0.0014$, Fisher's LSD Test) and after late switch points ($P = 0.0431$, Fisher's LSD Test). We found no difference between OFC and VS at either point (before late switch points: $P = 0.9312$, Fisher's LSD Test, after late switch points: $P = 0.1982$, Fisher's LSD Test) (Fig. 6).

Taken together, the above results indicate that OFC and VS neurons demonstrate greater correct-stimulus selectivity than DS neurons both before and after rule acquisition, while neurons in both OFC and DS increase selectivity after rule acquisition. These findings are consistent with our results regarding switch modulation. Specifically, the populations of OFC and DS neurons both demonstrate greater switch modulation at the point of rule acquisition compared with the early periods of trial-and-error learning, while both regions also demonstrate an increase in correct-stimulus selectivity after rule acquisition.

Discussion

In the current study, we describe two new findings based on responses of the OFC neurons in an analogue of the WCST. First, we show that OFC neurons demonstrate switch-related modulation. That is, their firing rates change systematically on trials when monkeys adjust strategies. These signals were observed both on early switches, when monkeys abandoned their earlier strategy and, more strongly, on late switches, when monkeys committed to a new strategy. We also observed associative learning signals in the OFC neurons. That is, we found phasic changes in firing rate associated with the presentation of the correct option in a sequence of stimuli, which presumably reflect the learned association between the stimulus and the reward it predicts because of the perceptual rule that is used. These putative associative signals were stronger in the OFC following rule acquisition; this finding echoes our finding that switch signals in the OFC are greater at the point of rule acquisition than at early switch points.

While the OFC is sometimes thought of as a purely economic structure, a great deal of research indicates that it may have executive roles as well; these roles include rule encoding, working memory for both gustatory and abstract information, conflict-monitoring, information-seeking and curiosity, and linking outcomes with information about the spatial world (Wallis *et al.*, 2001; Wallis & Miller, 2003; Lara *et al.*, 2009; Tsujimoto *et al.*, 2009; Luk & Wallis, 2013; Mansouri *et al.*, 2014; Blanchard *et al.*, 2015a,b; Kidd & Hayden, 2015; Strait *et al.*, 2016). Our new findings do not resolve this debate entirely, but they fit in with these ideas. We suspect that, while there are differences between dorsal and ventral regions, the differences may not be as simple as economic vs. executive. Instead, they may have to do with variables like informational modality (Lara *et al.*, 2009).

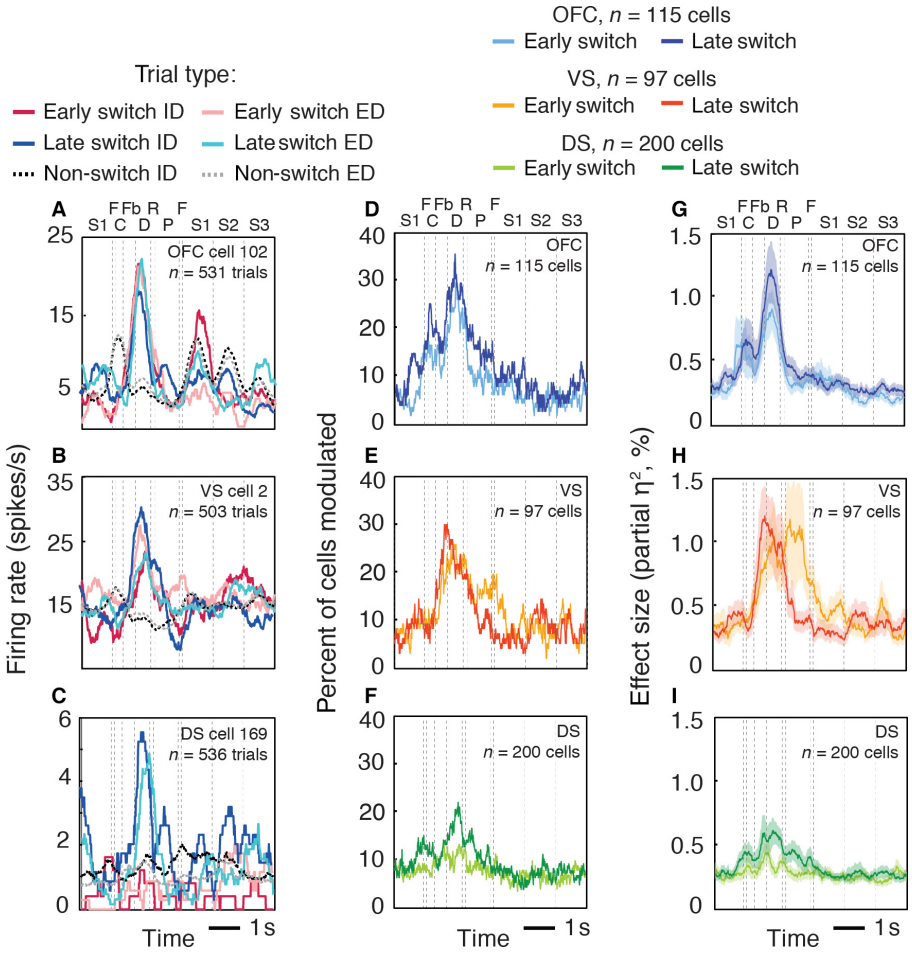

FIG. 6. Switching effects by switch type (A–C) Example cells for the OFC, VS, and DS, respectively. (D–F) Population measures of percent of cells modulated by early and late switches. (G–I) Proportion of variance explained by each measure. [Colour figure can be viewed at wileyonlinelibrary.com].

More generally, we think that it may be fatuous to insist on a strict divide between executive and economic functions. One important idea about the OFC function is that it encodes expectancies associated with specific stimuli and that these linkages may be relevant for driving learning (Schoenbaum & Roesch, 2005; Ostlund & Balleine, 2007; Rudebeck & Murray, 2008, 2011; Walton *et al.*, 2010; Rudebeck *et al.*, 2013). Another one is that the OFC encodes the set of task variables relevant for correct responding, even non-economic ones; this set may be known as an abstract version of Tolman's cognitive map (Wilson *et al.*, 2014, Schuck *et al.*, 2016). Such encoding moves away from a narrowly economic view and towards one more associated with flexible control of input-output mappings. Whether this type of function ought to be classified as executive is debatable, but we would support such an interpretation.

The role of OFC in switching is unclear. Several studies suggest that the OFC does not contribute to rule-based switching (Dias *et al.*, 1996a,b, 1997; Rudebeck *et al.*, 2013); however, one recent study suggests it may. Specifically, a recent study in rodents indicates that the OFC lesions disrupt switching performance (Chase *et al.*, 2012). They further proposed that previous studies faced some methodological limitations. Our current findings provide supporting evidence for the idea that the OFC has a positive role in switching and extend upon it in several ways. First, we show that switching correlates are observed for both early and late switches. Second, we show that the results are not limited to rodents. Third, our finding that the strength of associative learning signals in the OFC increases following late switch signals further suggests that switch signals in the OFC may play a role in guiding or initiating stable target identification and selection. Finally, our finding of switch signals in the OFC provides a neural basis for a theory heretofore based solely on behavioural patterns following lesions.

There are some limitations to this idea as well. Most important, unlike lesion studies, our data are correlational and thus cannot establish causality. Second, the homology between primate and rodent OFC is not patent, although a reasonable case can be made (Heilbronner *et al.*, 2016). Third, it is not clear that attentional set works the same way in primates and rodents. In any case, our results ought to be interpreted with caution.

These results complement our recent recordings in DS and VS in the same task. In our previous study (Sleezer & Hayden, 2016), we found correlates of switching in both of these regions that resembles those reported here for the OFC. We also found correlates of associative encoding as well. One striking finding is the broad similarity across the regions. In another study, we also found a similarity in rule encoding in all three regions (Sleezer *et al.*, 2016). This similarity is reminiscent of a different study using a different task showing functional overlap between OFC and VS in decision processes related to risky choice (Strait *et al.*, 2015). These results endorse the idea that striatum and its cortical inputs can, in many cases, have some overlap in their functions.

This is not to say that the OFC and striatum were strictly identical, even when faced with the same task. For example, we previously found that VS neurons demonstrate context-dependent switch signals. In contrast, we did not find the context-dependent switch signals in the OFC in the present study. In addition, while general switch signals appear to be stronger in VS when monkeys switch away from previously relevant rules, these signals in the OFC and DS are stronger when monkeys switch to newly relevant rules. These findings suggest that VS may play a greater role in guiding the identification of newly relevant rules when the correct rule is uncertain, while the OFC and DS may play a greater role in guiding stable rule selection once the correct rule is known.

One important difference between our CCST and other tasks using the WCST is that the rules in our task were somewhat more concrete. That is, the matching rule for the monkey was a specific shape or colour (triangle, circle, cyan, etc) rather than the category of shape or colour (cf. Mansouri *et al.*, 2006; Buckley *et al.*, 2009; Kamigaki *et al.*, 2012). This difference changes the emphasis somewhat; instead of focusing on encoding and switching abstract rules, our findings may be more related to encoding of perceptual templates. We would argue that the terms 'rule' and 'cognitive set-shifting' are broad enough to encompass both types of shifting.

The present results complement earlier research from several labs showing task-switching signals in many brain regions, including the OFC, striatum, parietal cortex, dorsal anterior cingulate cortex, and even posterior cingulate cortex (Mansouri *et al.*, 2006; Kamigaki *et al.*, 2009; Hayden *et al.*, 2010, 2011; Blanchard & Hayden, 2014; Heilbronner & Hayden, 2016; Sleezer & Hayden, 2016). Taken together, this body of work supports the idea that task-switching is both widespread and distributed, and provides evidence against the idea that this function is the exclusive domain of a small and highly specialized piece of brain tissue.

The associative encoding signals we found were the manifest as an enhanced or suppressed response to cues that matched the learned rule. This finding is intriguing because it is the same type of modulation that has previously been linked to target selection. Specifically, neurons in prefrontal and association cortex show significantly enhanced or suppressed responses to to-be-chosen cues when they appear in a sequence of options (Chelazzi *et al.*, 1998; Mazer & Gallant, 2003; Lui & Pasternak, 2011; Hayden & Gallant, 2013). Indeed, what we call rule here could potentially, in such tasks, be called feature-based attention (McAdams & Maunsell, 2000; David *et al.*, 2008).

The data do not identify the mechanisms by which neurons gain the ability to discriminate the different offers and respond differently to the one that matches the current rule. However, the fact that rule encoding and switching are observed in the same set of neurons that participate in associative encoding raise an interesting possibility. Perhaps the processes associated with learning the new rule cause a change in the response properties of the OFC neurons. This change in responsiveness is observable in the form of tonic changes in firing rate, and these changes are what we call rule encoding (Sleezer *et al.*, 2016). It is then further observable in the form of its direct effect: changes in the responses of the neurons to the offers. This idea is borrowed from the literature on memory-guided decision-making, and is consistent with the idea that rule-based and memory-based decisions reflect common underlying mechanisms (Chelazzi *et al.*, 1998; Machens *et al.*, 2005; Lui & Pasternak, 2011; Hayden & Gallant, 2013).

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Conflicts of interest

The authors declare no competing financial interests.

Author contributions

BJS lead the design of the task and designed and performed all analyses. BJS and BYH wrote the manuscript. GAL and MDC supervised the data collection.

Data accessibility

All data will be posted on Figshare and data and code will be available at haydenlab.com/data.

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