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

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ABSTRACT

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24   We are often faced with the need to abandon no-longer beneficial rules and adopt

25 new ones. This process, known as cognitive set reconfiguration, is a hallmark of

26 executive control. Although cognitive functions like reconfiguration are most often

27 associated with dorsal prefrontal structures, recent evidence suggests that the

28 orbitofrontal cortex (OFC) may play an important role as well. We recorded activity of

29 OFC neurons while rhesus macaques performed a version of the Wisconsin Card Sorting

30 Task that involved a trial-and-error stage. OFC neurons demonstrated two types of

31 switch-related activity, an early (switch-away) signal and a late (switch-to) signal, when

32 the new task set was established. We also found a pattern of *match modulation*: a

33 significant change in activity for the stimulus that matched the current rule (and would

34 therefore be selected). These results extend our understanding of the executive functions

35 of the OFC. They also allow us to directly compare OFC with complementary datasets

36 we previously collected in ventral (VS) and dorsal (DS) striatum. Although both effects

37 are observed in all three areas, the timing of responses aligns OFC more closely with DS

38 than with VS.

39 **INTRODUCTION**

40   The orbitofrontal cortex (OFC) is a critical site for decision-making and adaptive

41 behavior. Its contributions to the evaluation and comparison of rewards are well

42 established (Padoa-Schioppa and Assad, 2006; Wallis, 2007). Perhaps less well-known

43 are its executive roles. OFC is critical for linking stimuli to values, in monitoring

44 consequences of actions, in detecting and resolving conflict, in metacognition, and

45 encoding rules and storing sensory information in working memory (Abe and Lee, 2011;

46 Kepecs et al., 2008; Lara et al., 2009; Mansouri et al., 2014; Rushworth et al., 2011;

47 Schoenbaum et al., 1999; Sleezer et al., 2016; Strait et al., 2016; Tsujimoto et al., 2009;

48 Wallis and Miller, 2003; Wallis et al., 2001). Indeed, the list of executive functions of the

49 OFC is almost as long as those associated with classical executive structures like

50 dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC).

51   One executive function for which the role of OFC is not as well understood is

52 cognitive set reconfiguration. This term refers to the adjustment of cognitive strategies or

53 mental representations in response to changing goals or environmental circumstances

54 (Robbins, 2007). It is often called switching for short. A classic example of switching is

55 recognizing that a familiar driving route to work is blocked and identifying and changing

56 to an alternative route. Switch-related signaling is a classic executive function and is most

57 closely associated with executive regions in the dorsal prefrontal cortex and parietal

58 cortex (Alan et al., 1994; Dias et al., 1996a; Kamigaki et al., 2012; Mansouri et al., 2006).

59 Specific evidence for this linkage comes, in part, from physiological studies showing

60 systematic modulations of firing rate during switch trials relative to other trials.

61   Although a number of studies suggest that OFC contributes to simpler types of

62 flexible decision-making (Dias et al., 1996a, 1996b, 1997; McAlonan and Brown, 2003),

63 there are several reasons to believe that OFC may participate directly in switching,

64 especially between rules. First, as noted above, recent evidence supports a role for OFC

65 in many executive functions. Second, we and others have delineated a role for OFC in

66 maintenance of rules or in updating based on rules (Buckley et al., 2009; Sleezer et al.,

67 2016; Tsujimoto et al., 2011; Wallis et al., 2001; Yamada et al., 2010). Third, recent

68 work indicates that OFC lesions disrupt the ability to switch between behavioral rules in

69 rodents (Birrell and Brown, 2000). Finally, we previously showed switching-related

70 activity in two basal ganglia structures - the dorsal (DS) and ventral (VS) striatum -

71 which are not generally associated with switching. Specifically, we found that switch

72 signals in VS were strongest when switching away from previously relevant rules, while

73 switch signals in DS were strongest when switching toward newly relevant rules.

74 Because OFC has direct anatomical projections to both VS and DS, we hypothesized that

75 it may have a direct role in switching as well.

76   In our earlier study on striatal contributions to switching, we also found that the

77 appearance of switch signals in VS and DS was consistent with the appearance of

78 associative learning signals (i.e. the systematic enhancement or suppression in firing rate

79 for task-relevant targets when they appear in a sequence of stimuli) in both regions. We

80 therefore wondered whether OFC neurons would demonstrate similar patterns of activity.

81 Such signals likely relate to executive function, as they correspond to a linkage between

82 mental representations of rules and presentation of specific offers.

83   To examine the role of OFC in switching, we recorded the activity of single

84   neurons as macaques performed a version of the Wisconsin Card Sorting Task. In our

85   version, rules were never cued, so subjects had to go through a trial-and-error phase to

86   determine the currently relevant rule (this normally took 3-4 trials). They could then take

87   advantage of the newly learned rule and maintain responding until the rule changed again

88   (blocks were 15 trials long). We found systematic changes in firing associated with both

89   early (switch-away) and late (switch-to) switch trials - i.e. explicit switch signals - in

90   OFC neurons. We also found that switch signals in OFC were consistent with the

91   appearance of associative learning signals in this region; associative signals arose slowly

92   and only became strong once the rule was established. Our results are consistent with the

93   idea that switch signals are linked to associative learning, and may even serve to initiate

94   learning processes during flexible rule updating. More generally, these findings endorse a

95   broader executive role for OFC and are consistent with a recent theory proposing that

96   OFC instantiates a cognitive map of task space (Schuck et al., 2016; Wilson et al., 2014).

MATERIALS AND METHODS

97

98 ***Surgical procedures***: All animal procedures were approved by the University

99 Committee on Animal Resources at the University of Rochester and were designed and

100 conducted in compliance with the Public Health Service's Guide for the Care and Use of

101 Animals. Two male rhesus macaques (*Macaca mulatta*) served as subjects. We used

102 standard electrophysiological techniques as described previously (Strait et al., 2014). A

103 small prosthesis for holding the head was used. Animals were habituated to laboratory

104 conditions and then trained to perform oculomotor tasks for liquid reward. A Cilux

105 recording chamber (Crist Instruments) was placed over the OFC. Position was verified by

106 magnetic resonance imaging with the aid of a Brainsight system (Rogue Research Inc.).

107 Animals received appropriate analgesics and antibiotics after all procedures. Recording

108 locations care shown in **Figure 1C**. Throughout both behavioral and physiological

109 recording sessions, the chamber was kept sterile with regular antibiotic washes and sealed

110 with sterile caps.

111 ***Recording sites***: We approached OFC through a standard recording grid (Crist

112 Instruments). We used the standard atlas for all area definitions (Paxinos et al., 2000). We

113 defined OFC as the coronal planes situated between 29 and 36 mm rostral to the

114 interaural plane, the horizontal planes situated between 0 and 9 mm from the ventral

115 surface, and lateral to the medial orbital sulcus. We recorded from Area 13m (Öngür and

116 Price, 2000). We confirmed recording locations before each recording session using our

117 Brainsight system with structural magnetic resonance images taken before the

118 experiment. Neuroimaging was performed at the Rochester Center for Brain Imaging, on

119 a Siemens 3T MAGNETOM Trio Tim using 0.5 mm voxels. We confirmed recording

120   locations by listening for characteristic sounds of white and gray matter during recording,

121   which in all cases matched the loci indicated by the Brainsight system. The Brainsight

122   system typically offers an error of <1 mm in the horizontal plane and <2 mm in the z-

123   direction.

124   ***Electrophysiological techniques***: Single electrodes (Frederick Haer & Co.,

125   impedance range 0.8 to 4M Ω) were lowered using a microdrive (NAN Instruments) until

126   waveforms between 1 and 3 neuron(s) were isolated. Individual action potentials were

127   isolated on a Plexon system (Plexon Inc., Dallas, TX). Neurons were selected for study

128   solely on the basis of the quality of isolation; we never pre-selected based on task-related

129   response properties.

130   ***Eye-tracking and reward delivery:*** Eye position was sampled at 1000 Hz by an

131   infrared eye-monitoring camera system (SR Research). Stimuli were controlled by a

132   computer running Matlab (Mathworks) with Psychtoolbox and Eyelink Toolbox. Visual

133   stimuli were presented on a computer monitor placed 57 cm from the animal and centered

134   on its eyes. A standard solenoid valve controlled the duration of juice delivery. The

135   relationship between solenoid open time and juice volume was established and confirmed

136   before, during, and after recording.

137   ***Behavioral task***: The task described here is the same as that used in two previous

138   manuscripts (Sleezer and Hayden, 2016; Sleezer et al., 2016). Subjects performed an

139   implementation of the Wisconsin Card Sorting Task (WCST, Moore et al., 2005). Our

140   version of the task uses two dimensions (color and shape) and six specific rules (three

141   shapes: circle, star, and triangle, and three colors: cyan, magenta, and yellow, **Figure**

142   **1A**). On each trial, three stimuli were presented asynchronously at the top, bottom left,

143   and bottom right of the screen (1 second asynchrony). The color, shape, position, and

144   order of stimuli were fully randomized on each trial. Each stimulus was presented for 400

145   ms and was followed by a 600 ms blank period. Subjects were free to fixate upon the

146   stimuli when they appeared. Then all three stimuli reappeared simultaneously with a

147   central fixation spot. The subject fixated on the central spot for 100 ms and then indicated

148   its choice by shifting gaze to its preferred stimulus and maintaining fixation on it for 250

149   ms. Failure to maintain gaze for 250 ms did not lead to the end of the trial, but instead

150   returned the subject to a choice state; thus, subjects were free to change their mind if they

151   did so within 250 ms (although in our observations, they almost never did so). Following

152   a successful 250 ms fixation, visual feedback was provided (a green/red outline around

153   the chosen stimulus for correct/incorrect choices, respectively). After visual feedback,

154   there was a 500 ms blank delay period; correct choices were followed by a liquid (water)

155   reward. All trials were separated by an 800 ms inter-trial interval (ITI), which we refer to

156   as the preparatory period. In each block, subjects responded according to one of the six

157   rules. Subjects were required to use a trial-and-error learning process to determine the

158   correct rule. Rule changes occurred after 15 correct trials and were not explicitly cued.

159   ***Analysis of behavioral performance across different types of rule changes:*** To

160   determine whether subjects' performance differed depending on the type of rule change

161   that occurred at the beginning of the block, we calculated the average number of trials

162   monkeys completed prior to rule acquisition (i.e. the first trial in a series of four

163   consecutive correct trials, Sleezer and Hayden, 2016) following intra-dimensional and

164   extra-dimensional rule changes. Intra-dimensional rule changes refer to instances when

165   the rule change occurs within one rule category (i.e. color to color or shape to shape),

166   while extra-dimensional rule changes refer to instances when the rule change occurs

167   across rule categories (i.e. color to shape or shape to color). To compare the number of

168   trials monkeys completed prior to rule acquisition across intra-dimensional and extra-

169   dimensional switches, we used a two-way repeated measures ANOVA with the between

170   subjects factor subject (Monkey B, Monkey C) and the within subjects factor block type

171   (intra-dimensional, extra-dimensional). We used post-hoc Fisher's LSD tests to compare

172   specific differences across groups.

173   ***Analysis of switch-related neural activity:*** On the first trial of each block,

174   subjects almost always chose according to the previously relevant rule. Because the block

175   transition was not explicitly cued, we called this the "inevitable error trial". On blocks

176   where the new rule happened to match the previous one by chance (1/6 of blocks), the

177   first trial did not produce an error, and monkeys did not change strategy, so, for purposes

178   of analysis, we treated these blocks as 30 trial blocks. Moreover, because there were three

179   stimuli on each trial, with two dimensions each, occasionally (1/3 of blocks), the correct

180   stimulus on the first trial was consistent with the previously relevant rule. We therefore

181   specified in our definition of the inevitable error trial that it referred to the first trial on

182   which choosing according to the previous rule would produce an error.

183   We examined switch-related neural activity during the 1,420 ms post-feedback

184   period following feedback (that is, the combined duration of the delay, reward, and

185   preparatory periods) and prior to the start of switch and non-switch trials. We analyzed

186   this period because monkeys likely reconfigured their cognitive rule set on switch trials

187   during this period. Non-switch trials were defined as all trials other than switch trials. The

188   two types of switch trials are defined below.

189   We identified two points in the block when monkeys likely reconfigured (i.e.

190   switched) their cognitive rule set. The ***early switch*** was the post-feedback period

191   following an incorrect choice and immediately prior to the start of the first correct trial.

192   We chose this trial because subjects had switched but had not yet begun consistently

193   responding according to the new rule. We excluded early switch points that were also

194   identified as late switch points. The ***late switch point*** was on the trial immediately

195   following the first trial of at least 4 consecutive correct trials.

196   Task-related activity during the post-feedback period was determined using

197   ANOVA with the factors trial type (switch or nonswitch), block type (intradimensional or

198   extradimensional), trial outcome (reward or no-reward), and next trial outcome (reward

199   or no-reward). In these analyses, trial outcome refers to the outcome during the reward

200   period during the post-feedback period, while next trial outcome refers to the outcome

201   during the reward period on the following trial. Although we were interested in the

202   effects of trial type, block type, and their interaction, we included trial outcome and next

203   trial outcome in the ANOVA model to control for the potential influence of reward or

204   error related activity. Because current trial outcome and next trial outcome were not fully

205   crossed with trial type in this model (that is, switch trials always consisted of a non-

206   rewarded trial followed by a rewarded trial), we used a nested ANOVA in which current

207   and next trial outcome were nested in trial type. A nested ANOVA measures the effects

208   of a factor while partialling out the effects of a nesting factor. Thus, by utilizing a nested

209   ANOVA in which current and next trial outcome were nested in trial type, this model

210   includes an estimate of the effects of current and next trial outcome, which thus serves as

211   control for reward outcome related effects. We conducted these analyses separately for

212   early and late switch points. Based on the ANOVA results, we classified task-related

213   activity into two types. The first type showed a significant main effect ($P < 0.05$) of trial

214   type, the second showed a significant interaction ($P < 0.05$) between trial type and block

215   type. Post-hoc comparisons (Fisher's LSD test) were conducted if the interaction was

216   significant ($P < 0.05$). We refer to neurons with a main effect of trial type as *general*

217   *switch signaling neurons* and neurons with an interaction between trial type and block

218   type as *context-specific switch signaling neurons*.

219   To determine if the proportion of cells demonstrating a significant switch-related

220   effect (a main effect of trial type or a significant interaction between trial type and block

221   type) was significantly above chance, we conducted binomial tests, and adjusted the p-

222   value using a Bonferroni correction for two comparisons. We corrected for two

223   comparisons because we analyzed activity at both early and late switch points. We chose

224   to maintain an alpha of 0.05 and multiply the resultant p-values by two as a way of

225   implementing the Bonferroni correction. Thus, the p-values reported for binomial tests in

226   this paper have been adjusted for two comparisons, where appropriate. To determine if

227   proportions of cells demonstrating an effect were significantly different across OFC, VS

228   and DS, we implemented a mixed model binary logistic regression procedure using the

229   between subjects factor brain region (OFC, VS, DS) and the within subjects factors trial

230   period (early, late) and modulation type (general switch, context dependent switch). The

231   model was fit using a generalized estimating equation (GEE) procedure, implemented in

232   SPSS. In this analysis, "within subjects" and "between subjects" refer to neurons. In this

233   procedure, an omnibus Wald Chi-Square test was applied to determine the significance of

234   group effects, followed by pairwise comparisons using Fisher's LSD tests to examine

235   specific group effects.

236   To examine the percent of variance explained by each switch-related effect across

237   the populations of OFC, VS and DS neurons, we calculated the average partial η^2. Partial

238   η^2 is a measure of effect size in ANOVA, which measures the proportion of variance

239   attributable to a factor after partialling out other factors from the non-error variance

240   (Cohen, 1973). Partial η^2 is calculated as:

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

241   where SS_{factor} is the variation attributable to the factor (sum of squares for the factor), and

242   SS_{error} is the error variation (sum of squares error). To compare the average partial η^2 for

243   switch-related effects at early and late switch points and in OFC, VS and DS, we used a

244   two-way repeated measures ANOVA with the factors brain region (OFC, VS and DS)

245   and switch period (early and late), followed by post-hoc Fisher's LSD tests.

246   ***Analysis of Associative Learning-Related Activity***: To examine associative

247   learning-related neural activity, we calculated the average firing rate during each of the

248   three stimulus presentation epochs on all correct trials. We defined the stimulus

249   presentation epoch as the 1000 ms period consisting of 400 ms when the stimulus was on

250   the screen and the following 600 ms when the stimulus was off the screen. We then used

251   two-way t-tests to compare the average firing rate during epochs in which the correct

252   stimulus was presented to the average firing rate during epochs in which the correct

253   stimulus was not presented.

254   To examine the magnitude of correct-stimulus selectivity, we calculated Hedge's

255   g, a measure of effect size similar to Cohen's d. Hedge's g is recommended when groups

256   have different sizes, and was also developed to remove a positive bias affecting Cohen's

257   d (Hedges, 1981). Since the sample sizes for the presentation of incorrect stimuli were

258   always larger than the sample sizes for the presentation of correct stimuli (since each trial

259   consisted of one correct stimulus and two incorrect stimuli), we chose to calculate effect

260   size using Hedge's g, rather than Cohen's d. Hedge's g is calculated as:

261

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

262

263   where M1 and M2 are the means of each group, and SD_{pooled} is the pooled standard

264   deviation, calculated as:

265

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

266

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

268   deviations for each group.

269   To compare selectivity across brain regions, we first determined the average time

270   of maximum selectivity within trials in each region (averaged across all correct trials) and

271   analyzed a 200 ms period surrounding that time (100 ms before and 100 ms after). We

272   then used these analysis epochs to compare selectivity in OFC, VS, and DS before and

273   after late switch points. We compared selectivity across switch periods and brain regions

274   using a 2-way repeated-measures ANOVA with the factors switch period (pre-late switch

14

275   and post-late switch) and brain region (OFC, VS, and DS), following by post-hoc

276   Fisher's LSD tests.

277   Statistical analyses were carried out using MATLAB release 2012b (MathWorks

278   Inc), SPSS Statistics version 24 (IBM Analytics), and GraphPad Prism version 6

279   (GraphPad Software).

RESULTS

Behavioral 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 (**Figure 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 intradimensional (ID) or extradimensional (ED) switch to the new rule. To determine

whether subjects' performance differed following intradimensional and extradimensional

rule changes, we examined the number of trials monkeys completed prior to 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 ($F(1,267) =$

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 **Figure 2B**. We found that both subjects completed more trials

prior to rule acquisition following extra-dimensional rule changes compared to intra-

dimensional rule changes (**Figure 2B**, $P < 0.0001$ for both subjects, Fisher's LSD Tests).

On average, subjects completed 14.94 ± 5.79 early switches and 27.62 ± 9.53 late

switches per session. Prior to early switch trials, monkeys completed 3.12 ± 0.66 trials

303   (3.34 ± 0.77 for monkey B and 2.97 ± 0.52 for monkey C), and prior to late switch trials,

304   monkeys completed an average of 6.69 ± 2.31 (8.04 ± 2.74 for monkey B and 5.74 ± 1.29

305   for monkey C). These numbers include the inevitable error trial.

306

307   ***Neurons in the orbitofrontal cortex demonstrate switch-related activity***

308   We first characterized neural responses associated with switch trials. To do this,

309   we compared firing rates on non-switch trials (all trials besides early- and late-switch

310   trials) with those obtained on early switch trials (that is, the first correct trial after a

311   switch). Then, in a separate analysis, we compared non-switch trials with late switch

312   trials (the first correct trial in a series of at least 4 consecutive correct trials). We analyzed

313   firing rate activity during the post-feedback period separately for each cell using ANOVA

314   (see Methods).

315   Our assessment of switch-related activity focused on both preponderance and

316   effect size during the post-feedback period, measured by the proportion of cells

317   demonstrating a significant effect and the proportion of variance explained (partial η^2) by

318   the main effect of trial type ("general switch" modulation) and the interaction between

319   trial type and block type ("context-dependent switch" modulation).

320   **Figure 3A** shows an example of an OFC neuron demonstrating general switch-

321   related activity at both early and late switch points. The average firing rate response for

322   this neuron was significantly greater on early switch trials than non-switch switch trials

323   for both ID switches (red line and black dotted line, $P < 0.0001$, Fisher's LSD test) and

324   ED switches (pink line and gray dotted line, $P = 0.0015$, Fisher's LSD test), and also

325   significantly greater on late switch trials than non-switch trials for ID switches (dark blue

326   line and black dotted line, $P < 0.0001$, Fisher's LSD test) and ED switches (light blue line

327   and gray dotted line, $P < 0.0001$, Fisher's LSD test). This neuron showed no response

328   difference for ID versus ED switches, whether looking at early switch points (red line and

329   pink line, $P = 0.9263$, Fisher's LSD test), or late switch points (dark blue line and light

330   blue line, $P = 0.6720$, Fisher's LSD test).

331   To determine whether the proportion of OFC cells demonstrating general switch

332   modulation was above chance, we calculated the average proportion of cells

333   demonstrating a significant effect across the 1,420 ms post-feedback epoch and

334   performed binomial tests. We corrected for two comparisons (because we looked at early

335   and late switch points) using a Bonferroni correction. These results are shown in **Figure**

336   **4A**. We found that the proportion of cells demonstrating general switch modulation was

337   significantly above chance at early switch points (n = 20/115 cells) and at late switch

338   points (n = 30/115 cells, $P < 0.0001$ in both cases).

339   In a previously published report, we examined the same effects in two striatal

340   regions, ventral (VS) and dorsal (DS) striatum (Sleezer and Hayden, 2016). Data for VS

341   and DS are shown as well, for comparison (**Figure 4A**). We found that the number of

342   cells demonstrating switch modulation in these areas was significant at early switch

343   points (VS: n = 29/97 cells; DS: n = 24/200 cells, Bonferroni adjusted $P < 0.0001$ for all

344   three regions, corrected for two comparisons, binomial test) and at late switch points (VS:

345   n = 24/97 cells; DS: n = 41/200 cells, Bonferroni adjusted $P < 0.0001$ for all three

346   regions, corrected for two comparisons).

347   To compare the proportions of cells demonstrating each type of modulation across

348   brain regions and across early and late switch points, we implemented a mixed model

349   binary logistic regression procedure using the between subjects factor brain region (OFC,

350   VS, DS) and the within subjects factors trial period (early, late) and modulation type

351   (general switch, context dependent switch). In this analysis, the terms "within subjects"

352   and "between subjects" refer to neurons. In this procedure, an omnibus Wald Chi-Square

353   test was applied to determine the significance of group effects, followed by Fisher's LSD

354   tests to examine specific group differences. This analysis revealed a significant main

355   effect of brain region ($\chi^2 = 6.4922$, $P = 0.0389$), a significant main effect of modulation

356   type ($\chi^2 = 68.3523$, $P < 0.0001$), and a significant interaction between brain region and

357   trail period ($\chi^2 = 8.1057$, $P = 0.0174$).

358   Pairwise comparisons are shown in **Figure 4A**. These analyses revealed a

359   significantly greater proportion of cells demonstrating general switch modulation at late

360   switch points compare to early switch points in both OFC and DS (OFC: $P = 0.0461$, DS:

361    $P = 0.0090$, Fisher's LSD tests). In contrast, we found no difference in the proportion of

362   cells demonstrating general switch modulation at early and late switch points in VS ($P =$

363   0.3672). However, we did find that the proportion of cells demonstrating general switch

364   modulation at early switch points was significantly greater in VS compared to both OFC

365   and DS at the same time point (VS vs. OFC: $P = 0.0322$; VS vs. DS: $P = 0.0006$).

366   **Figure 3B** shows the average proportion of variance explained (partial η^2) by the

367   main effect of trial type in OFC across time within trials. **Figures 3C, and 3D** show the

368   corresponding data in VS, and DS for comparison. To compare the average partial η^2

369   across OFC, VS, and DS, we calculated the average partial η^2 across the 1,420 sec post-

370   feedback epoch and used a mixed-model ANOVA with the between subjects factors brain

371   region (OFC, VS, and DS), and the within subjects factors trial period (early, late), and

372   modulation type (general switch, context-dependent switch). As above, in this analysis,

373   "within subjects" and "between subjects" refer to neurons. This analysis revealed a main

374   effect of brain region ($F_{(2,409)} = 4.6948$, $P = 0.0096$), a main effect of modulation type

375   ($F_{(1,409)} = 62.4911$, $P < 0.0001$), and an interaction between brain region and trial period

376   ($F_{(2,409)} = 9.9800$, $P = < 0.0001$). Post-hoc comparisons are shown in **Figure 4B**.

377   We found a greater modulation in OFC at late switch points compared to early

378   switch points, although this effect was not significant ($P = 0.0502$, Fisher's LSD test). At

379   early switch points, we found a greater magnitude of general switch modulation in VS

380   compared to both OFC and DS ($P = 0.0029$ and $P < 0.0001$), but no difference between

381   OFC and DS at the same time point ($P = 0.2482$). At late switch points, we found no

382   difference between any of the three regions (OFC vs. VS: $P = 0.3027$; OFC vs. DS: $P =$

383   0.2694; VS vs. DS: $P = 0.9174$).

384   These results indicate that VS neurons demonstrate greater switch-related

385   modulation during early periods of trial-and-error learning compared to later periods of

386   rule acquisition and compared to OFC and DS neurons at the same time point. In

387   addition, OFC, VS, and DS appear to demonstrate equal levels of switch-related

388   modulation at later points of rule acquisition, while OFC and DS neurons demonstrate

389   greater switch-related modulation during later periods of rule acquisition compared to

390   early periods of trial-and-error learning.

391

392   **Latencies of switching signals**

393   We next examined the latency of general switch signal appearance in OFC, VS,

394   and DS at early and late switch points. None of these analyses were reported in our

395   earlier study (Sleezer et al., 2016). To estimate latency, we calculated the average partial

396   η^2 for the main effect of trial type (switch or non-switch) across time within trials using a

397   50 ms sliding window slid in 10 ms steps across the 1,420 ms post-feedback period. To

398   determine whether these latencies were significantly different across populations of

399   neurons, we calculated the time of maximum selectivity across neurons and performed a

400   one-way ANOVA using the factor brain region (OFC, VS, DS), separately at early and

401   late switch points. This analysis revealed no significant differences in group latencies

402   across brain regions at early ($P = 0.1027$) or late switch points ($P = 0.5793$).

403

404   ***Context-specific switch signals arise during the early trial-and-error period in VS, but***

405   ***not OFC or DS***

406   We next investigated context-specific switching activity (i.e. encoding of switches

407   specific to either extra- or intra-dimensional switches, but not both). These results are

408   similar to those reported in our previous paper (Sleezer and Hayden, 2016), however, the

409   analysis technique used here is more sensitive and the OFC data were not reported in the

410   previous paper. We found that the proportion of cells demonstrating context-dependent

411   switch modulation at early switch points was significantly above chance in VS (n = 11/97

412   cells, Bonferroni adjusted $P = 0.0067$, corrected for two comparisons, binomial test), but

413   not OFC or DS (OFC: n = 3/115 cells, Bonferroni adjusted $P = 1.6642$; DS: n = 9/200

414   cells, Bonferroni adjusted $P = 1.0906$, corrected for two comparisons). At late switch

415   points, the proportion of cells demonstrating a significant effect was not significant in

416   OFC, VS, or DS (OFC: n = 6/115 cells, Bonferroni adjusted $P = 0.7051$; VS: n = 5/97

417   cells, Bonferroni adjusted $P = 0.7410$; DS: n = 15/200 cells, Bonferroni adjusted $P =$

418   0.0887, corrected for two comparisons). In comparing proportions across brain regions at

419   early switch points, we found a significantly greater proportion of cells demonstrating

420   context-dependent switch modulation in VS compared to OFC ($P = 0.0138$) and a greater

421   proportion of cells in VS compared to DS, which was marginally significant ($P =$

422   0.0542). We found no difference between OFC and DS at early switch points ($P =$

423   0.2033), or between any of the three regions at late switch points (OFC vs. VS: $P =$

424   0.9836; OFC vs. DS: $P = 0.4128$; VS vs. DS: $P = 0.4241$).

425   In comparing the strength of context-dependent switch modulation across early

426   and late switch points, we found significantly greater modulation in VS at early switch

427   points compared to late switch points ($P = 0.0004$, Fisher's LSD test), but no difference

428   between the two time points in OFC or DS ($P = 0.7328$, $P = 0.3469$). In comparing the

429   strength of modulation across brain regions at early switch points, we found significantly

430   greater modulation in VS compared to both OFC and DS ($P < 0.0001$ for both

431   comparisons). We found no difference between OFC and DS at early switch points ($P =$

432   0.8194), nor did we find any differences between the three regions at late switch points

433   (OFC: $P = 0.9855$, VS: $P = 0.5200$, DS: $P = 0.5564$).

434   Taken together with our findings regarding general switch-related activity, the

435   above results suggest that VS neurons demonstrate greater switch modulation during the

436   early trial-and-error period of the block compared to the later point of rule acquisition,

437   and that a portion of these cells carry information about the rule context (i.e. whether the

438   switch is intradimensional or extradimensional). In contrast, OFC and DS neurons

439   demonstrate greater switch modulation during the later period of the block, and these

440   signals carry no information regarding the switch context.

441   *Neurons in the OFC demonstrate associative learning related activity*

442   We next wanted to know how OFC responses reflect learning of associations

443   between stimuli and outcomes (i.e. reward or no reward), and how these responses relate

444   to switch modulation. To do this, we examined the neural response to the three probe

445   stimuli at the beginning of each trial (**Figure 1A**).

446   **Figure 5A** shows the responses of an example OFC neuron with these effects.

447   This neuron responded weakly to options as they appeared in sequence, but responded

448   strongly when the correct option appeared. To assess this response statistically, we

449   calculated the average firing rate during each of the three stimulus presentation epochs on

450   all correct trials. We then used two-way t-tests to compare the average firing rate during

451   epochs in which the correct stimulus was presented to the average firing rate during

452   epochs in which the correct stimulus was not presented, separately for each of the three

453   presentation epochs. This cell demonstrated a significantly greater firing rate when the

454   correct stimulus was presented compared to when the correct stimulus was not presented

455   during all three presentation epochs (first epoch: $P < 0.0001$, second epoch: $P = 0.0048$,

456   third epoch: $P < 0.0001$, two-way t-tests).

457   A significant proportion of cells in OFC demonstrated modulation associated with

458   the presentation of the correct stimulus during all three presentation epochs (first epoch:

459   35.65%, n = 41/115 cells; second epoch: 46.96%, n = 54/115 cells; third epoch: 49.57%,

460   n = 57/115 cells, $P < 0.0001$ for all comparisons, binomial tests). Significant percentages

461   were also observed in VS (first epoch: 45.63%, n = 47/103 cells; second epoch: 47.57%,

462   n = 49/103 cells; third epoch: 50.49%, n = 52/103 cells, $P < 0.0001$ for all comparisons)

463 and DS (first epoch: 35.47%, n = 72/204 cells; second epoch: 36.95%, n = 75/204 cells;

464 third epoch: 41.87%, n = 85/204 cells, $P < 0.0001$ for all comparisons).

465

466 ***Associative learning related activity increases after rule acquisition in OFC and DS,***

467 ***but arises early in learning and remains constant across the block in VS***

468 We next examined the average magnitude of correct-stimulus selectivity using

469 Hedge's g (a bi-directional effect size measure similar to Cohen's d, see methods). The

470 average selectivity across time within trials for the population of OFC cells is shown in

471 **Figure 5B**. Data for VS and DS are shown as well, for comparison (**Figure 5C and 5D**).

472 Within trials, we observed that the timing of neural responses in OFC and VS appeared to

473 arise sooner after the presentation of stimuli compared to DS, which is consistent to the

474 general pattern we observed for single neurons. Thus, to directly assess the timing of

475 correct stimulus selectivity, we first determined the average time of maximum selectivity

476 within trials in each region (averaged across all correct trials and all three presentation

477 epochs). We found that correct stimulus selectivity peaked 370 ms after the start of the

478 stimulus presentation period in OFC, 340 ms after the start of the stimulus presentation

479 period in VS, and 520 ms after the start of the stimulus presentation period in DS. To

480 determine whether these latencies were significantly different across populations of

481 neurons, we calculated the time of maximum selectivity across neurons and performed a

482 one-way ANOVA using the factor brain region (OFC, VS, DS). This analysis revealed a

483 significant effect of brain region ($P = 0.0478$), which was due to a significantly greater

484 latency across the population of DS neurons compared to the populations of OFC neurons

485 ($P = 0.0442$, Fisher's LSD Test) and VS neurons ($P = 0.0466$, Fisher's LSD Test).

486   We then examined correct stimulus selectivity before and after late switch points

487   (**Figure 5E**). Because the populations of OFC, VS, and DS neurons demonstrated

488   significantly different latencies for correct stimulus selectivity, we calculated the average

489   selectivity in a 200 ms window surrounding the average time of maximum selectivity for

490   each population of neurons. We calculated this measure for all correct trials before late

491   switch points and all correct trials after late switch points, averaged across all three

492   presentation epochs. We found no difference in the magnitude of selectivity before or

493   after late switch points in the VS ($P = 0.5145$, Fisher's LSD Test), but found a

494   significantly greater magnitude of selectivity after late switch points compared to before

495   late switch points in OFC ($P = 0.0171$, Fisher's LSD Test) and DS ($P = 0.0072$, Fisher's

496   LSD Test). We also found a significantly greater magnitude of selectivity in OFC

497   compared to DS prior to late switch points ($P = 0.0016$, Fisher's LSD Test) and after late

498   switch points ($P = 0.0005$, Fisher's LSD Test), and a significantly greater magnitude of

499   selectivity in VS compared to DS prior to late switch points ($P = 0.0014$, Fisher's LSD

500   Test) and after late switch points ($P = 0.0431$, Fisher's LSD Test). We found no

501   difference between OFC and VS at either point (before late switch points: $P = 0.9312$,

502   Fisher's LSD Test, after late switch points: $P = 0.1982$, Fisher's LSD Test).

503   Taken together, the above results indicate that OFC and VS neurons demonstrate

504   greater correct stimulus selectivity than DS neurons both before and after rule

505   acquisition, while neurons in both OFC and DS increase selectivity after rule acquisition.

506   These findings are consistent with our results regarding switch modulation. Specifically,

507   the populations of OFC and DS neurons both demonstrate greater switch modulation at

508   the point of rule acquisition compared to early periods of trial and error learning, while

509   both regions also demonstrate an increase in correct stimulus selectivity after rule

510   acquisition.

511

512   **DISCUSSION**

513   In the current study, we describe two new findings based on responses of OFC

514 neurons in a version of the WCST. First, we show that OFC neurons demonstrate switch-

515 related modulation. That is, their firing rates change systematically on trials when

516 monkeys adjust strategies. These signals were observed both on early switches, when

517 monkeys abandoned their earlier strategy and, more strongly, on late switches, when

518 monkeys committed to a new strategy. We also observed associative learning signals in

519 OFC neurons. In other words, we found phasic changes in firing rate associated with the

520 presentation of the correct option in a sequence of stimuli, which presumably reflect the

521 learned association between the stimulus and the reward it predicts because of the rule

522 that is used. These putative associative signals were stronger in OFC following rule

523 acquisition; this finding echoes our finding that switch signals in OFC are greater at the

524 point of rule acquisition than at early switch points.

525   While the OFC is sometimes thought of as a purely economic structure, a great

526 deal of research indicates that it may have executive roles as well; these roles include rule

527 encoding, working memory for both gustatory and abstract information, conflict-

528 monitoring, information-seeking and curiosity, and linking outcomes with information

529 about the spatial world (Blanchard et al., 2015; Kidd and Hayden, 2015; Lara et al., 2009;

530 Luk and Wallis, 2013; Mansouri et al., 2014; Strait et al., 2016; Tsujimoto et al., 2009;

531 Wallis and Miller, 2003; Wallis et al., 2001). Our new findings fit in with these ideas.

532 Taken together, this work suggests that OFC plays an executive role that is

533 complementary to that of executive dorsal structures, such as the dorsolateral prefrontal

534 cortex and the dorsal anterior cingulate cortex. We suspect that, while there are

535   differences between these regions, the differences may not be as simple as economic vs.

536   executive. Instead, they may have to do with variables like informational modality (Lara

537   et al., 2009).

538   Although several studies suggest that OFC does not contribute to rule-based

539   switching (Dias et al., 1996a, 1996b, 1997), one recent study suggests it may.

540   Specifically, a recent study in rodents indicates that OFC lesions disrupt switching

541   performance (Chase et al., 2012). Our current findings provide confirmatory evidence for

542   this idea and extend upon it in several ways. First, we show that switching is observed at

543   the single unit level, and that switching correlates are observed for both early and late

544   switches. Second, we show that the results are not limited to rodents. Third, our finding

545   that the strength of associative learning signals in OFC increases following late switch

546   signals further suggests that switch signals in OFC may play a role in guiding or initiating

547   stable target identification and selection. Finally, our finding of switch signals in OFC

548   provides a neural basis for a theory heretofore based solely on behavioral patterns

549   following lesions.

550   These results complement our recent recordings in DS and VS in the same task. In

551   our previous study (Sleezer and Hayden, 2016), we found correlates of switching in both

552   of these regions that resembles those reported here for OFC. We also found correlates of

553   associative encoding as well. One striking finding is the broad similarity across the

554   regions. In another study, we also found a similarity in rule encoding in all three regions

555   (Sleezer et al., 2016). This similarity is reminiscent of a different study using a different

556   task showing functional overlap between OFC and VS in decision processes related to

557   risky choice (Strait et al., 2016). These results endorse the idea that striatum and its

558   cortical inputs can, in many cases, have some overlap in their functions.

559   This is not to say that OFC and striatum were strictly identical, even when faced

560   with the same task. For example, we previously found that VS neurons demonstrate

561   context-dependent switch signals. In contrast, we did not find context-dependent switch

562   signals in OFC the present study. In addition, while general switch signals appear to be

563   stronger in VS when monkeys switch away from previously relevant rules, these signals

564   in OFC and DS are stronger when monkeys switch to newly relevant rules. These

565   findings suggest that VS may play a greater role in guiding the identification of newly

566   relevant rules when the correct rule is uncertain, while OFC and DS may play a greater

567   role in guiding stable rule selection once the correct rule is known.

568   The present results complement earlier research from several labs showing task-

569   switching signals in many brain regions, including OFC, striatum, parietal cortex, dorsal

570   anterior cingulate cortex, and even posterior cingulate cortex (Blanchard and Hayden,

571   2014; Hayden et al., 2010, 2011; Heilbronner and Hayden, 2016; Kamigaki et al., 2009;

572   Mansouri et al., 2006; Sleezer and Hayden, 2016). Taken together, this body of work

573   supports the idea that task-switching is both widespread and distributed, and provides

574   evidence against the idea that this function is the exclusive domain of a small and highly

575   specialized piece of brain tissue.

576   The associative encoding signals we found were manifest as an enhanced or

577   suppressed response to cues that matched the learned rule. This finding is intriguing

578   because it is the same type of modulation that has previously been linked to target

579   selection. Specifically, neurons in prefrontal and association cortex show significantly

580   enhanced or suppressed responses to to-be-chosen cues when they appear in a sequence

581   of options (Chelazzi et al., 1998; Hayden and Gallant, 2013; Lui and Pasternak, 2011;

582   Mazer and Gallant, 2003). Indeed, what we call rule here would, in such tasks, be called

583   feature-based attention.

584   The data do not identify the mechanisms by which neurons gain the ability to

585   discriminate the different offers and respond differently to the one that matches the

586   current rule. However, the fact that rule encoding and switching are observed in the same

587   set of neurons that participate in associative encoding raise an interesting possibility.

588   Perhaps the processes associated with learning the new rule cause a change in the

589   response properties of the OFC neurons. This change in responsiveness is observable in

590   the form of tonic changes in firing rate, and these changes are what we call rule encoding

591   (Sleezer et al., 2016). It is then further observable in the form of its direct effect: changes

592   in the responses of the neurons to the offers. This idea is borrowed from the literature on

593   memory-guided decision-making, and is consistent with the idea that rule-based and

594   memory-based decisions reflect common underlying mechanisms (Chelazzi et al., 1998;

595   Hayden and Gallant, 2013; Lui and Pasternak, 2011; Machens et al., 2005).

596
603
604 **Conflicts of interest**: The authors declare no competing financial interests.
605
606 **Author contributions:** BJS lead the design of the task and designed and performed all
607 analyses. BJS and BYH wrote the manuscript. GL and MDC supervised the data
608 collection.
609
610 **Data accessibility statement:** All data will be posted on Figshare and data and code will
611 be available at haydenlab.com/data.

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732

733 **FIGURES**

734
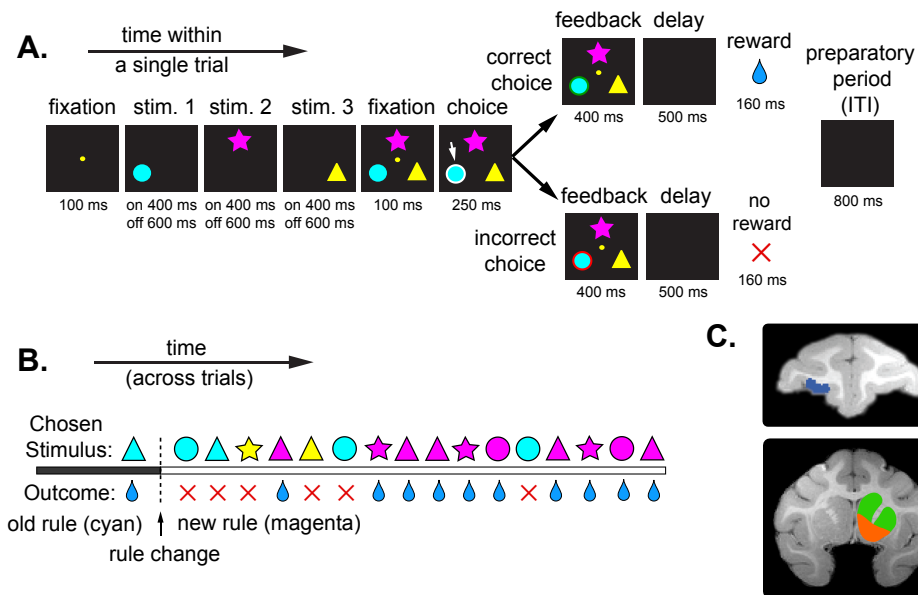
735 **Figure 1. Task and recording locations**
736 (A) Timeline of Wisconsin Card Sorting Task. (B) Example block. In this example, the
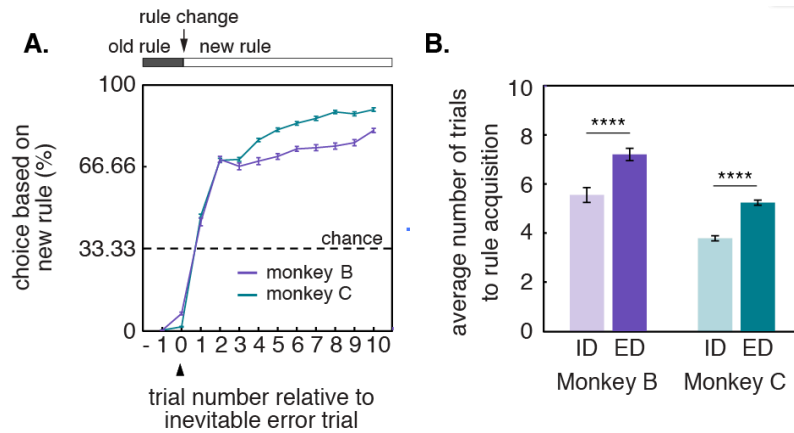737 correct rule is magenta. (C) Magnetic resonance image of subject C. Recordings were
738 made in orbitofrontal cortex (highlighted in blue). Comparison sites were in the ventral
739 striatum (highlighted in orange), and dorsal striatum (highlighted in green).
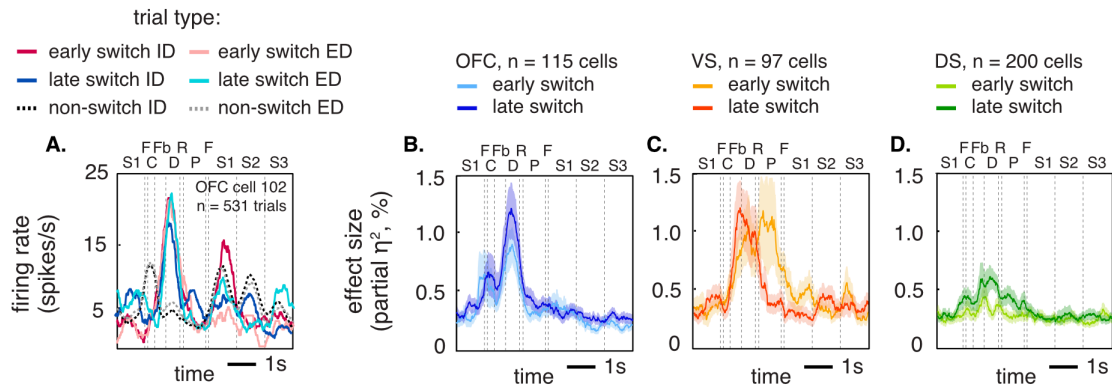740

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744
745 **Figure 2**. **Behavioral performance**
746 (A) Average choice accuracy on trials surrounding rule changes. (B) Average number of
747 trials to rule acquisition following intra-dimensional (ID) and extra-dimensional (ED)
748 rule changes.
749

750

751
Figure 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 intradimensional (ID) and extradimensional (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; S1, first stimulus appearance; S2, second stimulus appearance; S3, third
stimulus appearance. (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 6 from VS and 4 from DS that were excluded due
to an insufficient number of trials).

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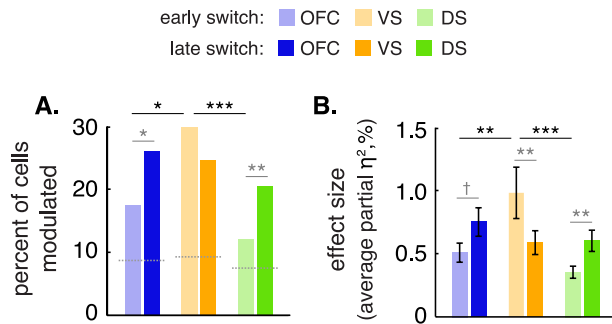
Figure 4: General switch modulation at early and late switch points
(A) Proportion of cells demonstrating a significant main effect of trial type at early and late switch points. (B) Proportion of variance explained (partial η2) by the main effect of trial type at early and late switch points. OFC (light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

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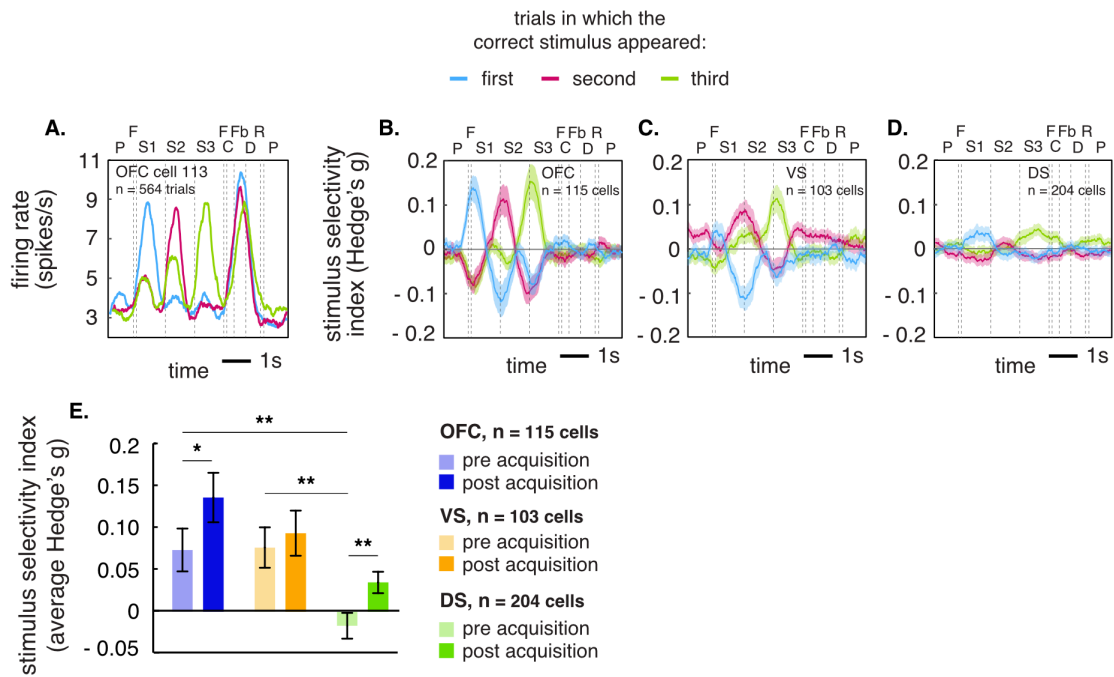
Figure 5: Correct stimulus selectivity (A) Average response of a single OFC neuron demonstrating selectivity for the presentation of the correct stimulus during the first (blue line), second (red line), and third (green line) presentation epochs. C, choice; Fb, feedback; D, delay; R, reward; P, preparatory 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 ($\pm$ SEM) during these epochs. Selectivity measures reflect averages across all neurons. * $P < 0.05$, ** $P < 0.01$.