

1 **TITLE: Amygdala input differentially influences prefrontal local field potential and single**
2 **neuron encoding of reward-based decisions**

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4 **RUNNING TITLE:** Amygdala influence on ERPs and prefrontal neurons

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6 **AUTHORS:** Frederic M. Stoll¹, Clayton P. Mosher¹, Sarita Tamang¹, Elisabeth A. Murray², and Peter H.
7 Rudebeck¹

8
9 **ADDRESS:**

10 ¹ Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA

11 ² Section on the Neurobiology of Learning and Memory, Laboratory of Neuropsychology, Building 49,
12 Suite 1B80, 49 Convent Drive, Bethesda, Maryland 20892, USA

13
14 **CORRESPONDENCE SHOULD BE ADDRESSED TO:**

15 Dr. Peter H. Rudebeck

16 Icahn School of Medicine at Mount Sinai

17 One Gustave L. Levy Place

18 New York, NY, 10029, USA

19 Tel: +1 212 824-9307

20 E-mail: peter.rudebeck@mssm.edu

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22 **FIGURES** 6

23 **TABLES** 0

24 **PAGES** 39

25 **WORDS** Abstract: 197 of 250 words

26 Significance statement: 118 of 120 words

27 Introduction: 496 of 650 words

28 Discussion: 2,048 of 1500 words

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30
31 **KEYWORDS:** Amygdala, reward, affect, emotion, orbitofrontal cortex, local field potential, medial
32 prefrontal cortex, decision making, choices, valuation, outcome.

33
34 **CONFLICT OF INTEREST:** None

35
36 **ACKNOWLEDGEMENTS:** This work was supported by a National Institute of Mental Health BRAINS
37 award to PHR (R01 MH110822), a young investigator grant from the Brain and Behavior Foundation
38 (NARSAD) to PHR, a Philippe Foundation award to FMS, seed funds from the Icahn School of
39 Medicine at Mount Sinai to PHR, and the Intramural Research Program of the NIMH. We thank Kevin
40 Blomstrom, Kevin Fomalont and Joshua Ripple for assistance with data collection, and James Fellows,
41 Ping Yu Chen and David Yu for help with surgery and histology.

42 **ABSTRACT**

43

44 Reward-guided behaviors require functional interaction between amygdala, orbital (OFC), and
45 medial (MFC) divisions of prefrontal cortex, but the neural mechanisms underlying these
46 interactions are unclear. Here, we used a decoding approach to analyze local field potentials
47 (LFPs) recorded from OFC and MFC of monkeys engaged in a stimulus-choice task, before
48 and after excitotoxic amygdala lesions. Whereas OFC LFP responses were strongly
49 modulated by the amount of reward associated with each stimulus, MFC responses best
50 represented which stimulus subjects decided to choose. This was counter to what we
51 observed in the level of single neurons where their activity was closely associated with the
52 value of the stimuli presented on each trial. After lesions of the amygdala, stimulus-reward
53 value and choice encoding were reduced in OFC and MFC, respectively. However, while the
54 lesion-induced decrease in OFC LFP encoding of stimulus-reward value mirrored changes in
55 single neuron activity, reduced choice encoding in MFC LFPs was distinct from changes in
56 single neuron activity. Thus, LFPs and single neurons represent different information required
57 for decision-making in OFC and MFC. At the circuit-level, amygdala input to these two areas
58 play a distinct role in stimulus-reward encoding in OFC and choice encoding in MFC.

59

60

61 **SIGNIFICANCE STATEMENT**

62

63 Dynamic interaction between amygdala, orbitofrontal (OFC) and medial frontal cortex (MFC) is
64 required for adaptive foraging. To determine the nature of these neural mechanisms, we
65 compared single neuron and local field potential responses (LFPs) in monkeys making reward-
66 guided choices both before and after amygdala lesions. LFP responses in OFC best
67 represented stimulus-reward values available on each trial, whereas MFC LFP responses
68 were closely associated with monkeys' choices. By contrast, single neurons, in both areas
69 primarily encoded stimulus-reward value. Removing amygdala input to OFC and MFC
70 heightened these differences between encoding of task variable by LFPs and single neurons.
71 Thus single neurons and LFPs in frontal cortex represent different aspects of decision-making
72 and are differentially influenced by the amygdala.

73

74 **INTRODUCTION**

75 Interaction between the prefrontal cortex (PFC) and limbic system is required for normal
76 patterns of affective behavior and cognition. In particular, reward-guided behaviors
77 require functional interaction between the amygdala and the orbital and medial divisions of the
78 PFC (OFC and MFC, respectively). For instance, lesions that disconnect the OFC and
79 amygdala are associated with impairments in updating the value of rewards (Baxter et al.,
80 2000). Similarly, disconnection of the MFC and amygdala leads to deficits in correctly
81 weighting the costs and benefits of different courses of action (Floresco and Ghods-Sharifi,
82 2007) as well as emotional responding (Felix-Ortiz et al., 2016). Disruption of functional
83 interaction between the PFC and limbic system, most notably the amygdala, is also associated
84 with a host of psychiatric disorders (Pezawas et al., 2005; Almeida et al., 2009; Dutta et al.,
85 2014). Determining how these brain areas interact at the neural level when one of the nodes of
86 the network is dysfunctional or damaged is therefore a key first step to understanding circuit-
87 level interactions.

88 We previously showed that in monkeys, bilateral excitotoxic lesions of the amygdala
89 attenuate reward-value signals of individual neurons recorded from OFC, but not MFC
90 (Rudebeck et al., 2013). The response properties of single neurons, however, only reflect the
91 local processing and output of an area (Einevoll et al., 2013). A more complete understanding
92 of this network might be informed by considering population-level activity and the inputs to an
93 area, which can be studied using local field potentials (LFPs). Indeed there is evidence that
94 there are differences in the types of information encoded by single neurons and LFPs
95 (Kreiman et al., 2006). For example, during a working memory task where object locations and
96 features had to be held online, differences emerged between the information encoded in spike
97 trains and LFPs in lateral frontal cortex (Lara and Wallis, 2014). In the context of the present
98 data, we previously reported that stimulus-reward encoding in OFC was independent of
99 concurrently presented options, suggesting that the activity of single neurons was not encoding
100 the monkeys' choices (Rudebeck et al., 2013). However, it is possible that choices might be
101 being encoded at the level of LFPs instead of the activity of single neurons in OFC and MFC.

102 To better determine the dynamics of reward-value and choice coding in the amygdala-
103 MFC-OFC network, we analyzed LFPs recorded from the OFC and MFC in three monkeys
104 engaged in a stimulus-choice task. Recordings were made both before and after excitotoxic

105 lesions of the amygdala. Specifically we looked for signals that were associated with encoding
106 stimulus-reward associations and monkeys' choices and compared this to encoding by single
107 neurons. Here we report that prior to lesions of the amygdala we could, mirroring the spike
108 data, decode stimulus-reward values in OFC to a greater extent than MFC. By contrast, the
109 choice that would ultimately be taken was more strongly encoded in MFC than OFC.
110 Removing amygdala input led to reduced signals in OFC and MFC related to stimulus values
111 and choices, respectively.

112 **METHODS**

113 **Subjects**

114 Three adult male rhesus macaques (*Macaca mulatta*), monkeys H, N and V, served as
115 subjects; they weighed 8.5, 8.0 and 8.4 kg, respectively, at the beginning of training. Animals
116 were pair housed when possible, kept on a 12-h light dark cycle and had access to food 24
117 hours a day. Throughout training and testing each monkey's access to water was controlled for
118 6 days per week. All procedures were reviewed and approved by the NIMH Animal Care and
119 Use Committee.

120

121 **Apparatus**

122 Monkeys were trained to perform a two-choice visually guided task for fluid reward. All
123 trial events and timing were controlled using the open source NIMH Cortex program
124 (<ftp://helix.nih.gov/lsn/cortex/>). Eye position and pupil size were monitored and acquired at 60
125 frames per second with an infrared oculometer (Arrington Research, Scottsdale, AZ).

126 During training and testing monkeys sat in a primate chair with their heads restrained.
127 Directly in front of the chair, three buttons were spaced horizontally 7 cm apart (center to
128 center). These buttons had embedded infrared sensors to detect contact.

129

130 **Task and behavior**

131 Three monkeys were trained to perform a choice task for fluid rewards. On each trial,
132 monkeys had to press and hold a central button and then fixate a central light spot for 0.5–1.5
133 s (**Fig. 1A**). Two visual stimuli, associated with different amounts of fluid reward, were then
134 sequentially presented. The onset of the second stimulus (S2) followed the onset of the first
135 (S1) by 1.0 s and, by random selection, one stimulus appeared to the left of the central spot
136 and one appeared to the right. We presented the two stimuli for choice sequentially in an
137 attempt to separate the valuation process of the individual items. Stimuli were randomly
138 selected from a pool of ten stimuli (**Fig. 1A**). Monkeys had learned that each of the stimuli was
139 associated with a fixed amount of fluid — 0.8, 0.4, 0.2, 0.1 or 0 ml of water — two stimuli for
140 each quantity. A total of 14 pairs were tested (S1/S2 values): 0/0.1 ml, 0/0.2 ml, 0.1/0 ml,
141 0.1/0.2 ml, 0.1/0.4 ml, 0.2/0 ml, 0.2/0.1 ml, 0.2/0.4 ml, 0.2/0.8 ml, 0.4/0.1 ml, 0.4/0.2 ml, 0.4/0.8
142 ml, 0.8/0.2 ml, and 0.8/0.4 ml. All sessions also included pairs with stimuli associated with the

143 same reward values for S1 and S2 (i.e. 0.1/0.1 ml, 0.2/0.2 ml and 0.4/0.4 ml) on 10% of the
144 trials. Given the limited number of these trials, they were not included in the present analyses.
145 After a variable delay of 0.0–1.5 s, the central spot brightened as a “go” signal, and the
146 monkeys could then choose between the two stimuli by reaching to the left or right response
147 button. The amount of fluid reward corresponding to the chosen stimulus was delivered 0.5 s
148 later.

149

150 **Surgical procedures, neural recordings, imaging and histological reconstruction**

151 For detailed information on surgical procedures, see Rudebeck et al. (2013). In brief,
152 each monkey was implanted with a titanium head restraint device and then, in a separate
153 surgery, a plastic recording chamber was placed over the exposed dura mater of the left frontal
154 lobe. After the preoperative recordings were completed, MRI-guided bilateral excitotoxic
155 lesions of the amygdala were made in each monkey.

156 Potentials from single neurons and local field potentials were recorded with tungsten
157 microelectrodes (FHC, Inc. or Alpha Omega, 0.5-1.5 M Ω at 1 KHz) advanced by an 8-channel
158 micromanipulator (NAN instruments, Nazareth, Israel) attached to the recording chamber.
159 Spikes from putative single neurons were isolated online using a Plexon Multichannel
160 Acquisition Processor and later verified with Plexon OffLine Sorter on the basis of principal-
161 component analysis, visually differentiated waveforms and interspike intervals. Neurons were
162 isolated before monkeys were engaged in any task. Other than the quality of isolation, there
163 were no selection criteria for neurons. Local field potentials were recorded using the same
164 system and digitized at 1kHz. Recordings were referenced on guide tubes containing the
165 electrodes and in contact with the dura.

166 OFC recordings were made on the ventral surface of the frontal lobe between the lateral
167 and medial orbital sulci, roughly corresponding to Walker’s areas 11 and 13. All OFC
168 recordings were between +27 and +38 mm anterior to the interaural plane. Recording locations
169 in MFC were primarily in the dorsal bank of the cingulate sulcus (areas 9 and 24), although
170 some sites were in the ventral part of the fundus of the cingulate sulcus. MFC recordings were
171 made between the anterior tip of the cingulate sulcus (approximately +38 mm) and +24 mm.

172 Both before and after lesions of the amygdala, recordings were made in overlapping
173 regions in each of the three monkeys (**Fig. 1C**). Recording sites were verified by T1-weighted

174 MRI imaging of electrodes after recording sessions and by placing electrolytic marking lesions
175 (15 μ A direct current for 25 seconds, electrode positive) at selected locations in OFC after
176 recordings had been completed (see Rudebeck et al., 2013). At the conclusion of the study,
177 monkeys were deeply anesthetized and transcardially perfused with saline (0.9%) followed by
178 formalin. The brains were removed, sectioned in the coronal plane, Nissl-stained and mounted
179 onto glass slides for visual inspection.

180 The extent and location of the amygdala lesions was assessed using T2-weighted MRI
181 conducted within one week of each surgery (e.g. **Fig. 1B**, top row). Lesion volume was then
182 confirmed from histology (e.g. **Fig. 1B**, bottom row). The locations and extents of the lesions
183 were largely as intended. There was near complete cell loss in all nuclei in the amygdaloid
184 complex (mean = 95.5%). Inadvertent damage was evident in the entorhinal and perirhinal
185 cortex, portions of the ventral claustrum, and anterior hippocampus (see Rudebeck et al.,
186 2013). Importantly, with the possible exception of the entorhinal cortex, this unintended
187 damage was slight (e.g., extending less than 2 mm in antero-posterior extent) and asymmetric
188 between the hemispheres. Finally, one monkey (Monkey N) sustained an infarction in the
189 dorsal striatum, bilaterally. Overall, damage in all three monkeys consistently centered on the
190 amygdala, bilaterally.

191

192 **Electrophysiological data processing**

193 Data analysis was performed offline using the FieldTrip toolbox (Oostenveld et al.,
194 2011) and custom Matlab scripts (Matlab, MathWork Inc.).

195 Preoperatively, a total of 234 and 155 LFPs were recorded from 3 monkeys in the OFC
196 and MFC respectively. Following the bilateral amygdala lesions, we recorded 324 and 204
197 more LFPs in the OFC and MFC, respectively. To avoid biasing our results, we required a
198 minimum of 5 trials for each possible pair of S1 and S2 values, and we did not include trials in
199 which there was no delay between S2 presentation and the Go signal (i.e., delay needed to be
200 at least 500 ms or more). A few recordings did not meet the trial number requirement and were
201 therefore excluded from further analyses (PreOp: OFC=12/234, MFC=11/155 sites; PostOp:
202 OFC=26/324, MFC=20/204 sites).

203

204

205 *Pre-processing*

206 Here, our analyses focused specifically on the event-related potentials (ERPs) evoked
207 by stimuli presentation. We did not report data on possible oscillatory activities as no clear
208 modulations have been observed apart from the direct ERP signature in the low frequency
209 spectrum (data not shown). For each recorded site, the LFP signal was first band-pass filtered
210 from 1 to 30 Hz and then aligned around S1 presentation (from -3 to +3 s). We then
211 normalized the LFP signal for each individual trial relative to a baseline period (-0.6 to -0.1 s
212 before S1 onset), and derived a z-score. Finally, we sub-sampled our dataset using a sliding
213 window of 50 ms stepped in 10 ms increments.

214

215 *ERPs latency and amplitude*

216 The latency of the different ERP components was extracted for each trial by detecting
217 peaks with amplitude greater than 0.3 sd and with a minimal distance restriction between 2
218 consecutive peaks of 75 ms (using the Matlab function *findpeaks.m*). Latencies for negative
219 components were considered only if they fell between 200 and 350 ms relative to stimulus
220 onset, whilst latencies for the later positive components needed to be between 300 and 550
221 ms. These time windows were defined based on the visual inspection of all the detected
222 latencies. We then used Kruskal-Wallis (KW) tests to assess differences between conditions.

223 Finally, differences in ERP amplitudes between areas (OFC vs. MFC) or relative to
224 amygdala lesions (PreOp vs. PostOp) were also extracted using KW tests at each time bin.

225

226 *ANOVA on individual LFPs*

227 To assess how the different factors of our task modulated the amplitude of the trial-by-
228 trial ERP signals, we first fitted a sliding hierarchical ANOVA model to the normalized ERP
229 activity of each recorded LFP. Our model included factors of S1 reward value (five levels), S2
230 reward value (five levels), S1 identity (two levels), S2 identity (two levels) and S1 presentation
231 side (two levels). S1 and S2 identity factors were nested within S1 and S2 reward value,
232 respectively. P-values extracted for each factor were subjected to a specific threshold to
233 account for multiple testing over time (see *Statistical procedures* below). To complement our
234 time-resolved observations, we also extracted the overall number of significant sites for 3
235 different periods: a reference period (REF: -1000 to 0 ms, relative to S1 onset), the S1 period

236 (0 to 1000 ms) and S2 period (1000 to 2000 ms). Finally, to extract the latency of stimulus
237 value or stimulus side encoding, we detected the first significant time bin during the time period
238 considered (S1 or S2 periods). As before, differences in latencies were evaluated using KW
239 tests.

240

241 *Statistical procedures applied to individual LFPs analyses*

242 Individual sites were considered as significantly encoding a task factor if they
243 discriminated that factor for 6 consecutive bins (covering a time period of 100ms) with a
244 threshold of $p < 0.01$. This threshold was applied to all time-resolved analyses (e.g. hierarchical
245 ANOVA and KW test on ERP amplitude over time).

246 We also assessed statistical significance by computing two-tailed Chi-square tests with
247 Yates' correction when testing for differences in the proportion of sites encoding a given factor,
248 either when comparing areas (OFC vs. MFC) or periods (PreOp vs. PostOp).

249

250 *Relationship to single neuron recordings*

251 We previously reported the encoding properties of the individual neurons recorded in
252 this task (Rudebeck et al., 2013; PreOp: OFC=280; MFC=233; PostOp: OFC=317; MFC=237
253 neurons). Here, we were able to assess whether there was a relationship between neurons
254 and ERPs as the same analyses were applied with the two datasets. In particular, we tested
255 whether neurons and ERPs recorded simultaneously on the same electrode (i.e., at a similar
256 site) were modulated by the different factors in a similar manner. To do this, we extracted the
257 proportion of sites where, based on the hierarchical ANOVAs, both neurons and ERPs showed
258 significant encoding of S1 or S2 values. To test if these proportions were significant (e.g.,
259 whether neurons recorded on an electrode showing significant ERP modulations were more
260 likely, or not, to also encode the same factor), we used permutation testing, by shuffling the
261 labels assigned to the different neurons (significant or not) 1000 times. This procedure enabled
262 us to take into account the relative number of both significant LFP sites and neurons, and
263 therefore avoid any confounds.

264 We also looked at the correlation between the variance explained by the S1 or S2
265 values from the hierarchical ANOVAs in recordings where both neurons and ERPs (recorded
266 on the same electrode) showed significant modulations.

267

268 *Population decoding of choices and stimulus reward values*

269 We applied multiple linear regressions to decode information from population ERP
270 activity vectors in both regions. This method assesses the capability of a linear readout to
271 extract a given response variable (e.g., choosing S1 or S2) from trial-by-trial ERP responses of
272 the whole population. In this procedure, a Tikhonov regularization procedure was used to
273 minimize the sum of squared errors and thus avoid overfitting by placing constraints on
274 regression coefficients.

275

276 To extract an accurate estimate of the classifiers' performance, we included only sites
277 with 3 repetitions of each of the 14 possible S1/S2 pairs. We also only included the same
278 number of predictors (i.e., recording sites) for both areas, as well as for pre- and post-operative
279 recordings. This was done so that we could directly compare the strength of coding between
280 the different recording populations, as more predictors might spuriously increase the accuracy
281 (see for example, Astrand et al., 2014). Applying these criteria meant that the datasets used to
282 extract choice-predictive activity contained the ERP signals recorded at 47 randomly selected
283 sites during 42 randomly selected trials. Our training set contained 2 instances of each
284 possible pair (i.e., 28 trials), and our testing set contained the remaining third of the data (14
285 trials). It is important to note that classifiers did not have any information relative to the S1 or
286 S2 reward values, nor did it have information regarding S1/S2 pair identities. To determine the
287 regularization parameter, we further subdivided the training partition to perform a 5-fold cross-
288 validation procedure. The sum of squared errors (SSE) across the five folds was computed for
289 each regularization parameter tested. The value with the lowest SSE was then selected and
290 used to train the classifier on the whole training partition. We then tested the classifier on the
291 remaining testing partition, which contained the 14 trials. This meant that the testing partition
292 was never used during the optimization and/or training of the classifier. Given our under-
293 sampling procedure, an unbiased readout of performance was extracted by randomly selecting
294 trials and performing all computations 1000 times, which generated a vector of 1000 estimated
295 choices for each of the 14 S1/S2 pairs. We then used the average choice binary output over
296 these 1000 computations. Classifiers were trained and tested at each time bin.

297 Chance levels and statistical significance were defined using a permutation approach.

298 Specifically, we randomly permuted monkeys' choices 1000 times without removing the
299 relationship between ERP signal and the different S1/S2 pairs and conducted the same
300 decoding approach described above. Importantly, the temporal structure of the ERP signal
301 also remained unaffected by the permutation procedure. All subsequent computations were
302 done in a similar manner to that described above. Finally, classifiers' performances were
303 averaged across the 14 S1/S2 pairs for each permutation and used to assess statistical
304 significance.

305

306 The same analysis methods were also applied to the recordings of single neuron activity
307 (OFC and MFC neurons, both before and after lesions). Here we used the activity of a
308 subsample of 47 randomly selected neurons for each population of neurons from OFC and
309 MFC to predict monkeys' choices. Just as we had done for the ERP analyses, described
310 above, we first used the average firing rate for 50 ms bins each 10 ms step. With such time
311 averaging, we were almost unable to decode choices from either OFC (PreOp=1/14 and
312 PostOp=3/14 significantly decoded S1/S2 pairs) or MFC (PreOp=2/14 and PostOp=0/14).
313 However, it is unclear if this null result was due to a limitation inherent to the nature of the
314 signal (i.e., spiking activity is a point-process, as opposed to the continuous ERP signal) or a
315 true absence of encoding. Our objective being the comparison between neuronal and ERP
316 populations, we therefore reported the decoding performance using longer bins of 200 ms for
317 neuronal populations, a common window size used to analyze neuronal activity (e.g.
318 Rudebeck et al., 2013; Lara and Wallis, 2014; Stoll et al., 2016).

319

320 We report the results of our time-resolved approach, but also after averaging 2 time
321 periods (t_1 , from 300 to 400 ms; and t_2 , 1250 to 1350 ms, relative to S1 onset). These time
322 windows were defined to match the ERPs components and based on the overall decoding
323 performance. Statistical estimates for these time windows were extracted by averaging the
324 results of the 1000 permutations over time in a similar manner. Differences between recorded
325 populations were assessed using Chi-square tests with Yates' corrections. We used a
326 threshold of $p < 0.05$ after correcting for multiple tests.

327 To further compare the decoding performance for the different conditions, we fitted a
328 mixed-effect logistic regression on the output of the classifiers (average number of S1 choices

329 out of the 1000 permutations during time bin t_2). The full model included fixed-effect for all
330 three categorical fixed-effect factors (Type: neurons vs. LFPs; Area: OFC vs. MFC, Surgery:
331 PreOp vs. PostOp) and all interactions. Also, S1/S2 pairs were dummy-coded and included as
332 a random-effect factor, allowing changes in intercept (i.e., choosing more S1 or S2 depending
333 on their respective values). Thus, this model compared the overall performance of the
334 classifiers independently of the S1/S2 pair considered. Model coefficients were derived by
335 maximum likelihood estimation using Laplace approximation. We report the output from the full
336 model in the results given that a similar model without the 3-way interaction (Type x Area x
337 Surgery) was significantly less adapted to fit our dataset (Log-Likelihood test, LR=37.6,
338 $p=8.7e-10$). We also validated our model by ensuring that normalized residuals plotted against
339 fitted values and factors did not show inhomogeneity.

340

341 Finally, we investigated whether it was also possible to extract stimulus-reward values
342 using population decoding methods. Here, we applied support vector machine (SVM)
343 algorithms with Gaussian kernel on the ERP signals recorded from 47 randomly selected
344 channels. This procedure was performed to extract S1 and S2 values using the average ERP
345 amplitude during time bins t_1 and t_2 , respectively, for each trial and each predictor (recording
346 sites). We used the ERP activity of 10 randomly selected trials for each S1 or S2 values (for a
347 total of 50 trials). Readout performances were extracted by randomly selecting trials and
348 performing all computations 100 times. We then averaged the decoding performance and
349 compared it with a set of 1000 randomly-generated permutations.

350

351 *Experimental Design and Statistical Analysis*

352 Three adult male rhesus macaques (*Macaca mulatta*) were used in this study.
353 Recordings in OFC and MFC were made in each monkey before and after amygdala lesions.
354 This means that each monkey served as its own control. Statistical comparisons (OFC vs.
355 MFC, PreOp vs. PostOp, ERPs vs. single neurons) were performed at the level of the
356 population as well as for each subject when possible (see above). For count-based data
357 statistics we used chi-square tests and where appropriate, ANOVAs, Kruskal-Wallis or
358 permutation tests for continuous data.

359

360 **RESULTS**

361

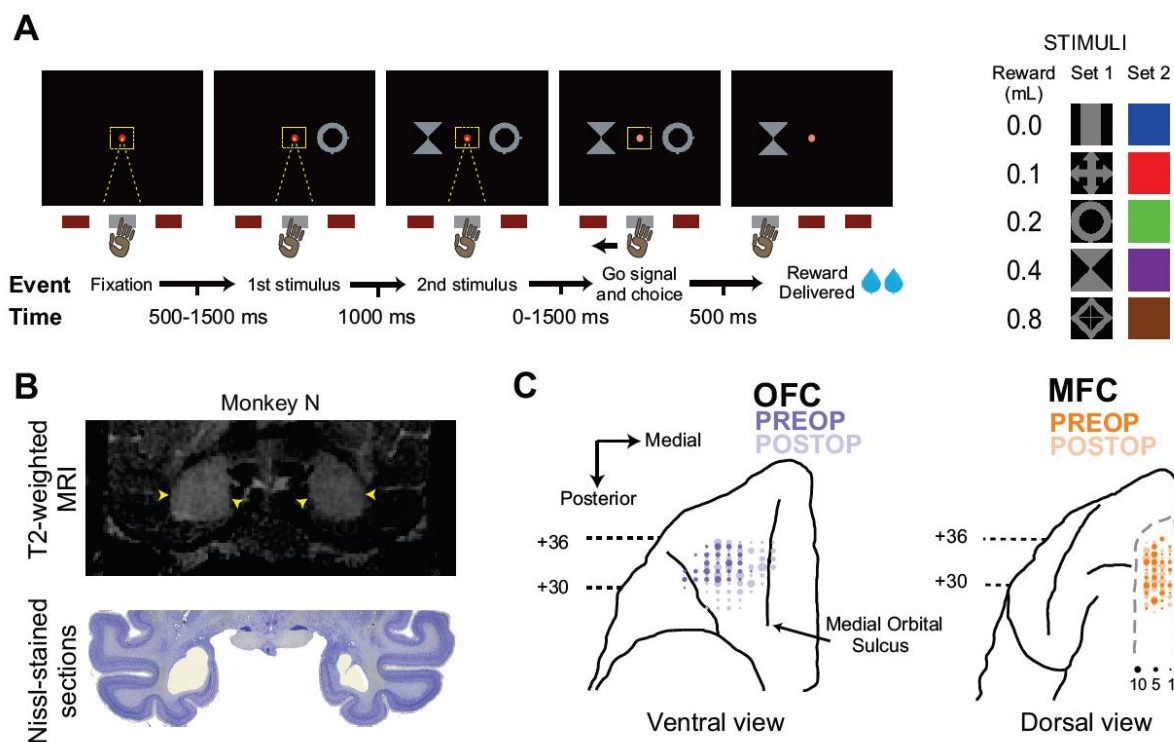
362 ***Task and Behavioral performance***

363 Three monkeys were trained to perform a two-choice reward-guided task for fluid
364 rewards (see Methods, **Fig. 1A**). On each trial, monkeys had to choose one of two visual
365 stimuli, associated with different amounts of reward, that were sequentially presented. Stimuli
366 were randomly selected from a total of ten stimuli, each one associated with a fixed amount of
367 fluid (0, 0.1, 0.2, 0.4 or 0.8 ml, two stimuli for each quantity, **Fig. 1A**).

368 Behavioral performance during the task has been described in detail elsewhere
369 (Rudebeck, et al., 2013). In brief, each monkey chose the stimulus associated with the
370 greatest amount of reward on nearly every trial (>95%). Bilateral excitotoxic lesions of the
371 amygdala did not alter monkeys' performances; monkeys continued to select the stimulus
372 associated with the greatest amount of reward on more than 95% of trials. Although it might
373 seem counterintuitive, the task was specifically designed, based on prior work (Izquierdo and
374 Murray, 2007), to ensure that performance would not be affected by the lesions. This aids the
375 interpretation of the results; if there had been a behavioral deficit postoperatively it would be
376 difficult to interpret any postoperative changes in neural activity, as effects could be due to
377 either the lesion or the change in behavior. In addition, we confirmed that the lesions were
378 effective in a separate task that required the learning of new stimulus-reward associations
379 (Rudebeck et al., 2017).

380 Choice response times, defined as the amount of time between the go signal being
381 delivered and the monkey lifting its hand to make a movement, were modulated by the amount
382 of reward that the monkeys would receive for making a particular choice ($p < 0.01$, see
383 Rudebeck et al., 2013). Lesions of the amygdala did not consistently alter the effect of value
384 on monkeys' choice latencies ($p > 0.3$).

385



386

387 **Figure 1. Two-choice reward-guided task and recording positions** (a) On each trial, two stimuli
 388 were sequentially presented on the right and left side of the screen (randomized from trial to trial) while
 389 monkeys maintained central fixation. After a random delay, the central fixation spot changed color, and
 390 monkeys were allowed to select with their hand the stimulus of their choice. The reward amount
 391 associated with the selected stimulus was then delivered. Two sets of stimuli were used (shapes or
 392 color), each containing 5 different stimuli associated with 0, 0.1, 0.2, 0.4 or 0.8 ml of water. (b) T2-
 393 weighted MRI (top) and post-mortem Nissl-stained section (bottom) illustrating the extent of the bilateral
 394 excitotoxic amygdala lesion performed in one representative monkey (see Rudebeck et al., 2013 for a
 395 complete description). (c) Preoperative (dark colors) and postoperative (light colors) recording locations
 396 in both the OFC (left) and the dorsal bank of the MFC (right). Dot sizes indicate the number of
 397 recordings for each site. Antero-posterior values indicate distance in mm relative to the ear bars.

398

399

400 **Encoding of stimulus value in the ERP**

401 While monkeys performed the task, we recorded both single neurons and local field
 402 potentials in the OFC and MFC. Here, we report the analysis of a total of 366 LFPs (OFC=222
 403 sites, MFC=144 sites) recorded from the 3 monkeys before bilateral excitotoxic lesions of the
 404 amygdala (monkey N: 81 OFC, 77 MFC; monkey H: 20 OFC, 56 MFC; monkey V: 121 OFC,
 405 11 MFC). The presentation of each stimulus (S1 or S2) was associated with a strong ERP
 406 response at both OFC and MFC recording sites (**Fig. 2A,D**). The early visual responses
 407 induced by the presentation of S1 were followed by two main components: a negativity
 408 peaking around 250 ms (average \pm std, OFC = 274.4 ± 28 ms; MFC = 259.4 ± 21 ms) followed

409 by a late positivity around 400 ms (OFC = 433 ± 52 ms; MFC = 411.6 ± 48 ms). Both the early
410 negativity and late positivity were significantly earlier in the MFC compared to the OFC (KW
411 test; negativity: $H=21.04$, $p=4.49e-6$; positivity: $H=15.46$, $p=8.43e-5$). The presentation of S2
412 elicited similar ERP responses to those following S1.

413

414 To characterize the relationship between stimulus values and the different components
415 of the ERP responses, we performed a sliding hierarchical ANOVA based on single-trial
416 responses around the presentation of both S1 and S2 (see Methods). Stimulus value coding
417 was found in both OFC and MFC ERPs, in particular at the time of the described early
418 negativity and later positivity of the ERP responses (**Fig. 2B**). No difference in the latency of
419 value coding between OFC and MFC was found for the encoding of S1 values (average \pm std,
420 OFC = 282.4 ± 102 ms; MFC = 275.9 ± 121 ms; KW test, $H=0.03$, $p=0.8606$). However, S2
421 value was encoded earlier in OFC compared to MFC (average \pm std, OFC = 237.7 ± 106 ms;
422 MFC = 278.7 ± 129 ms; KW test, $H=8.47$, $p=0.0036$).

423 To further quantify the contribution of OFC and MFC to stimulus reward-value coding,
424 we looked at the proportion of sites encoding each factor during 3 time periods around
425 stimulus presentation (Reference period: -1 to 0 s; S1 period: 0 to 1s; S2 period: 1 to 2 s, all
426 relative to S1 onset, **Fig. 2C**). During the S1 period, the encoding of S1 values was observed
427 at more OFC sites than MFC sites (OFC=118/222, 53.15%; MFC=62/144, 43.05%; $\chi^2=3.56$,
428 $p=0.059$). A similar pattern was seen during the S2 period (OFC=129/222, 58.1%;
429 MFC=58/144, 40.2%; $\chi^2=11.11$, $p=0.0009$). However, only monkeys H and N displayed a
430 consistent difference between areas for S1 and S2 values (**Fig. 2D**). No differences were
431 observed in monkey V, although this is likely due to the small number of recorded sites in the
432 MFC ($n=11$). Finally, a small percentage of sites also encoded the value of S1 during the S2
433 period, and again this was higher in OFC (OFC=20.7% and MFC=9%, $\chi^2=7.988$, $p=0.0047$,
434 **Fig. 2C**). It should be noted that S1 remained on the monitor screen at the time of S2
435 presentation. The percentage of sites that coded S1 value during the S2 period was
436 consistently higher in the OFC than the MFC of all three monkeys (**Fig. 2D**).

437 Recording sites showing an encoding of the value of S1 in the ERPs during S1 period
438 were highly likely to encode the value of S2 during the S2 period in both the OFC ($n=90/118$,
439 76.3%) and the MFC ($n=33/62$, 53.2%). The encoding of both S1 and S2 values in similar sites

440 was significantly greater in the OFC than the MFC ($\chi^2=8.939$, $p=0.0028$). Qualitative
441 inspection of the data did not reveal any topological differences related to stimulus value
442 coding across the anatomical extent of either OFC or MFC.

443 Importantly, the encoding of reward values can also be extracted using population
444 measures, by applying nonlinear Support Vector Machines (SVM) with a Gaussian kernel.
445 Both OFC and MFC populations discriminated S1 values when the stimulus was presented
446 (OFC: decoding rate \pm std = 60.9 ± 11.1 %, $p=0.001$; MFC: decoding rate = 49.4 ± 10.4 %, $p=0.001$;
447 average permutation chance level being 20%), with higher decoding performance in
448 the former (KW test, $H=45.92$, $p=1.23e-11$). A significant discrimination of S2 values was also
449 observed (OFC: 58 ± 10.5 %, $p=0.001$; MFC: 47 ± 9.5 %, $p=0.001$), again with better
450 performance in the OFC population than the MFC one (KW test, $H=47.2$, $p=6.35e-12$).

451 Additional analyses revealed that the side on which the stimulus was presented
452 (randomized from trial to trial, see Methods) explained a sizable proportion of the ERP
453 responses (**Fig. 2C**). While there was no apparent difference between OFC and MFC during
454 S1 presentation (OFC=55.8% and MFC=63.8%, $\chi^2=2.33$, $p=0.13$), we found significant
455 differences during S2 presentation (OFC=59.9% and MFC=44.4%, $\chi^2=8.40$, $p=0.0037$).
456 However, large discrepancies between monkeys, both during S1 (monkey H: OFC=9/20,
457 MFC=21/56; monkey N: OFC=76/81, MFC=71/77; monkey V: OFC=39/121, MFC=0/11) and
458 S2 period (monkey H: OFC=6/20, MFC=12/56; monkey N: OFC=75/81, MFC=50/77; monkey
459 V: OFC=52/121, MFC=2/11), mean that this result should be treated with caution. Contrary to
460 the encoding of stimulus value, the modulation of the ERP by the stimulus side was almost
461 exclusively observed during the initial ERP responses (stimulus side discrimination peaked at
462 225 ms and 215 ms after S1 onset for OFC and MFC respectively).

463 We also found that the encoding of the identity of S1 or S2, either color or shape stimuli,
464 was only apparent in the OFC (S1=33/222, 14.8%; S2=34/222, 15.3%). Only ~5% of sites in
465 MFC signaled stimulus identity (S1=8/144, 5.5%; S2=7/144, 4.8%). This was lower than in
466 OFC ($\chi^2>7.6$, $p<0.0058$) and also no different to chance levels.

467 In summary, these analyses of the ERPs from OFC and MFC reveal that: 1) OFC
468 exhibited more prevalent and reliable encoding of stimulus-reward values compared to MFC;
469 2) stimulus location modulated the early ERP component in both OFC and MFC; 3) sites in the
470 OFC and MFC encoding of the value of S1 during the S1 period were highly likely to also

471 encode the value of S2 during the S2 period, and 4) stimulus identity encoding was only
472 evident in OFC, not MFC.

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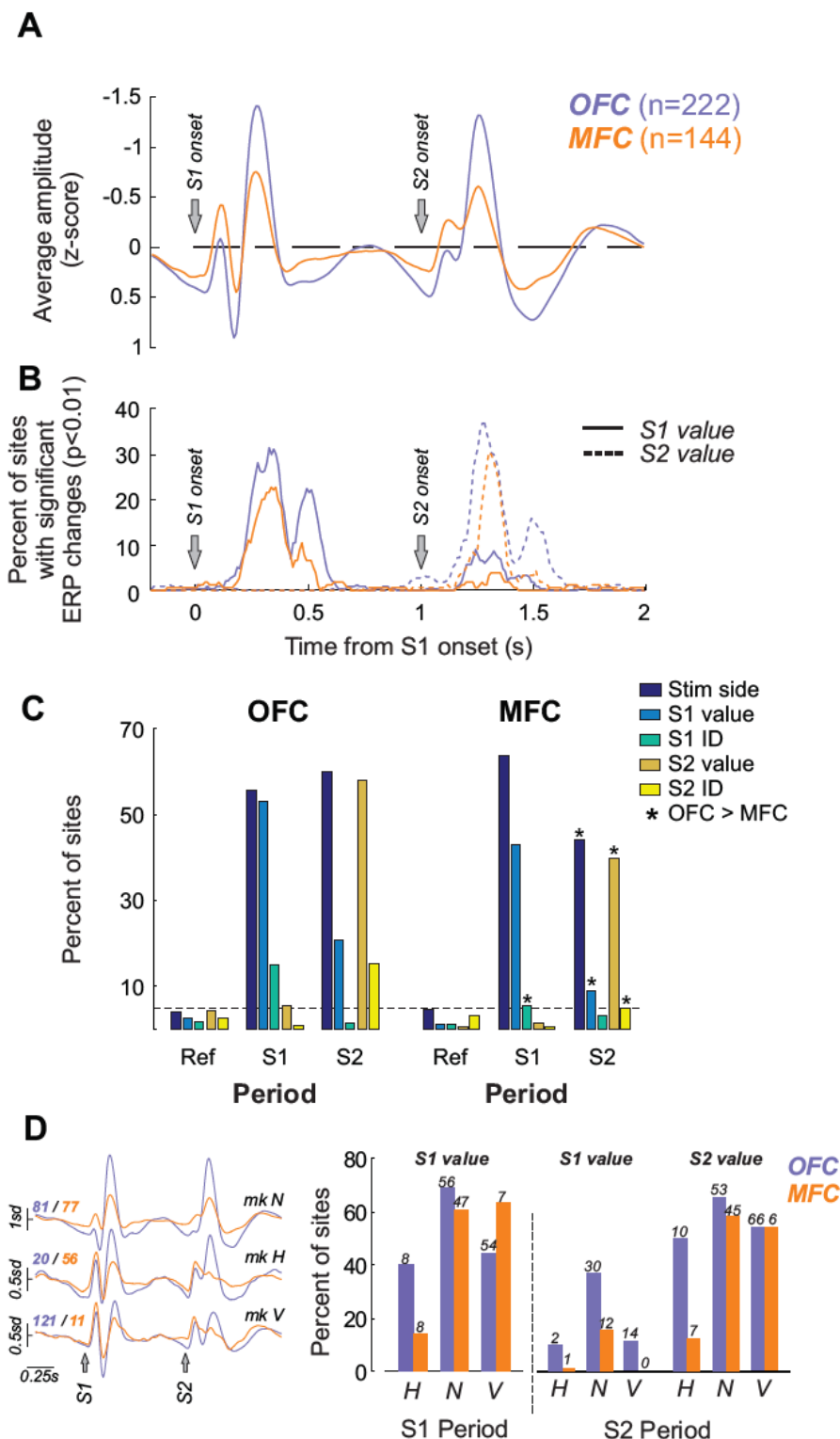
474 ***Comparison of ERPs and single-unit encoding of stimulus value***

475 As reported by Rudebeck et al (2013), single units recorded in both OFC and MFC
476 during performance of the task encoded stimulus values, i.e., the anticipated value of the
477 reward outcome associated with a stimulus. Here, we investigated whether ERPs encoding
478 stimulus values were more likely to be recorded on electrodes where the spiking activity of
479 single neurons also encoded stimulus values. In total, 83.3% and 87.5% of analyzed LFP sites
480 in OFC and MFC respectively (OFC=185/222 and MFC=126/144 sites) contained at least one
481 well-isolated and simultaneously recorded single neuron. When we considered only these
482 sites, similar effects to the ones previously described were found for the percentage of sites
483 showing ERP encoding of S1 and S2 value (S1 value during S1 period, OFC=50.8% and
484 MFC=42.06%; and S2 value during S2 period, OFC=58.38% and MFC=39.68%). We then
485 looked at whether single neurons simultaneously recorded at these sites also encoded
486 stimulus values. We found that single neurons encoding either the value of S1 (OFC=73/185
487 and MFC=36/126 neurons) or S2 (OFC=58/185 and MFC=22/126 neurons) were no more
488 likely to be recorded at sites where ERPs also represented stimulus values. This was true for
489 both for S1 (OFC=37/73, 50.7% and MFC=17/36, 47.2%) and S2 (OFC=37/58, 63.8% and
490 MFC=9/22, 40.9%). None of these proportions were greater than expected by chance
491 (permutation tests $p > 0.18$). We found a similar pattern of results when we compared the
492 explained variance related to S1 and S2 values encoded by either single neurons or ERPs (S1
493 value: OFC, $r=0.08$, $p=0.62$; MFC, $r=0.15$, $p=0.57$; S2 value: OFC, $r=0.25$, $p=0.13$; MFC,
494 $r=0.32$, $p=0.44$). Therefore, our findings demonstrate that there is no direct relationship
495 between the encoding of value in single neurons and ERPs simultaneously recorded at the
496 same site in this task.

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501 **Figure 2. Stimulus-reward modulation of ERPs in the OFC and MFC** (a) Grand average normalized
 502 ERP responses induced by the presentation of S1 and S2 in the OFC (purple) and MFC (orange).
 503 Black lines indicate significant differences in power between OFC and MFC (KW test, $p < 0.01$). (b)
 504 Time-resolved percentage of significant sites (hierarchical ANOVA thresholded at $p < 0.01$, see

505 Methods) encoding either S1 (solid lines) or S2 values (dashed lines) in both OFC and MFC. (c)
506 Percentage of sites in the OFC (left) and MFC (right) showing a significant effect of one of the factors in
507 the hierarchical ANOVA for the 3 different time periods (Ref: -1 to 0 s; S1: 0 to 1 s; S2: 1 to 2 s). Stars
508 indicate a significant difference between OFC and MFC for the factor considered (Chi-square tests,
509 $p < 0.05$). (d) Individual monkeys' normalized ERP responses (left) and percentage of sites in the OFC
510 and MFC showing a significant effect of S1 and S2 values either during S1 or S2 periods (right).
511 Numbers on top of bars indicate the numbers of significant sites. H, N and V represent the three
512 monkeys.

513

514 ***Population encoding of choices during stimuli presentation***

515 To further explore how reward-value signals in OFC and MFC might contribute to choice
516 behavior, we applied multiple linear regressions to decode monkeys' choices on each trial from
517 ERP population activity vectors in both regions (see Methods and **Fig. 3**). Here when we refer
518 to the choice, we mean the option, either S1 or S2 that the monkey will subsequently choose
519 on each trial. Linear classifiers were trained on a subset of trials to discriminate the 2
520 categories: choosing S1 (=1) or choosing S2 (=−1). The training set contained 2 instances of
521 each of the 14 possible S1-S2 pairs; the testing set contained 1 instance of each (total number
522 of trials used was 48). This procedure was performed in order to retrieve *a posteriori* the
523 classifier's performance for each trial type without any bias in the number of their occurrences.
524 Note that neither information concerning the identity of the different pairs, nor the value of S1
525 or S2, was given to the classifiers; only the chosen stimulus (S1 or S2) was used. It is also
526 important to keep in mind that monkeys' choices in this task are entirely based on the reward
527 values associated with the different stimuli. Because monkeys nearly always chose the
528 stimulus associated with the highest amount of reward, fully disentangling value and choice-
529 related signals is beyond the scope of this study.

530 Decoding monkeys' choices was studied here using ERP population activity vectors
531 combining sites from all monkeys. Due to our trial number requirement, the total number of
532 available recording sites for the different monkeys varied in both the OFC (monkey H=2,
533 monkey N=51, monkey V=59 sites) and MFC (monkey H=8, monkey N=35, monkey V=3 sites)
534 populations. As a result, most of the sites included in the OFC population were recorded from
535 two monkeys (N and V), whereas most sites included in the MFC population were recorded
536 from one monkey (N).

537 This analysis showed that LFPs in both OFC and MFC represented which option
538 monkeys would choose on a trial-by-trial basis (**Fig. 3A, B**). This encoding was evident during

539 both S1 and S2 presentations, typically at the time of the late ERP components previously
540 described as associated with stimulus-reward values (see for comparison **Fig. 2A, B**). The
541 different stimulus pairs presented on each trial also affected the performance of the classifiers
542 trained on the OFC and MFC data. Notably, the classifiers' choice prediction evolved as the
543 stimuli were sequentially presented and the predicted choice often matched the actual choice,
544 at least after both stimuli were presented (**Fig. 3B**).

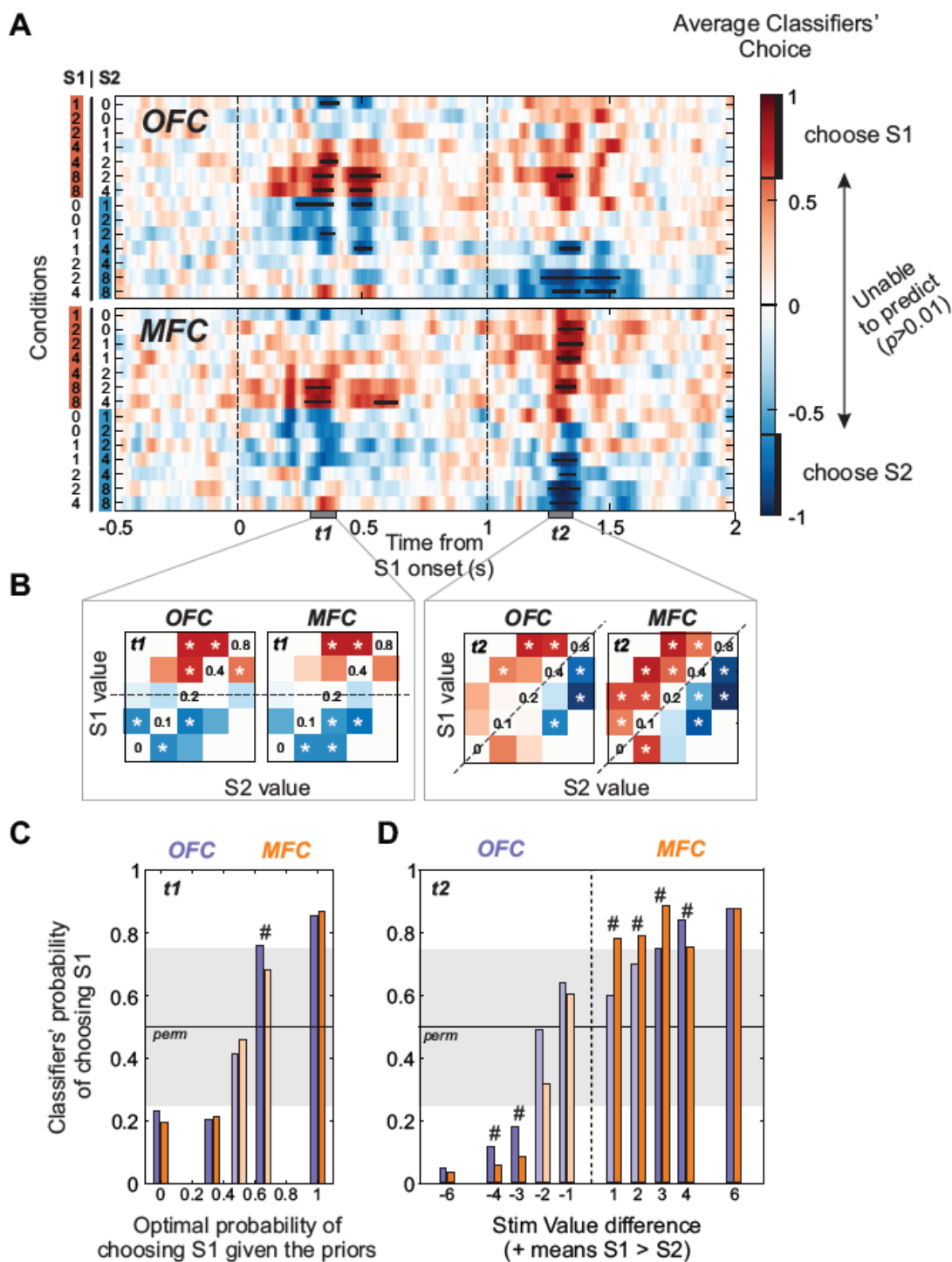
545 To better understand the dynamics of these signals, we looked at how monkeys used
546 the learned statistics of the task to augment their decisions. At the time of S1, monkeys didn't
547 have any information about the upcoming S2 value, but given that monkeys had significant
548 experience with the task, it is likely that they were using the value of S1 to predict S2. This is
549 possible in the present task because the uncertainty about the upcoming S2 value varied with
550 the value of S1. For example, if the value of S1 was 0.2 ml on a given trial, there was a 50%
551 chance that S2 value will be greater or lower (i.e. the maximum uncertainty in this task). On the
552 other hand, if the value of S1 was 0 or 0.8 ml, there was no uncertainty about the following
553 choice. Alternatively, if S1 was a stimulus associated with 0.1 or 0.4 ml this was associated
554 with an intermediate level of uncertainty, respectively a 66.6% or 33.3% chance that S2 value
555 will be greater than S1 (for full information on pairs, see Methods).

556 Taking the choice uncertainty into account we observed that the decoding performance
557 of the decision from OFC population activity during the S1 period was strongly correlated with
558 the estimated optimal choice probability at that time (**Fig. 3C**). A similar relationship was
559 observed for the MFC population. These analyses therefore reveal that monkeys were biasing
560 their potential choices on each trial based on the value of the first stimulus that was presented.
561 Notably, the fact that we were able to significantly decode monkeys' choices during S1 does
562 not imply that the coding accurately predicted the subsequent choice. Although, knowledge
563 about the task structure might be an efficient strategy to maximize reward, by reducing the
564 time before reward, it might result in an incorrect prediction and a planned motor response
565 associated with a lower value option. This planned response would need to be updated if a
566 higher value option is presented second. Indeed, careful inspection of Figure 3A shows that
567 strong encoding of S1 choice was reversed when the less likely S2 stimulus were presented,
568 violating monkeys' expectation (notably when S1/S2=0.1/0 ml and S1/S2=0.4/0.8 ml, see also
569 **Fig. 3B**).

570 Following the presentation of S2, both OFC and MFC classifiers reached better overall
571 performance in predicting monkeys' actual choices (**Fig. 3A, B**). However, differences were
572 observed between the two areas. In particular, the decoding accuracy from the OFC
573 population appeared linearly scaled with the stimulus value difference (**Fig. 3D**). This was not
574 the case for the MFC. Instead, the estimated probability of choosing mostly discriminated the 2
575 possible choices in a step-wise manner (at least when the decoding accuracy reached
576 significance), without being affected by the difference in value between the stimuli. This is
577 reflected by significantly higher accuracy levels in the MFC compared to the OFC in 6 different
578 stimulus pairs (highlighted in **Fig. 3D**). Also, more pairs of stimuli were significantly decoded
579 from the MFC than the OFC population after S2 presentation (time bin t₂, OFC=5/14 and
580 MFC=11/14 significantly decoded pairs; $\chi^2=5.25$, $p=0.02$; **Fig. 3B** right panel).

581 The very low number of sites in some individual subjects (e.g. monkey H: OFC=2 and
582 MFC=8; monkey N: MFC=3 sites) prevented us from confirming the robust existence of these
583 effects in all subjects. As shown in **Fig. 5B** (top row), the choice decoding accuracy from the
584 two remaining monkeys in OFC revealed large inter-individual variability. Ultimately, the choice
585 classifiers could only be tested using the MFC recordings of monkey N, meaning that the
586 effects reported should be treated with caution.

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Figure 3. Population encoding of choices during stimuli presentation (a) Average classifiers' choice performance (red=S1 and blue=S2; a value of 1 or -1 means always choosing S1 or S2 respectively) for each individual pairs of stimuli (labeled as *Conditions*, y-axis) over time (x-axis). Black bars represents a significant statistical preference for choosing S1 or S2 based on permutation testing (threshold at $p < 0.01$ for at least 6 consecutive time bins). (b) Time bin averages (for t1 and t2) of classifiers' choices in each condition. Stars indicate significant decoding performance. (c) Average classifiers' probability of choosing S1 during time bin t1 against the optimal probability of such choice

596 given the S1 value and the task design (see Methods). (d) Average classifiers' probability of choosing
597 S1 during time bin t2 against stimuli value difference. In panel c and d, # indicates significant
598 differences between OFC and MFC. Gray shading represent the noise level extracted from
599 permutations. OFC=Purple; MFC=Orange bars. Dark and light colors show significant and non-
600 significant probabilities respectively.
601

602 In summary, these analyses demonstrated that the ERPs recorded in the MFC, and to a
603 lesser extent in OFC, contained information about the impending choice (S1 or S2). Together
604 with the results on the encoding of value by ERPs, this suggests that LFPs in OFC and MFC
605 represent distinct but complementary information associated with choice behavior.
606

607 ***Amygdala lesions altered stimulus value coding***

608 Following the acquisition of the preoperative recordings, all 3 monkeys received bilateral
609 excitotoxic lesions of the amygdala, covering both centromedial and basolateral nuclei (**Fig.**
610 **1B**). Details regarding the method and extent of the lesions can be found in Rudebeck et al.
611 (2013). We then recorded LFP signals from 298 and 184 sites postoperatively in the OFC and
612 MFC respectively (monkey N: 169 OFC and 114 MFC; monkey H: 70 MFC; monkey V: 129
613 OFC). Postoperatively, the presentation of S1 and S2 elicited both the early negativity and late
614 positivity observed before the lesion (**Fig. 4A**). S1 elicited an early negativity around 250 ms
615 (average \pm std, OFC=268.8 \pm 31 ms; MFC=268.8 \pm 35 ms) and a late positivity after 400 ms
616 (OFC=425.7 \pm 69 ms; MFC=424.6 \pm 64 ms). Both components were also observed after S2
617 (negativity: OFC=260.2 \pm 24 ms, MFC=243.9 \pm 32 ms; positivity: OFC= 446.6 \pm 59 ms;
618 MFC=431.5 \pm 63 ms). Amygdala lesions abolished the latency differences previously observed
619 between the OFC and the MFC for S1 components (KW test OFC vs. MFC, negativity: H=0.02,
620 p=0.88; positivity: H=6.3e-4, p=0.98) but not for S2 (negativity: H=27.89, p=1.28e-7; positivity:
621 H=3.32, p=0.07). Compared to the preoperative recordings, the latency of the different
622 components was decreased following the amygdala lesion in OFC (KW test PreOp vs. PostOp,
623 S1 negativity: H=4.29, p=0.038; S1 positivity: H=7.34, p=0.007; S2 negativity: H=11.68,
624 p=6.3e-4; S2 positivity: H=22.63, p=1.9e-6). This was not the case in the MFC, except for the
625 S2 negativity (KW test PreOp vs. PostOp, S1 negativity: H=1.23, p=0.27; S1 positivity: H=1.74,
626 p=0.187; S2 negativity: H=17.88, p=2.35e-5; S2 positivity: H=0.35, p=0.55). Finally, we also
627 observed a clear overall decrease in the amplitude of the ERP responses in both OFC and
628 MFC relative to the preoperative recordings (**Fig. 4A**).

629

630 During the S1 period, the encoding of S1 values was still observed at a substantial
631 number of OFC and MFC sites (OFC=107/298, 35.9%; MFC=37/184, 20.1%), with more sites
632 in the OFC ($\chi^2=13.55$, $p=2.32e-4$) (**Fig. 4B,C**). Similarly, more sites in the OFC compared to
633 the MFC encoded S2 values during S2 period (OFC=90/298, 30.2%; MFC=34/184, 18.5%;
634 $\chi^2=8.18$, $p=0.0042$). This difference in proportions of site encoding S1 or S2 value was highly
635 consistent between monkeys (**Fig. 4D**). More importantly, these proportions were smaller than
636 before the amygdala lesion, for both S1 value during S1 period (PreOp vs. PostOp, OFC:
637 $\chi^2=15.42$, $p=8.6e-5$; MFC: $\chi^2=20.18$, $p=7e-6$) and S2 value during S2 period (PreOp vs.
638 PostOp, OFC: $\chi^2=40.6$, $p=1.8e-10$; MFC: $\chi^2=19$, $p=1.3e-5$). This decrease was robust for OFC
639 sites in the two monkeys during both S1 (PreOp/PostOp, monkey N: 69.1/36.1%; monkey V:
640 44.6/35.6%) and S2 values (monkey N: 65.4/27.8%; monkey V: 54.5/33.3%). For the MFC,
641 however, only monkey N showed a decrease in the proportion of sites encoding S1 (PreOp vs.
642 PostOp, monkey N: 61/20.1%; monkey H: 14.3/20%) and S2 reward-values (monkey N:
643 58.4/21.9%; monkey H: 12.5/12.8%). Thus, caution needs to be taken when interpreting the
644 effect of amygdala lesions on the encoding of stimulus-reward value in the MFC, given the
645 variability between monkeys.

646 Furthermore, only ~5% of sites encoded the value of S1 during the S2 period
647 (OFC=7.7% and MCC=4.89%, $\chi^2=1.46$, $p=0.2259$). This was lower than pre-operatively in the
648 OFC (PreOp vs. PostOp, $\chi^2=18.69$, $p=1.5e-5$), and was evident in both monkeys
649 (PreOp/PostOp, monkey N: 37/9.4%; monkey V: 11.5/5.4%) (**Fig. 4**).

650 Thus, stimulus-reward value encoding by LFPs was reduced following amygdectomy
651 in both OFC and MFC, but differences in encoding between the areas was maintain (OFC >
652 MFC encoding of S1 and S2). This pattern of effects is different to the changes we observed in
653 single neuron encoding of stimulus values, where lesions reduced the difference between OFC
654 and MFC as a result of diminished encoding in OFC (Rudebeck et al., 2013). These analyses
655 suggest that amygdala input has different effects on single neuron and LFPs in prefrontal
656 cortex.

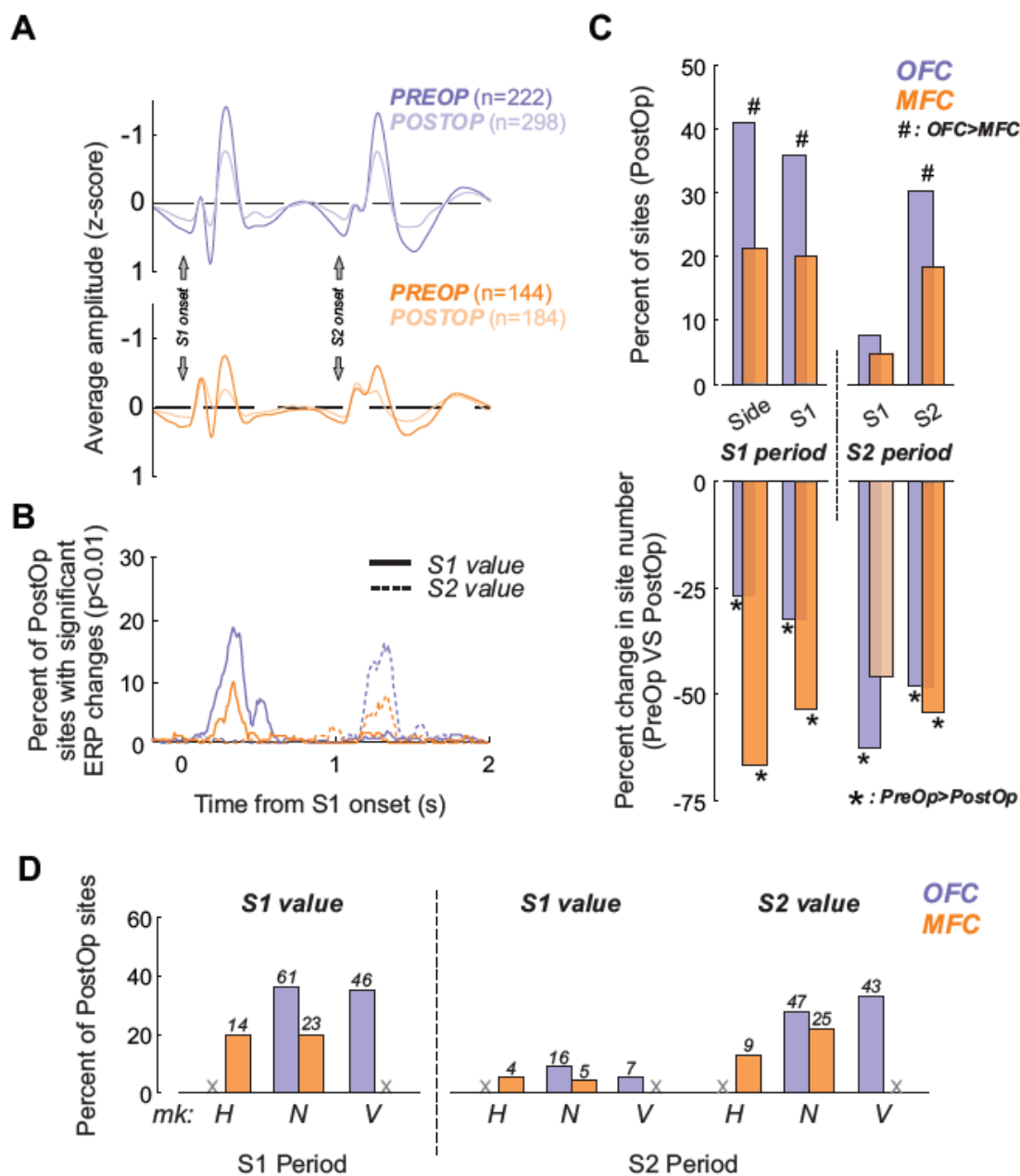
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658 Postoperatively, stimulus side was encoded at more sites in OFC than in MFC, both
659 during S1 presentation (OFC=40.9% and MFC=21.2%, $\chi^2=19.93$, $p=8.01e-6$) and S2

660 presentation (OFC=40.2% and MFC=23.3%, $\chi^2=14.51$, $p=1.39e-4$) (**Fig. 4C**). Compared to
661 before amygdala lesions, fewer sites encoded the side of the stimuli in the OFC and MFC,
662 during both S1 (PreOp vs. PostOp, OFC: $\chi^2=11.35$, $p=7.5e-4$; MFC: $\chi^2=61.4$, $p=4.7e-15$) and
663 S2 (PreOp vs. PostOp, OFC: $\chi^2=19.6$, $p=9.3e-6$; MFC: $\chi^2=16.32$, $p=5.3e-5$). Although the
664 proportions were different between monkeys (as reported preoperatively), the decrease in
665 coding was consistent across monkeys in the OFC for both S1 (PreOp/PostOp: monkey
666 N=93.8/62.7%, monkey V=32.2/12.4%) and S2 (monkey N=92.6/63.3%, monkey V=43/10.1%).
667 This was also true in the MFC for both S1 (monkey H=37.5/21.4%, monkey N=92.2/21.1%)
668 and S2 (monkey H=21.4/11.4%, monkey N=64.9/30.7%).

669 Finally, we also found a significant decrease in the encoding of the identity of S1 or S2,
670 either color or shape stimuli, in the OFC (S1=16/298, 5.4%; S2=21/298, 7%; PreOp vs.
671 PostOp: $\chi^2>9.19$, $p<0.0024$). This coding was still relatively absent in the MFC following the
672 amygdala lesion (S1=5/184, 2.7%; S2=3/184, 1.6%; PreOp vs. PostOp: $\chi^2<2.85$, $p>0.09$).
673 Changes following amygdala lesions were consistent across monkeys in the OFC for both S1
674 (PreOp/PostOp: monkey N=12.3/3.6%, monkey V=17.4/7.8%) and S2 (monkey N=18.5/7.1%,
675 monkey V=17.4/7.8%). This was also true in the MFC for both S1 (PreOp/PostOp: monkey
676 H=5.4/4.3%, monkey N=6.5/1.8%) and S2 (monkey H=1.8/2.9%, monkey N=7.8/0.9%).

677



678
679 **Figure 4. Effect of amygdala lesions on ERP signals** (a) Grand average normalized ERP responses
680 induced by the presentation of S1 and S2 in the OFC (top panel) and MFC (bottom panel) before and
681 after amygdala lesions. Black lines indicate significant differences in power between recordings
682 acquired before and after amygdala lesions (KW test, $p < 0.01$). (b) Time-resolved percentage of
683 significant sites (hierarchical ANOVA thresholded at $p < 0.01$, see Methods) encoding either S1 (solid
684 lines) or S2 values (dashed lines) in both OFC and MFC. (c) Top panel: Percentage of sites
685 significantly encoding stimulus side and values in the hierarchical ANOVA during S1 or S2 periods (S1:
686 0 to 1s; S2: 1 to 2 s) after amygdala lesion. Bottom panel: Percent change in site number
687 compared to the preoperative data. Hashtags and stars indicate a significant difference between OFC and MFC or
688 between PreOp and PostOp, respectively (Chi-square tests, $p < 0.05$). (d) Individual monkeys'
689 percentage and number of sites in the OFC and MFC showing a significant effect of S1 and S2 values
690 either during S1 or S2 periods. Grey crosses show that no recordings were performed on the given
691 region of the corresponding monkey (H, N and V represent the three monkeys).

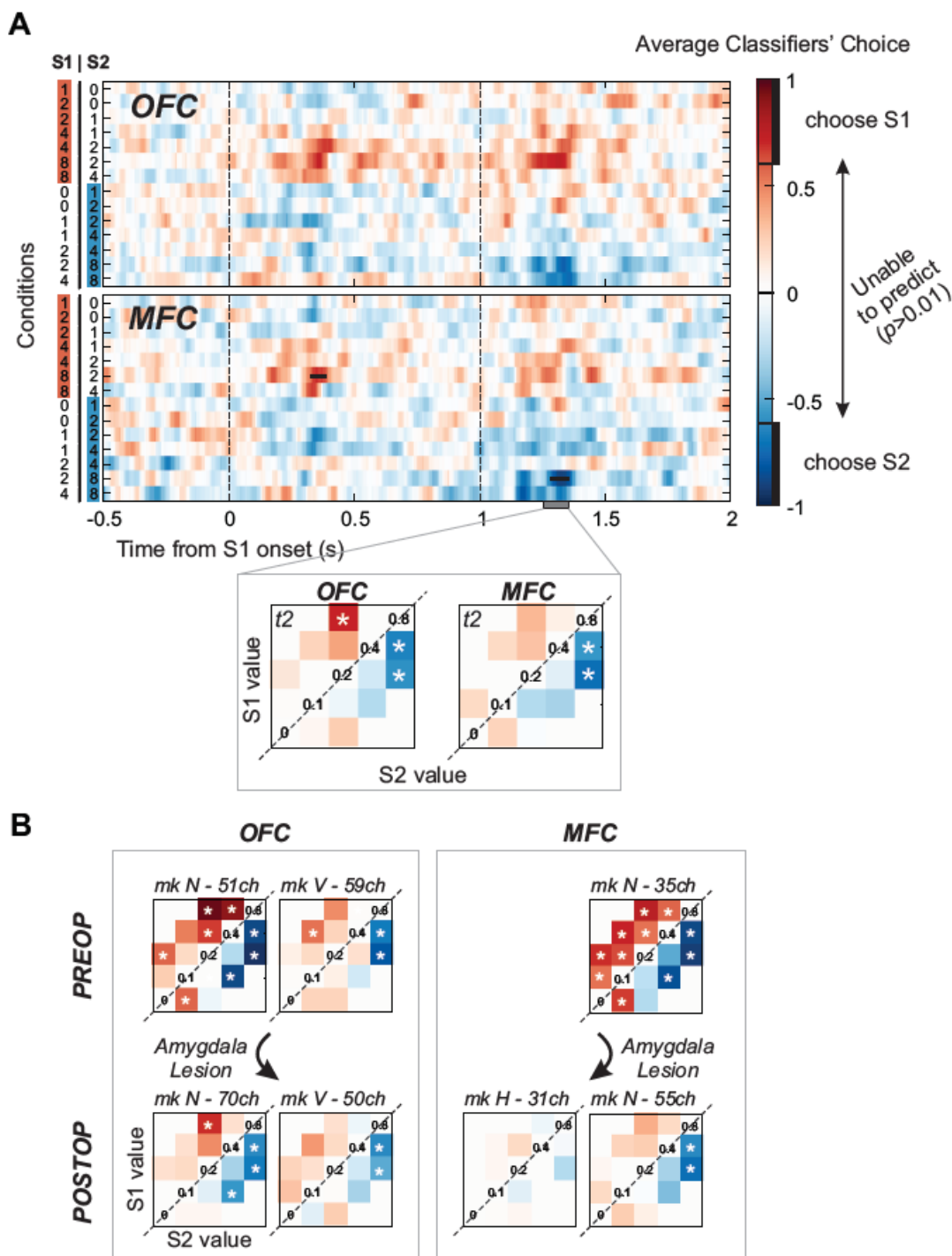
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693 To summarize, we observed major alterations of the ERPs in both OFC and MFC
694 following amygdala lesions. Although a significant proportion of sites still encoded the reward-
695 value associated with the different stimuli, amygdectomy markedly reduced the encoding of
696 this aspect of the task in both areas.

697

698 ***Amygdala lesions abolished the encoding of choices***

699 We applied the same multiple linear regressions method on the postoperative
700 population ERP activity to investigate whether the encoding of choice was affected by the
701 removal of the amygdala. Classifiers were trained and tested on 47 randomly selected sites
702 (total number of available sites exceeding trial number requirements, n=120 OFC and n=86
703 MFC). Postoperatively, it was not possible to decode monkeys' choices using either OFC or
704 MFC population ERP activity (**Fig. 5A**). The accuracy of the classifiers to predict monkeys'
705 choices almost never reached significance in the time-resolved analysis. Similarly, we were
706 only able to show a significant decoding during time bin t_2 in 3/14 and 2/14 pairs in OFC and
707 MFC, respectively (see white stars in **Fig. 5A**, bottom panel). Consistent results were observed
708 in the three subjects (**Fig. 5B**). This reveals the major influence of the amygdala in the
709 computation of choice-related activity in the MFC. Despite this change in MFC, it is important
710 to keep in mind that monkeys were still able to perform the task, with similar near-optimal
711 performance than before lesions.



712

713 **Figure 5. Amygdala lesions abolished the encoding of choices in the ERP** (a) Average classifiers'
 714 choice performance after amygdala lesion (red=S1 and blue=S2) for each individual pairs of stimuli
 715 (labeled as *Conditions*, y-axis) over time (x-axis). Black bars represents a significant statistical
 716 preference for choosing S1 or S2 based on permutation testing (threshold at $p < 0.01$ for at least 6
 717 consecutive time bins). Inset at the bottom represents the average choice performance during time bin
 718 t_2 . (b) Average classifiers' choice performance derived from individual monkeys during time bin t_2
 719 for each S1/S2 pairs and for both OFC (left) and MFC (right) populations, before and after amygdala
 720 lesions. White stars represent a significant performance for the considered S1/S2 pair ($p < 0.01$).

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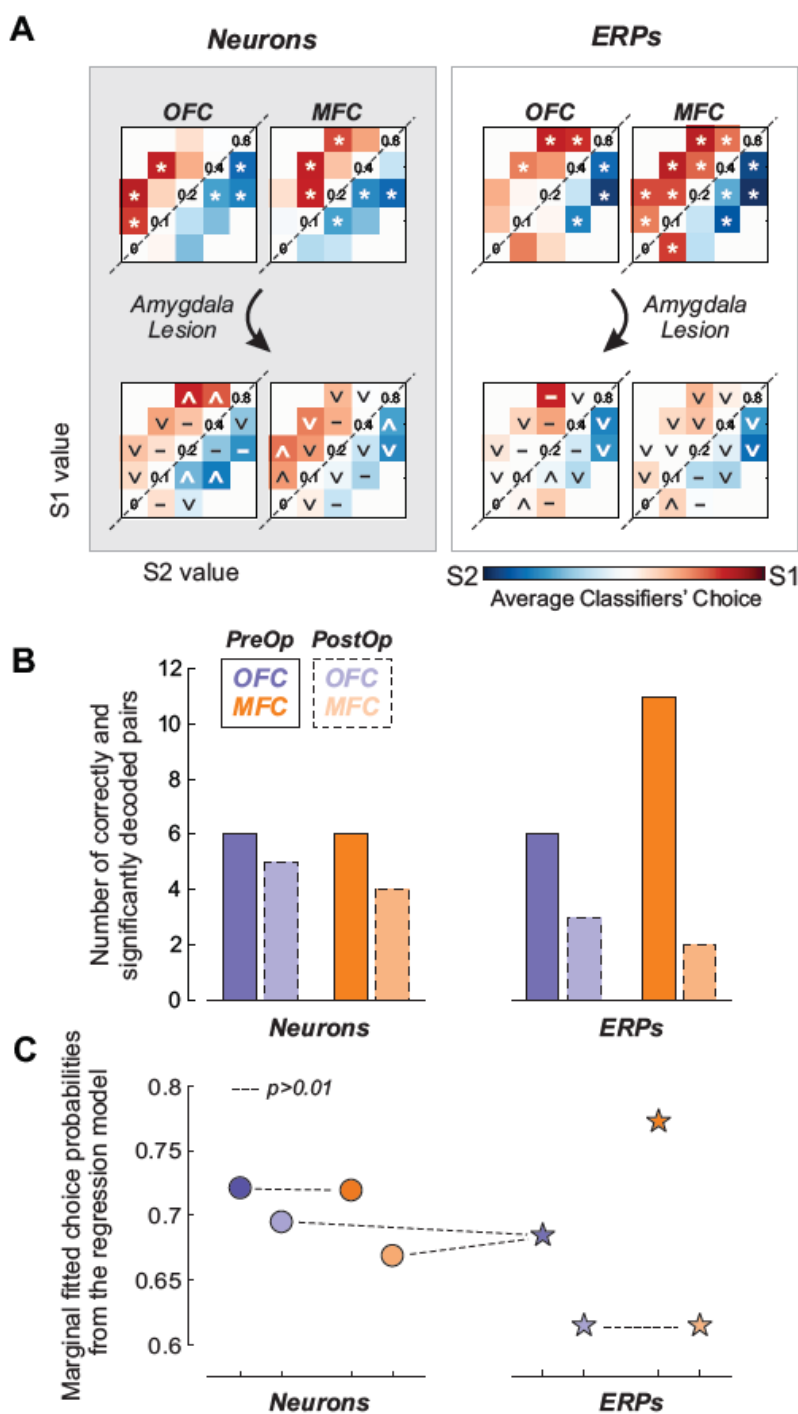
723 ***ERPs and single neuron activity convey different information related to choices***

724 Preoperatively, we found that choice decoding of ERP signals was more accurate in the
725 MFC compared to OFC (**Figs 3B,C**). Further, our analyses showed that amygdala lesions
726 almost abolished the encoding differences between OFC and MFC and the ability to decode
727 the monkey's choices. By contrast, individual neurons in both OFC and MFC are only weakly
728 tuned to monkeys' choices during this task (Rudebeck et al. 2013), revealing a possible
729 dissociation between the information carried by single neurons and LFPs. However, different
730 methods were applied with the two datasets, and it is possible that using population decoding
731 measures on the single neuronal recordings might reveal other aspects of choice-related
732 signaling. We therefore applied the same decoding analyses to both measures of neural
733 activity (see Methods). As before, the number of predictors (ERP sites or neurons) was similar
734 to avoid potential nonspecific biases of classifiers' performance.

735 It was possible to decode monkeys' choice using either single neuron or ERP activity
736 recorded in OFC or MFC, at least when specific S1/S2 pairs were presented (shown for time
737 bin t2 in **Fig. 6A**). Overall, classifiers using single neuron activity from either OFC or MFC
738 reached similar decoding performance to that from ERPs recorded in OFC, although the
739 significantly decoded pairs differed between the two measures and brain regions. Following
740 amygdala lesions, we observed a decrease in the classifier's accuracy compared to the
741 preoperative single neurons recordings; we were unable to decode monkeys' choices in as
742 many S1/S2 pairs (**Fig. 6B**, bar plot). This occurred in both MFC and OFC. Interestingly,
743 lesions were not simply associated with decreased classifier performance; a significant
744 increase in performance was observed in a few S1/S2 pairs (4 and 2 pairs for OFC and MFC
745 respectively; see upward arrows in **Fig. 6A**, bottom panel). This analysis indicates that the
746 information contained in single neuron and ERP populations was differentially affected by
747 amygdectomy.

748 To statistically compare whether the overall choice coding strength was different in the
749 different neural signals and/or modulated following amygdala lesions, we fitted a mixed-effect
750 logistic regression to the output from the different classifiers (see Methods). Categorical fixed-
751 effect factors included recording types (single neurons vs. LFPs), areas (OFC vs. MFC) and

752 surgery (PreOp vs. PostOp). S1/S2 pairs were included as a random-effect factor, allowing
753 only changes in the intercept (i.e. choosing more S1 or S2 depending on their values). The
754 model results are summarized in **Fig. 6C**. All interactions survived model selection and were
755 statistically significant (Type x Area: $t_{(104,1)}=11.71$, $p=1.03e-20$; Type x Surgery: $t_{(104,1)}=-5.16$,
756 $p=1.1e-6$; Area x Surgery: $t_{(104,1)}=-3.25$, $p=1.5e-3$). The three-way interaction (Type x Area x
757 Surgery) also remained in the best model ($t_{(104,1)}=-6.13$, $p=1.6e-8$), highlighting the existence of
758 a strong dissociation between the factors considered. Post-hoc comparisons using a threshold
759 at $p<0.01$ revealed that: 1) choices were more strongly encoded by single neurons compared
760 to ERPs in the OFC, whereas the opposite was true for the MFC (**Fig. 6C**). 2) Choice encoding
761 was also significantly greater in MFC than OFC, but only for ERPs, not single neurons (**Fig.**
762 **6C**). 3) Amygdala lesions significantly reduced the performance of the classifiers on both
763 single neurons and ERPs, although the effect was more pronounced for ERPs (relative to that
764 for single neurons) and in the MFC populations (relative to OFC). In summary, amygdala
765 lesions differentially affected choice coding in OFC and MFC at the level of single neurons and
766 ERPs. The most prominent change was the reduction in spike encoding of choices in OFC and
767 the decrease ERP encoding of choices in MFC.
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Figure 6. Single neurons and ERPs differences in the encoding of choices (a) Average classifiers' choice performance during time bin t_2 for each S1/S2 pairs and for both single neuron (left) and ERP (right) populations. White marks indicate a significant decoding performance for the considered S1/S2 pair (stars in PreOp, increase / null / decrease marks in PostOp). Marks for PostOp represent significant (increase or decrease signs) and non-significant changes (dash) when compared to the PreOp populations. (b) Number of significantly and accurately decoded S1/S2 pairs for the different population considered (c) Overall choice probabilities extracted from the mixed-effect logistic regression for each population. Non-significant post-hoc comparisons are represented by dash lines ($p > 0.01$). Conventions as in previous figures.

779 **DISCUSSION**

780 Here we analyzed the local field potentials recorded in OFC and MFC of monkeys
781 engaged in a task where they chose between two sequentially presented stimuli associated
782 with different sized fluid rewards on each trial. Before lesions of the amygdala, ERPs in OFC,
783 and to a lesser extent in MFC, encoded the reward value of the two stimuli presented (**Fig. 2**).
784 Furthermore, if a site encoded the value of S1 it was highly likely to encode the value of S2.
785 This closely matched findings from our previously published single neuron recordings. Despite
786 this correspondence, we found that there was no direct relationship between the encoding of
787 value by single neurons and ERPs simultaneously recorded on the same electrode. We then
788 looked at how ERPs encoded the choices that the monkeys would make on each trial. We
789 found that ERPs recorded in MFC, and to a lesser extent in OFC, contained relevant
790 information about the upcoming choices that monkeys would make (**Fig 3**). Taken together,
791 the findings indicate that local field potentials in OFC and MFC represent the relevant
792 information to make adaptive and optimal decisions.

793 Removing amygdala input to OFC and MFC strongly reduced ERP encoding of stimulus
794 reward value in both areas (**Fig. 4**). It also decreased the encoding of monkey's choices. This
795 was most apparent in MFC where the lesions completely abolished choice-related signals
796 encoding (**Fig. 5**). When we compared the effects of lesions on ERP and single neuron
797 encoding of choices, the lesions appeared to mostly affect ERP, not single neuron. This was
798 especially prominent in MFC (**Fig. 6**). Taken together these data suggest that amygdala inputs
799 are important for augmenting reward-value and choice signals in PFC, most notably ERP
800 choice-related signals in MFC.

801
802 ***Encoding of reward-value and choices in OFC and MFC***

803 Both OFC and MFC have been linked to reinforcement-guided decision making, notably
804 when monkeys have to choose between different stimuli or courses of action associated with
805 reward (e.g., Thorpe et al., 1983; Matsumoto et al., 2003; Wallis and Miller, 2003; Amiez et al.,
806 2006; Kennerley et al., 2006; Walton et al., 2010; Stoll et al., 2016). It has also been
807 emphasized that encoding in OFC and MFC is not identical (Kennerley et al., 2009, 2011), and
808 that each area makes distinct contributions to different aspects of decision-making (Rudebeck
809 et al., 2008; Camille et al., 2011). Here, we observed that both brain structures appeared to

810 reflect stimulus-reward values and the upcoming choices. However, the strength of coding of
811 each factor differed between OFC and MFC and a clear dissociation was apparent: ERPs in
812 OFC strongly encoded the reward value associated with the stimuli presented on each trial
813 whereas ERPs in MFC were more closely aligned to the *product* of value signals, reflecting the
814 encoding of monkeys' choices. The effect in MFC should, however, be taken with caution as
815 decoding choice-related signals was performed using a non-homogeneous and limited number
816 of channels from the different monkeys (see **Fig. 5B**). Nevertheless, this could be related to
817 our previous observation, where single neuron encoding of the amount of reward associated
818 with S2 in MFC was more influenced by the value of S1 (i.e., was more akin to a relative
819 valuation; Rudebeck et al., 2013).

820 Indeed, based on work in humans, encoding of choice in MFC might be expected. MFC
821 and medial OFC have both been proposed to play a role in the comparison process depending
822 on the context (Rushworth et al., 2012). In addition, MFC is critical for combining multiple
823 variables important for the decision processes, including both costs and benefits (Rudebeck et
824 al., 2006; Kennerley et al., 2009; Stoll et al., 2016). Hence, it has been argued that the MFC
825 could represent the value of exploring alternative courses of actions (Kolling et al., 2016).
826 Although our task doesn't specifically depend on action values, representing which actions
827 have been performed and their potential value could be a crucial part of deciding whether to
828 stay engaged in the task.

829 It is important to note that the design of our task and highly consistent choice patterns of
830 our subjects prevented us from fully disentangling value and choice-related signals (as is the
831 case in nearly every value-based decision-making task). As noted earlier, this aspect of the
832 design was necessary to ensure that any alterations in neural activity consequent to the lesion
833 could be interpreted. Because of this aspect of our study, monkeys' choice information could
834 be seen as a binary version of the difference in value of both stimuli. Therefore, the
835 dissociation we observed between OFC and MFC could be linked to the specific way value-
836 related information is represented in these regions.

837 Nevertheless, both OFC and MFC ERPs contained information about stimulus-reward
838 values and choices. This observation supports the notion of permeability of information
839 throughout the PFC. This could be the result of both the anatomical and functional properties
840 of the PFC. First, strong anatomical connections exist between the different parts of PFC,

841 notably between the OFC and the MFC (Carmichael and Price, 1996). Also, the associative
842 role that has been attributed to PFC, as well as the broad influence of motivational factors on
843 this structure, makes it suitable to represent multiple parameters related to value and decisions
844 (Wallis and Rich, 2011). Our results support the view that OFC and MFC, albeit being tuned
845 differently by value and choice information, work in unison when deciding between alternatives
846 in an adaptive and optimal manner.

847

848 ***Correspondence between ERPs and single neuron activity***

849 Despite the potential for LFPs to shed light on information processed in PFC, only a
850 handful of studies have assessed value and/or choice encoding by LFPs in PFC (Morrison et
851 al., 2011; Hunt et al., 2015; Rich and Wallis, 2016). We found that value encoding in ERP
852 signals was not predictive of whether a neuron recorded at the same location would encode
853 value as well. This result is somewhat surprising as it suggests that there are differences in the
854 type of information carried in these two measures of neural activity, and, ultimately, that they
855 are not simply the same process looked at from different angles. One simple explanation for
856 this dissociation is that differences between the two measures (continuous signal vs point
857 process) mean that it is difficult to truly compare the signals. This could be an especially acute
858 problem in OFC where spiking activity is typically sparse (e.g. Thorpe et al., 1983). Against
859 this, however, there have been reports of differences in the type of information signaled
860 between LFPs and single neuron activity in parts of temporal cortex (Kreiman et al., 2006;
861 Nielsen et al., 2006) and PFC in particular (Monosov et al., 2008; Lara and Wallis, 2014; but
862 see Rich and Wallis, 2016), indicating that this may be a valid difference.

863 An alternative explanation relates to the basis of ERP signals. ERPs are commonly
864 assumed to reflect postsynaptic events of thousands of neurons, depending on the recording
865 setup. Therefore, ERPs are thought to partly represent the input to a region from other cortical
866 or sub-cortical regions (Nguyen and Lin, 2014). However, given that many synapses between
867 neurons are short-range (i.e., within-area), ERPs could contain a mixture of information from
868 both inputs and outputs of a region (Douglas and Martin, 2004); by contrast, single neuron
869 activity only reflects the output of a region.

870 While there was a location specific dissociation between single neuron and ERP
871 encoding of value, at the population level both measures were highly similar (compare

872 example **Fig. 2C** with Fig. 3 in Rudebeck et al., 2013). This close correspondence, however,
873 was absent for one of our findings: encoding of choice by ERPs in MFC (**Fig. 6**). Given the
874 basis of the ERP signal noted above, it is possible that MFC receives choice-related signals
875 from amygdala (**Fig. 6**) or potentially other parts of PFC that require amygdala input, but this
876 does not result in a strong cascade of activity in individual neurons. Apart from amygdala, such
877 choice signal could potentially come from medial OFC where comparison related activity has
878 been reported in both macaques and humans (Boorman et al., 2009; Kolling et al., 2012; Strait
879 et al., 2014). The lack of single neuron encoding of choices during the present task could be
880 linked to the relatively low involvement of the MFC and OFC in this task, where values were
881 already learned. By contrast, if the value of stimuli changed unexpectedly or has to be learned,
882 this might trigger a cascade of events throughout the PFC, increasing the need for cognitive
883 control which could potentiate the processing of choice and value information in the MFC and
884 OFC, respectively. This idea would appear to fit with data from the same subjects showing that
885 during stimulus-reward learning, single neuron activity in MFC closely matches stimulus values
886 and is indistinguishable from OFC encoding (Rudebeck et al., 2017).

887 888 ***Amygdala influence on reward value and choice coding***

889 We found that amygdala lesions not only strongly affected ERP correlates of stimulus-
890 reward values and choices, but also the encoding of other parameters such as the stimulus
891 side or identity (**Fig. 4**). This is different to the effect of amygdala lesions on the activity of
892 individual neurons, where there was not a significant reduction in the encoding of these
893 parameters (Rudebeck et al., 2013). A wholesale reduction in ERP amplitude following lesions
894 could be responsible for the decrease in coding in the different parameters. Yet ERP
895 amplitudes in OFC postoperatively were still higher than MFC preoperatively, but nevertheless
896 less tuned to the different factors considered. Therefore, such changes might represent a
897 specific loss of information as opposed to a nonspecific reduction in signal-to-noise ratio. In
898 fact, neurons in the amygdala have been shown to reflect both the identity and the location of a
899 stimulus, possibly related to the role of amygdala in directing attentional processes (Peck et
900 al., 2013, 2014).

901 Previous studies where functional measures, either single neuron recording or
902 functional MRI, have been combined with amygdala lesions during reward based tasks have

903 reported changes in encoding in PFC (Schoenbaum et al., 2003; Hampton et al., 2007).
904 Although our findings are in broad agreement with this previous work in humans and rodents,
905 the change in choice encoding in MFC that we found is most pertinent to a human fMRI study
906 detailing the effects of amygdala damage (Hampton et al., 2007). Hampton and colleagues
907 reported that expected reward signals in MFC (i.e., the outcome of decisions) were reduced in
908 two humans with amygdala damage performing a reward-guided task. Our data therefore
909 confirm and extend these findings by showing the dynamic nature of these effects and that
910 choice signals are abolished irrespective of when the stimuli are presented (decoding on S1 or
911 S2, **Fig. 5**).

912 Given the strong reciprocal projections between PFC and amygdala (Morecraft and Van
913 Hoesen, 1998; Ghashghaei et al., 2007), it could be argued that the changes we observed
914 were the result of the loss of amygdala inputs to the OFC and MFC. This could be supported
915 by the relatively greater decrease in the encoding of value and choice in ERPs than in single
916 neurons given that ERPs could reflect inputs to these regions. However, we cannot rule out the
917 possible influence of other brain regions. For example, the loss of information related to value
918 and choice in the MFC could be an indirect result of the loss of amygdala inputs to the medial
919 and lateral OFC, which receive strong projections from the amygdala (Ghashghaei et al.,
920 2007). Alternatively, thalamic and dopaminergic inputs could play a role in the transmission of
921 information from the amygdala to the PFC (Williams and Goldman-Rakic, 1998; Timbie and
922 Barbas, 2015).

923

924 **Summary**

925 We recorded ERPs in the OFC and MFC of macaque monkeys while they performed a
926 reward-based choice task. We found that OFC and MFC carry distinct signals related to
927 decision-making at the level of single neurons and LFPs. While both single neurons and LFPs
928 in OFC predominantly encoded stimulus-reward values, ERP signals in MFC were specifically
929 related to monkey's choices. This correlate of decision-making in MFC was unique in that it
930 was not seen in the activity of single neurons and it was almost entirely dependent on input
931 from the amygdala. Given the prominent role of MFC-amygdala interactions in numerous
932 psychiatric disorders, alterations in choice-related signals in MFC could be used as a marker of
933 amygdala dysfunction.

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