Interneuron Specific Gamma Synchronization Encodes Uncertain Cues and Prediction Errors in Lateral Prefrontal and Anterior Cingulate Cortex

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Abstract

Interneurons are believed to realize critical gating functions in cortical circuits, but it has been difficult to ascertain the underlying type of interneuron and the content of gated information in primate cortex. Here, we address these questions by characterizing subclasses of interneurons in primate prefrontal and anterior cingulate cortex while monkeys engaged in attention demanding reversal learning. We find that subclasses of narrow spiking neurons exert a net suppressive influence on the local circuits indicating they are inhibitory. These putative interneurons encoded area-specific information showing in prefrontal cortex stronger encoding of choice probabilities, and in anterior cingulate cortex stronger encoding of reward prediction errors. These functional correlations were evident not in all putative interneurons but in one of three sub-classes of narrow spiking neuron. This same putative interneuron subclass also gamma - synchronized (35-45 Hz) while encoding choice probabilities in prefrontal cortex, and reward prediction errors in anterior cingulate cortex. These results suggest that a particular interneuron subtype forms networks in LPFC and in ACC that synchronize similarly but nevertheless realize a different area specific

computation. In the reversal learning task, these interneuron-specific computations were (*i*) the gating of values into choice probabilities in LPFC and (*ii*) the gating of chosen values and reward into a prediction error in ACC. This finding implies that the same type of interneuron plays an important role for controlling local area transformations during learning in different brain areas of the nonhuman primate cortex.

Introduction

Inhibitory interneurons in prefrontal cortex are frequently reported to be altered in neuropsychiatric diseases with debilitating consequences for cognitive functioning. Groups of fast spiking interneurons with basket cell or chandelier morphologies have consistently been found to be abnormal in individuals with schizophrenia and linked to dysfunctional working memory and reduced control of attention (Dienel and Lewis, 2019). Altered functioning of a non-fast spiking interneuron class is linked to reduced GABAergic tone in individuals with severe major depression (Levinson et al., 2010; Fee et al., 2017). These findings suggest that the circuit functions of different subtypes of interneurons in prefrontal cortices are critically important to regulate specific aspects of cognitive and affective functioning.

But it has remained a challenge to identify how individual interneuron subtype supports specific cognitive or affective functions in the nonhuman primate. For rodent prefrontal and anterior cingulate cortices, cells with distinguishable functions express differentially cholecystokinin (CCK), parvalbumin (PV) or somatostatin (SOM), amongst others (Roux and Buzsaki, 2015; Cardin, 2018). Prefrontal CCK expressing basket cells have been shown to impose inhibition that is required during the choice epoch, but not during the delay epoch of a working memory task

(Nguyen et al., 2020). In contrast, retention of visual information during working memory delays has been shown to require activation specifically of PV+ expressing fast spiking interneurons (Lagler et al., 2016; Kamigaki and Dan, 2017; Nguyen et al., 2020). In the same prefrontal circuits, the PV+ neurons have also been associated with attentional orienting (Kim et al., 2016), shifting of attentional sets and response strategies during reward learning (Cho et al., 2015; Canetta et al., 2016; Cho et al., 2020), and with spatial reward choices (Lagler et al., 2016), among other functions (Pinto and Dan, 2015). Distinct from PV+, the group of somatostatin expressing neurons (SOM+) have been shown to be necessary during the initial encoding phase of a working memory task but not during the delay (Abbas et al., 2018), and in anterior cingulate cortex they activate specifically during the approach of reward sites in anterior cingulate cortex (Kvitsiani et al., 2013; Urban-Ciecko and Barth, 2016). Taken together, these findings illustrate that rodent prefrontal cortex interneurons expressing PV, SOM or CCK fulfill separable, unique roles at different processing stages during goal-directed task performance (Pinto and Dan, 2015; Lagler et al., 2016).

The rich insights into cell-specific circuit function in rodent prefrontal stand it stark contrast to the limited empirical data from primate prefrontal cortex. While there are recent advances in optogenetical tools for use in primates (Acker et al., 2016; Dimidschstein et al., 2016; Gong et al., 2020), most existing knowledge about cell specific circuit functions are indirectly inferred from studies that distinguish only one group of putative interneuron that show narrow action potential spike width. Compared to broad spiking neurons the group of narrow spiking, putative interneurons in lateral prefrontal cortex have been found to more likely encode categorical information during working memory delays (Diester and Nieder, 2008), show stronger stimulus onset responses during cognitive control tasks (Johnston et al., 2009), stronger attentional

modulation (Thiele et al., 2016), more location-independent encoding of task rules (Johnston et al., 2009), stronger reduction of firing selectivity for task irrelevant stimulus features (Hussar and Pasternak, 2009), stronger encoding of errors and loss (Shen et al., 2015; Sajad et al., 2019), more likely encoding of outcome history (Kawai et al., 2019), and stronger encoding of feature-specific reward prediction errors (Oemisch et al., 2019), amongst other unique firing characteristics (Constantinidis and Goldman-Rakic, 2002; Ardid et al., 2015; Rich and Wallis, 2017; Voloh and Womelsdorf, 2018; Torres-Gomez et al., 2020).

These summarized findings suggest that there are subtypes of narrow spiking neurons that are particularly important to regulate prefrontal circuit functions, raising the question to which subtypes they belong. Comparison of protein expression with spike-width have shown for prefrontal cortex that >95% of all PV and ~87% of all SOM interneurons show narrow spike width (Ghaderi et al., 2018; Torres-Gomez et al., 2020), while narrow spikes are also known to occur in ~20% of VIP interneurons (Torres-Gomez et al., 2020) among other GABAergic neurons (Krimer et al., 2005; Zaitsev et al., 2009), and in (at least in motor cortex) in a subgroup of pyramidal cells (Soares et al., 2017). In addition, electrophysiological characterization have shown at least three different types of firing patterns in narrow spiking neurons of monkeys during attention demanding task (Ardid et al., 2015; Dasilva et al., 2019; Trainito et al., 2019). Taken together, these insights raise the possibility that spike width and electrophysiology will allow identifying the interneuron subtypes that are important to realize prefrontal cortex functions.

Here, we approached this question by recording narrow spiking cells in nonhuman primate prefrontal and cingulate cortex during an attention demanding reversal learning task. We found

that in both areas three narrow spiking neuron classes are well distinguished and show apparent suppressive influence on the local circuit activity, justifying labeling them interneuron. Among these interneurons the same sub-type showed the most apparent functional correlations, firing stronger to reward predictive cues when their predictability is still learned during the reversal, and firing stronger to outcomes when they are most unexpected during reversal. Notably, in both, ACC and in LPFC, these functions were evident in 35-45 Hz gamma rhythmic synchronization to the local field potential. These findings describe the specific electrophysiological subtype of narrow spiking interneurons that carries out area-specific functions during adaptive behavioral regulation.

Results

We used a color-based reversal paradigm that required subjects to learn which of two colors were rewarded with color-reward associations reversing ≥30 trials. Two different colors were assigned to stimuli appearing randomly left and right to a central fixation point (**Fig. 1a**). During the task the color information was presented independently from the up-/downward- direction of motion of the stimuli. The up-/downward- direction instructed the saccade direction that animals had to show to a go event in order to receive reward. Motion was thus the cue for an overt choice (with saccadic eye movements), while color was the cue for covert selective attention. Color was shown either before (as Feature-1) or after the motion onset (as Feature-2) (**Fig. 1b**). Both animals took on average 7/7 (monkey H/K) trials to reach criterion performance, i.e. they learned which color was associated with reward and which one was unrewarded within 7 trials (**Fig. 1c**). The asymptotic performance accuracy was 87/89% for monkeys H/K (excluding fixation break errors).

Characterizing narrow spiking neurons as inhibitory interneurons

During reversal performance we recorded the activity of 329 single neurons in LPFC areas 46/9 and anterior area 8 (monkey H/K: 172/157) and 397 single neurons in ACC area 24 (monkey H/K: 213/184) (**Fig. 1d)**. The average action potential waveform shape of recorded neurons distinguished neurons with broad and narrow spikes similar to previous studies in LPFC and ACC (Gregoriou et al., 2012; Ardid et al., 2015; Westendorff et al., 2016; Dasilva et al., 2019; Oemisch et al., 2019) (**Fig. 1e**). Broad and narrow spiking neurons had different spike durations as was evident in a bimodal distribution of their hyperpolarization rates and their time-of-repolarizations that was better fit with two than one gaussian (**Fig. 1e**, calibrated Hartigan's dip test $p<0.001$; Bayesian information criterion for two and one gaussian fit: 4.0450, 4.8784). We obtained in LPFC 21% narrow spiking neurons (n=259 broad, n=70 narrow cells) and in ACC we found 17% of neurons to have narrow action potentials (n=331 broad, n=66 narrow cells).

To assess the excitatory or inhibitory identity of the broad and narrow spiking neurons (*B*- and *N-type* neurons), we estimated the multi-unit activity (MUA) power around the time of spike for each cell and tested how spike-triggered MUA power changed before versus after the cell fired a spike (see **Methods** and **Suppl. Fig. 2**). This approach expects an excitatory neuron to spike concomitant with neurons in the local population reflected in a symmetric rise and fall of MUA before and after its spike. In contrast, inhibitory neurons are expected to spike when MUA rises, but when the spike occurs should suppress the local MUA activity (Oemisch et al., 2015). We found that B-*type* cells showed on average a symmetric spike-to-MUA relationship indicative of excitatory participation with local activity (**Fig. 1f**). In contrast, spikes of *N-type* cells were followed by decreased MUA activity indicating an inhibitory influence on MUA (**Fig. 1f**). The excitatory and inhibitory effects on local MUA activity were consistent across the populations and significantly distinguished *B*-

and *N-type* neurons (**Fig. 1g**, **i**; MUA modulation index: [(post MUA_{spike} - pre MUA_{spike}) / pre MUA_{spike}] for *B*- vs *N-type* cells, Wilcoxon test, $P<0.001$). On average interneurons are known to fire more regularly than pyramidal cells, which is quantifiable by low variability of their interspike-intervals (Markram et al., 2004; Ardid et al., 2015). We thus correlated the local variability of firing with the spike-triggered MUA modulation and found that *N-type* neurons showed more regular inter-spike intervals than *B-type* neurons (**Fig. 1i**; LV X spike-triggered MUA modulation: $r = 0.12$, $p<0.001$), providing additional evidence that *N-type* neurons encompass interneurons.

Putative interneurons in prefrontal cortex encode the choice probability of targets

To discern how *B*- and *N- type* neurons encoded the learning of the rewarded color during reversal we analyzed neuronal response modulation around the color onset, which instructed animals to covertly shift attention to the stimulus with the reward predicting color. In addition to this *color (attention) cue* we also analyzed activity around the motion onset that served as *action cue*. Its direction of motion indicated the saccade direction the animal had to elicit for receiving reward. This *action cue* could happen either 0.5-0.9 sec. before or 0.5-0.9 sec. after the *color cue*. Many single neurons in LPFC selectively increased their firing to the *color attention cue* with no apparent modulation to the *motion action cue* (n=71 cells with firing increases to the color but not motion cue) (for examples: **Fig. 2a**, **b**). These neurons increased firing to the color onset when it was the first, or the second feature that was presented, but did not respond to the motion onset when it was shown as first or second feature (for more examples, see **Suppl. Fig. S3**).

We found that N-type neurons in LPFC change transiently their firing to the attention cue when it occurred either early or late relative to action cue (significant increase within 25-275ms post-cue

for Feature 1 and within 50-250ms post-cue for Feature 2, $p<0.05$ randomization statistics, n=21 *N-type* cells with increases and 7 with decreases to the color cue, **Fig. 2c**). This attention cue-specific increase was absent for *B-type* neurons in LPFC (n.s., randomization statistics, n=44 *B-type* cells with increases and n=35 with decreases to the color cue, **Fig. 2c**). ACC *N-* and *B-type* neurons did not show on-response to the color cue (n=36 / 6 *B- and N- type* cells with increases, respectively, and n=31 / 12 *B- and N- type* cells with decreased firing, respectively, to the color cue, total cell number included in this analysis for *B- and N- type* n= 216 / 50 respectively) (**Fig. 2d**).

The *N-type* specific attention cue response might carry information about the rewarded stimulus color or the rewarded stimulus location. We found that the proportion of neurons whose firing rate significantly distinguished rewarded and nonrewarded colors sharply increased for *N-type* cells after the onset of the color cue in LPFC (proportion of color selective responses within 0-0.5 sec. after cue, 18%; n=10 of 54 N-type cells, randomization test $p<0.05$ within [175 575] ms after cue onset, but not in ACC (cells with significant information: 6%; n=3 of 50 N-type cells, ns., randomization test within [300 700] ms after cue onset) (**Suppl. Fig. S4a,b**). Similar to the selectivity for rewarded stimulus color *N-type* cells in LPFC (but not in ACC) showed significant encoding of the right versus left location of the rewarded stimulus (in LPFC: 22% with reward location information; n=12 of 54 N-type cells, randomization test $p<0.05$ within [200 500] ms after cue onset; in ACC: 10% with reward location information ;n=5 of 50 N-type cells, n.s. randomization test) (**Suppl. Fig. S4c,d**).

The color-specific firing increase and the encoding of the rewarded color by *N-type* neurons in LPFC suggest they support reversal learning. We tested this by correlating their firing rates around the color cue onset with the trial-by-trial variation on choice probability for choosing the stimulus with the rewarded color. Choice probability (*p(choice)*) was calculated with a reinforcement learning model that learned to optimize choices based on reward prediction errors (see **Methods** and (Oemisch et al., 2019)). Choice Probability rose after each reversal and asymptoted after around ~10 trials (**Fig. 1c**). We found that during the post-color onset time period 17% (n=20 of 120) of *B-type* cells and 27% (n=11 of 41) of *N-type* cells in LPFC significantly correlated their firing with p(choice), which was larger than expected by chance (binomial test B-type cells: $p<0.001$; NS cells: $p<0.001$). On average, *N-type* cells in LPFC showed positive correlations (Pearson $r=0.068$, Wilcoxon rank test, $p=0.011$), while *B-type* neurons showed on average no correlation (Wilcoxon rank test, $p=0.20$) (**Fig. 2e**). The positive p(choice) correlations of *N-type* neurons in LPFC grew following color onset and remained significant for 0.7s following color onset (N=41 N-type cells, randomization test, $p<0.05$ from 0-0.7 s post-cue, **Fig. 2e**). Compared to LPFC, significantly less *N-type* cells in ACC correlated with choice probability (6% (n=2 of 33) in ACC, versus 27% in LPFC, X^2-test for prop. Difference, X^2-stat= 5.45, $p=0.019$) and showed no p(choice) correlations over time (Wilcoxon rank test, $p=0.49$, n.s., **Fig. 2f**).

Putative interneurons in anterior cingulate cortex encode reward prediction errors.

Choice probabilities increase during reversal learning when reward prediction errors (RPEs) of outcomes decrease. Prior studies have shown that RPEs are prevalently encoded in the ACC (Kennerley et al., 2011; Oemisch et al., 2019). We therefore reasoned that reward prediction errors might be preferentially encoded by the same narrow spiking putative interneurons. We estimated

trial-by-trial RPEs with the same reinforcement learning model that also provided p(choice) for the previous analysis. We found that on average 23% of LPFC and 35% of ACC neurons showed significant firing rate correlations with RPE in the post-outcome epoch with only moderately and non-significantly more *N-type* than *B-type* neurons having significant rate-RPE correlations (n=9 *N-type* neurons, n=31 *B-type* neurons, X^2-test; p=0.64 for LPFC; n=15 *N-type* neurons, n=47 *B-type* neurons, X^2-test; p=0.83 for ACC; **Fig. 3 a,b**). However, time-resolved analysis of the correlations revealed a significant positive firing x RPE correlation in the 0.2-0.6 s after reward onset for ACC *N-type* neurons, which was absent in LPFC (ACC, n=43 *N-type* neurons, randomization test p<0.05; LPFC: n=31 *N-type* neurons, no time bin with sign.; **Fig. 3 c,d**).

Classification of neural subtypes of putative interneurons.

We next asked whether the narrow spiking, putative interneurons that encode p(choice) in LPFC and RPE in ACC are from the same electrophysiological cell type, or *e-type* (Markram et al., 2015). Prior studies have distinguished different narrow spiking *e-types* using the cells' spike train pattern and spike waveform duration (Ardid et al., 2015; Dasilva et al., 2019; Trainito et al., 2019; Banaie Boroujeni et al., 2020b). We followed this approach using a cluster analysis to distinguish *e-types* based on spike waveform duration parameters (hyperpolarization rate, time to 25% repolarization), on whether their spike trains showed regular or variable interspike intervals (local variability '*LV*'), or more or less variable firing relative to their mean interspike interval (coefficient of variation '*CV*'). Clustering resulted in eight *e-types* (**Fig. 3a,b**; see **Methods**) similar to previous clustering results (Ardid et al., 2015; Dasilva et al., 2019). Narrow spiking neurons fell into three *e-types*. The first narrow spiking 'N1' *e-type* (n=18, 13% of narrow spiking neurons) showed high firing rates and highly regular spiketrains (low LV's, mean LV 0.47, SE 0.05), an *N2 e-type* (n=27, 20%

of narrow spiking neurons) showed on average Poisson spiketrain variability (LVs's around 1) and the narrowest waveforms, and the *N3 e-type* (n=91, 67% of all narrow spiking neurons) showed intermediate waveform duration and regular firing (LV's < 1, mean LV 0.84, SE 0.02) (**Fig. 4c**). Neurons within an e-type showed similar feature characteristics irrespective of whether they were from ACC or LPFC. For example, N3 e-type neurons from ACC and in LPFC were indistinguishable in their firing and action potential characteristics ($LV_{ACC\ /\ LPFC}$= 0.79/0.88, ranksum-test, p=0.06; $CV_{ACC\ /\ LPFC}$ = 1.19 / 1.31, ranksum-test, p=0.07; Firing $Rate_{ACC/LPFC}$ = 4.41/4.29, ranksum-test p=0.71; action potential Repolarization Time (Hyperpolarization rate)$_{ACC\ /\ PFC}$= 0.18 sec. (97 sec^{-1})/0.17 Sec. (93 sec^{-1})). Beyond narrow spiking classes, spiketrains and LV distributions showed that five broad spiking neuron *e-types* B1-B5 varied from irregular burst firing in *e-types* B2, B3 and B4 (LV>1, class B2 mean LV 1.20, SE 0.02, class B3 mean LV 0.93, SE 0.02 , class B4 mean 1.24 , SE 0.03), regular firing in B1 (LV<1, class B1 mean LV 0.75, SE 0,02) to regular non-Poisson firing in B5 (LV<1, class B5 mean LV 1.68, SE 0.02) (number and % of broad spiking cells: B1: 109 (18%), B2: 103 (17%), B3: 94 (16%), B4: 146 (25%), B5: 138 (23%),) (**Fig. 4b**). LV values >1 indicate bursty firing patterns which is supported by a positive correlation of the LV of neurons with their probability to fire bursts defined as spikes occurring ≤ 5 ms apart ($r = 0.44$, $p < 0.001$). We next calculated the spike triggered MUA modulation for each of the e-type and found that all three narrow spiking *e-types* showed spikes with a suppressive effect on the local MUA (**Fig. 4d**) while broad spiking B *e-types* showed symmetric relation to MUA modulation (**Fig. 4e**, **Suppl. Fig. S6**).

The same putative interneuron subclass encodes p(choice) in PFC and RPE in ACC.

The distinct e-types allowed testing how they correlated their firing with choice probability and with RPE. We found that the only *e-type* with a significant correlation of firing and choice probability during the cue period was the *N3 e-type* in LPFC ($r = 0.08$, Kruskal Wallis test, $p=0.04$; randomization test difference to zero, multiple comparison corrected, $p<0.05$; **Fig. 5a,b**). Consistent with this correlation, neurons of the *N3-type* in LPFC also significantly increased firing to the color cue irrespective of whether the color cue appeared early or later in the trial ($p<0.05$ during 0.04-0.2 s after feature 2 onset**,** and $p<0.05$ during 0.175-0.225 s after feature 1 onset, **Suppl. Fig. S5**). There was no other *e-type* in LPFC and in ACC showing significant correlation with choice probability.

Similar to the *N3 e-type* in LPFC, in ACC it was the *N3 e-type* that was the only narrow spiking subclass with a significant functional firing rate correlation with reward prediction errors (RPE) (n=30 neurons; $r = 0.09$, Kruskal Wallis test, $p=0.01$, randomization test for sign. difference to zero, multiple comparison corrected $p<0.05$, **Fig. 5c,d**). The only other e-type with a significant firing rate x RPE correlation was the B4 class which fired stronger with lower RPE's E (n=18 neurons; $r = -0.08$, Kruskal Wallis test, $p=0.01$, randomization test for sign. difference to zero, multiple comparison corrected $p<0.05$). There was no subtype specific RPE correlation in LPFC (**Fig. 5c**,**d**).

Narrow spiking neurons synchronize to theta, beta and gamma band network rhythms.

Prior studies have suggested that interneurons have unique relationships to oscillatory activity (Cardin et al., 2009; Vinck et al., 2013; Womelsdorf et al., 2014a; Voloh and Womelsdorf, 2018), raising the possibility that N3 *e-type* neurons realize their functional role also through neuronal

synchronization. To discern this, we first inspected the spike triggered LFP averages (STA's) of neurons and found that STA's of many N3 *e-type* neurons showed oscillatory sidelobes in the 10-30 Hz range (**Fig. 6a**). We quantified this phase synchrony by calculating the spike-LPF pairwise phase consistency (PPC) and extracting statistically significant peaks in the PPC spectrum (Vinck et al., 2012; Banaie Boroujeni et al., 2020a), which confirmed the presence of significant synchrony peaks across theta/alpha, beta and low gamma frequency ranges (**Fig. 6b**). The density of spike-LFP synchrony peaks showed a high prevalence of 15-30 Hz beta synchrony for broad spiking neurons in both, ACC and LPFC, a peak of ~5-12 Hz synchrony that was unique to ACC, and a high prevalence of 35-45 Hz gamma synchronization in narrow spiking cells (but not broad spiking cells) in both areas (**Fig. 6c**). The synchrony peak densities of the N3 *e-type* neurons mimicked this overall pattern by showing beta to gamma synchrony peak density in LPFC and a 5-12 Hz theta/alpha and a gamma synchrony in ACC (**Fig. 6c**) (for other e-types, see **Suppl. Fig. S7**).

Interneuron-specific gamma synchrony to cues in LPFC and outcomes in ACC.

The overall synchrony patterns leave open whether the synchrony is task modulated or conveys information about choices and prediction errors. We addressed these questions by calculating spike-LFP phase synchronization time-resolved around the color cue onset (for LPFC) and around reward onset (for ACC) separately for trials with high and low choice probabilities (for LPFC) and high and low reward prediction errors (for ACC). We found in LPFC that the N3 *e-type* neurons shows a sharp increase in 35-45 Hz gamma band synchrony shortly after the color cue is presented and choice probabilities are low (i.e. when the animals are uncertain which stimulus is rewarded), while broad spiking neurons do not show gamma synchrony (**Fig. 7a-c**) (N3 *e-type* vs broad

spiking cell difference in gamma synchrony in the 0-700 ms after color cue onset: $p<0.05$ randomization test, multiple comparison corrected). When choice probabilities are high, N3 *e-type* neurons and broad spiking neurons showed significant increases of 20-35 Hz beta-band synchronization (**Fig. 7d**,**e**) with N3 *e-type* neurons synchronizing significantly stronger to beta and gamma than broad spiking neuron types (**Fig. 7f**) ($p<0.05$ randomization test, multiple comparison corrected).

For ACC, the N3 *e-type* neurons as well as the broad spiking neurons that significantly synchronized in a 35-42 Hz gamma band following the reward onset when RPE's were high (i.e. when the outcome was unexpected) (**Fig. 8a,b**). During these high RPE trials, the gamma synchrony emerged earlier (**Fig. 8a,b**) and significantly stronger in N3 *e-type* neurons than broad spiking neurons (**Fig. 8c**). In contrast, when RPE's were low the reward onset triggered increased 6-16 Hz theta/alpha frequency spike-LFP synchronization in N3 *e-type* and broad spiking neurons (**Fig. 8d,e**). The increase of 8-14 Hz synchrony was significantly stronger in the *N3 e-type* than in broad spiking neurons (**Fig. 8f**).

A circuit model of interneuron-specific gating of values and outcome predictions.

The described key results show interneuron-specific firing rate and synchrony modulations to changes in choice probabilities (CP) and reward prediction errors (RPE). These quantities are based on a reinforcement learning model that learns the values of object features, chooses among two objects based on their values, and updates the values of the chosen object features according to the magnitude of the prediction error. To understand mechanistically how these RL processes

could be supported by interneuron specific gamma activation in LPFC and ACC we constructed a biologically plausible circuit model (**Fig. 9**)(Womelsdorf et al., 2014b).

This model assumes that the two visual objects we present in our task drive two separate pyramidal cell ensembles in LPFC representing their expected value. These ensembles project to N3 *e-type* interneurons, presumed to be PV+, fast-spiking basket cells (*see* discussion), which are connected amongst themselves. When such an interneuron network is activated by excitatory inputs it can synchronize by way of mutual inhibition at beta or gamma frequencies depending on the total amount of drive the network receives (Wang and Buzsaki, 1996; White et al., 1998; Tiesinga and Jose, 2000). When both objects have similar values (*see* **Fig. 9a**), the drive to the network is high and it synchronizes in the gamma band. When one of the objects has a value that is much larger than the other (*see* **Fig. 9b**), it results in a medium level of drive that makes the network synchronize in the beta band. We observed such a switch from gamma to beta frequencies in N3 *e-type* interneurons in LPFC when the choice probabilities changed from low to high (**Fig. 7**). We therefore suggest that the N3 *type* inhibition accomplishes two things, it leads to a normalization that transforms the object value into a choice probability (a softmax gating of values) and its gamma synchrony selects a winner (**Fig. 9a**). A similar synchrony-based gating of diverse inputs has been described as a powerful circuit mechanism for selecting a target stimulus among distractors during visual attention and working memory tasks (Buia and Tiesinga, 2008; Sherfey et al., 2018; Sherfey et al., 2020). Modeling also suggests that the interneuron network is most likely heterogeneous, which means there will be N3 *e-type* neurons that increase their rate and others that decrease their rate upon synchronization (Tiesinga and Sejnowski, 2004). Importantly, the output of this gamma mediated gating in LPFC is a neural ensemble representing the values of

the chosen object ('V_t-*chosen*' in **Fig. 9**). We hypothesize that this chosen value V_t is projected to ACC where N3 *e-type* neurons combine it with input about the reward R_t to calculate the reward prediction error $RPE = R_t - V_t$ (Watabe-Uchida et al., 2017) (*see* eq. 2 in Methods). Since N3 *e-type* neurons fired stronger when RPE was large (i.e. when the chosen value was low (≤0.5)) we assume that N3 *e-type* neurons do not receive V_t inputs directly, but indirectly from an intermediate interneuron that disinhibits them when the chosen values are high (**Fig. 9a**). Such disinhibition could be realized by N1 *e-type* neurons which tended to correlate negatively with RPE in ACC (**Fig.5d**). The activation of this neuron suppresses N3 *e-type* neurons when the chosen value is high (**Fig. 9b**). But when the chosen value is low the N3 *e-type* neurons are not suppressed by V_t. They rather receive excitatory drive about the reward input R_t and show gamma synchronization, suggesting that the gamma synchronous RPE correlated N3 *e-type* neurons in ACC form an interneuron network that synchronizes at gamma when driven strongly (**Fig. 9a**), but does not show gamma when chosen values match the obtained reward (**Fig. 9b**). The described circuits entail that N3 *e-type* interneurons in ACC and LPFC form similar interneuron networks. In LPFC the N3 *e-type* interneuron network gates values of conflicting object values, and in ACC it gates reward outcomes according to the chosen values. In both networks, the N3 *e-type* interneurons synchronize at gamma when there is more synaptic excitatory drive during the reversal learning period of the task (**Fig. 7, 8**).

Discussion

We found that narrow spiking neurons in the medial and lateral prefrontal cortex of macaques show a suppressive effect on the local multiunit activity indicative of inhibitory interneurons. These putative interneurons increased their firing rates in LPFC to the color-cue onset, encoded

the rewarded color and correlated their rates with the choice probabilities, while in ACC their firing correlated with reward prediction errors during the processing of the reward outcome. These functional signatures were specifically linked to a putative interneuron subtype that showed intermediate narrow action potential waveforms and more regular firing patterns than expected from a Poisson process (LV's of N3 *e-type* neurons: 0.84). Moreover, this putative interneuron subtype (N3 *e-type*) engaged in prominent event-triggered 35-45 Hz gamma band synchronization in each of the recorded brain areas. In LPFC the N3 *e-type* gamma synchronized to the cue when choice probabilities were low and uncertain, and in ACC the N3 *e-type* gamma synchronized to the reward onset when the RPE was high and the reward outcome was unexpected. Thus, the same *e-type* showed functional firing correlations and gamma synchrony in LPFC and in ACC indicating an area specific functional contribution with the same activation signature.

Taken together, these findings point to a special role of the same type of interneuron in LPFC and in ACC to realize their area specific functional contribution to the color-based reversal learning task. This interpretation highlights several aspects of interneuron specific circuit functions.

Characterizing narrow spiking interneurons in vivo

The first implication of our findings is that narrow spiking neurons can be reliably subdivided in three subtypes based on their electrophysiological firing profiles. Distinguishing three narrow spiking neurons in vivo is a significant step forward to complement tripartite electrophysiological distinctions of interneurons in vitro (Zaitsev et al., 2009; Torres-Gomez et al., 2020) or using molecular and genetic classification schemas that show a multitude of distinguishable interneurons with ion channel make up that lead to narrow action potential shapes (Markram et al., 2004;

Monyer and Markram, 2004; Medalla et al., 2017). The genetic and molecular tools have the limitation that they are not easily applied to the whole population of activated neurons during task performance in primates. In this situation our study could prove particularly important in pinpointing the electrophysiological characteristics of those putative interneurons that are functionally activated during performance and thereby associated with essential task variables like the choice probability of the rewarded target feature and the strength of the reward prediction error.

We believe that the N3 *e-type* that showed functional correlations in two areas encompasses mostly parvalbumin PV+ expressing neurons, because of their narrow spikes, regular interspike intervals and their propensity to synchronize at gamma, which resemble the regular firing and gamma synchrony described for PV+ cells in the rodent (Cardin et al., 2009; Tiesinga, 2012; Stark et al., 2013; Amilhon et al., 2015). Moreover, similar to the N3 *e-type* responses to the attention cue, rodent dorsomedial frontal PV+ neurons systematically activate to preparatory cues while somatostatin neurons respond significantly less (Pinto and Dan, 2015). However, PV+ neurons are heterogeneous and entail Chandelier cells and variably sized basket cells (Markram et al., 2004; Markram et al., 2015). It might therefore be an important observation that the N3 *e-type* was distinguished from another narrow spiking neuron by having a lower baseline firing rate and an intermediate-narrow action potential shape as opposed to the narrowest waveform and highest firing rates that N1 e-types showed. The tentative suggestion that N3 *e-type* neurons will be mostly PV+ cells also entails for the primate brain that they would not be part of calretinin (CR+) or calbindin (CB+) expressing cells as their expression profiles do not apparently overlap (Dombrowski et al., 2001; Medalla and Barbas, 2009; Raghanti et al., 2010; Torres-Gomez et al., 2020).

What is the circuit role of the N3 interneuron *e-type*?

Firing of N3 *e-type* neurons suppressed multiunit activity in the circuit (**Fig. 1f-h**). Assuming they encompass PV+ neurons we speculate that this translates into gamma rhythmic inhibition of local circuit pyramidal cells close to their soma where they impose output gain control (Tiesinga et al., 2004; Bartos et al., 2007; Womelsdorf et al., 2014b; Tremblay et al., 2016). In our task, this putative N3 *e-type* mediated local inhibition was related to how uncertain the reward values of stimuli were (reflected in low choice probabilities) or how unexpected rewarded outcomes were (reflected in high RPE's). These conditions are periods that require a behavioral adaptation for which N3 *e-type* mediated inhibition could be instrumental. For example, LPFC pyramidal cells that encoded the rewarded color in trials prior to the un-cued reversal become irrelevant when the reversal links reward to the alternative color and hence need to be suppressed during the reversal. This suppression of neurons encoding the previously relevant but now irrelevant color might thus be realized through N3 *e-type* neuron activation in LPFC. In analogy to LPFC, the N3 *e-type* activation in ACC during unexpected reward (high RPE) reflects a rise in inhibition when there is a larger requirement to update values for future trials to facilitate choosing those stimuli that exceeded expectation. Reinforcement learning modeling and attention theories suggests that the size of the RPE is directly signaling how much the neuronal value representations should adjust their value expectations to optimize choices in subsequent trials (Sutton and Barto, 2018; Oemisch et al., 2019).

The described, putative functions of N3 e-type activity gives rise to a circuit model of behavioral regulation that shows how the functional roles of encoding choice probabilities and prediction

errors can emerge from interneuron specific circuit mechanisms. **Fig. 9a** highlights that during learning the N3 *e-type* neurons may gate the conflicting value representations of objects into a choice (softmax rule, eq. 4 in Methods), which would explain that they correlate with the choice probability of the actually chosen stimulus. This choice correlation emerged when the color cue was shown and thus was linked specifically to N3 *e-type* neurons in the LPFC. After a choice was made and a reward outcome R_t is received the value of the chosen object V_t is the key variable to compute the reward prediction error ($RPE = R_t - V_t$). N3 *e-type* neurons in ACC fired larger when *RPE* was larger suggesting they respond to the mismatch of R_t and V_t, which can be achieved by having excitatory drive of reward representing units and the lack of inhibitory drive from a disinhibitory intermediate neuron. Such disinhibition might balance the reward driven excitation either through direct connections to N3 *e-type* interneurons (as in **Fig. 9**), or through connections to reward representing pyramidal cells. Disinhibitory connections are typical for calretinin expressing interneurons that receive ~35% of excitatory afferent connections (while PV+ cells receive ~18% afferent connections and pyramidal cells receiving ~65%) neurons in primate prefrontal cortex (Medalla and Barbas, 2009, 2010). In our study such a disinhibition could include the N1 *e-type* population that tended to have opposite RPE correlation than N3 *e-type* neurons.

In summary, the proposed circuit model of behavioral regulation asserts that N3 *e-type* neurons will have a similar gating function for the output of the circuit in LPFC and in ACC, but they operate on different inputs in each area. The model hypothesizes that these interneurons in LPFC gate object values into choices, while in ACC gate chosen value and rewards into a scalar updating signal (the reward prediction error). It will require a combined electrophysiological and optogenetic approach to tag these cells in future studies for causally testing their importance for

the proposed circuit functions. The results presented here provide a powerful starting point for these causal experiments in primates to clarify cell-type specific circuit functions during higher cognitive functions.

Interneuron-specific gamma synchronization realizes area specific functions.

Two key findings of our study pertain to spike-LFP gamma band synchronization. First, we found that N3 *e-type* neurons showed an event-triggered synchrony increase in the same 35-45 Hz gamma frequency band in both LPFC and ACC (*see* **Fig. 7c and 8f**). The N3 *e-type* gamma synchrony was not paralleled by synchrony of broad spiking neurons, which either did not synchronize or synchronized to beta and theta/alpha rhythms. These observations suggest that gamma synchrony was intrinsically generated by the putative N3 *e-type* interneurons themselves as opposed to being inherited from pre-existing rhythmic activity of the larger network, e.g. from afferent connections to interneurons (Medalla and Barbas, 2009; Schmitt et al., 2017; Ahrlund-Richter et al., 2019). Such an intrinsic propensity for generating gamma rhythmic activity through, e.g. $GABA_a$ergic time constant, is well described for PV+ interneurons (Wang and Buzsaki, 1996; Bartos et al., 2007; Womelsdorf et al., 2014b; Chen et al., 2017) even at relatively low excitatory feedforward drive that might be more typical for prefrontal cortices than earlier visual cortices (Cardin et al., 2009; Vinck et al., 2013). Consistent with a cell-intrinsic gamma specific activity we found that gamma synchronization was selectively associated with narrow spiking neurons in LPFC and ACC while there was not a single broad spiking neural *e-type* that showed a ~40 Hz gamma peak in their overall spike-LFP spectrum (**Suppl. Fig. S7**). Taken together, these findings provide strong empirical evidence that narrow spiking interneurons are not only the main carriers of gamma rhythmic activity in nonhuman primate prefrontal cortex, but are also primary generators of

gamma activity in-vivo (Whittington et al., 2000; Hasenstaub et al., 2005; Bartos et al., 2007; Hasenstaub et al., 2016; Chen et al., 2017). This conclusion resonates well with rodent studies that document how interneurons in infra-/peri-limbic and cingulate cortex engage in gamma synchrony (Fujisawa and Buzsaki, 2011; Cho et al., 2015).

The second major implication of the gamma synchronous N3 *e-type* neurons is that gamma band synchrony was associated with task epochs in which neural circuits realize an area-specific circuit function. In LPFC, the gamma increase was triggered by the color-cue onset of two peripherally presented stimuli that instructed covertly shifting attention. Our circuit model (**Fig. 9a**) illustrates that cue related gamma was restricted to periods when object values were similar, and the animal still learned which object is most reward predictive. The control of learning what is relevant during cognitively demanding tasks is a key function of the lateral prefrontal cortex, suggesting that gamma activity emerges when this key function is called upon (Miller and Cohen, 2001; Szczepanski and Knight, 2014; Cho et al., 2020). A similar scenario holds for the ACC whose central function is often considered to monitor and evaluate task performance and detect when outcomes should trigger change in behavioral strategies (Shenhav et al., 2013; Heilbronner and Hayden, 2016; Alexander and Brown, 2019; Fouragnan et al., 2019). In ACC, the gamma increase was triggered by an unexpected rewarded outcome (high RPE). Thus, the N3 *e-type* specific gamma band signature occurred specifically in those trials with conflicting stimulus values requiring behavioral control to reduce the prediction errors through future performance (**Fig. 9a**). Considering this ACC finding together with the PFC finding suggest that gamma activity of N3 *e-type* neurons is particularly important when these areas exert their area specific key function, supporting recent causal evidence from rodent optogenetics (Cho et al., 2020).

Consistent with the proposed importance of interneurons for area-specific key functions prior studies have documented the functional importance of inhibition in these circuits. Blocking inhibition with GABA antagonists like bicuculline not only renders fast spiking interneurons nonselective during working memory tasks but abolishes the spatial tuning of regular spiking (excitatory) cells during working memory tasks in monkeys (Sawaguchi et al., 1989; Rao et al., 2000), disturbs accuracy in attention tasks (Paine et al., 2011) and reduces set shifting flexibility by enhancing perseveration (Enomoto et al., 2011). Similarly, abnormally enhancing GABAa levels via muscimol impairs working memory and set shifting behavior (Rich and Shapiro, 2007; Urban et al., 2014) and can result in either maladaptive impulsive behaviors (Paine et al., 2015), and when applied in anterior cingulate cortex to perseveration (Amiez et al., 2006). Thus, altered medial and lateral prefrontal cortex inhibition is closely linked to an inability to adjust attentional strategies given unexpected outcomes. This evidence provides additional evidence complementing our findings of the importance of inhibitory neuron involvement in RPE and choice probability coding.

Taken together, our interneuron specific findings in primate LPFC and ACC stress the importance of interneurons to influence circuit activity beyond a mere balancing of excitation. Multiple theoretical accounts have stressed that some types of interneurons 'control information flow' (Fishell and Kepecs, 2019), by imposing important filters for synaptic inputs to an area and gain-control the output from that area (Akam and Kullmann, 2010; Kepecs and Fishell, 2014; Womelsdorf et al., 2014b; Roux and Buzsaki, 2015; Cardin, 2018). Testing these important circuit functions of interneurons has so far been largely limited to studies using molecular tools. Our study

addresses this limitation by characterizing putative interneurons, delineating their suppressive effects on the circuit and highlighting their functional activation during reversal learning. The observed interneuron specific, gamma synchronous coding of choice probabilities and prediction errors lends strong support for studying the cell-type specific circuit function of neurons to support higher cognitive functions.

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Competing Interests

The authors declare no competing interests.

Supplementary Information is available for this paper

Figures:

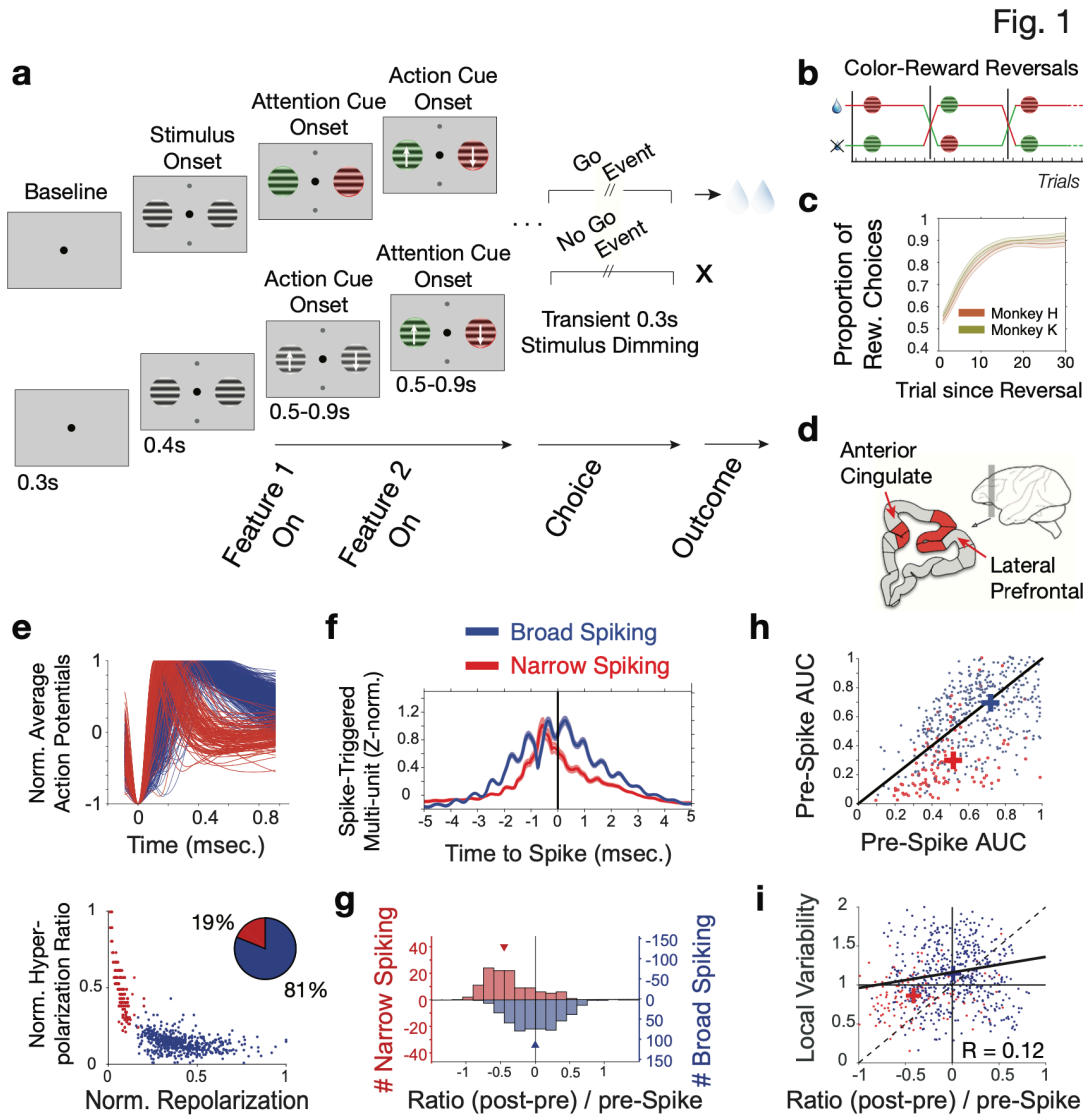

Figure 1. Task Paradigm and Cell Classification. (**a**) Trials required animals to covertly attend one of two peripheral stimuli until a dimming (Go-event) instructed to make a saccade in the direction of the motion of the attended stimulus. During the trial the two stimuli were initially static black/white and then either were colored first or started motion first. Following this feature 1 Onset the other feature (Feature 2 on) was added 0.5-0.9 s later. (**b**) The task reversed the color (red or green) that was rewarded over at least 30 trials. (**c**) Two monkeys learned through trial-and-error the rewarded associated colors evident in increased probability of rewarded choices (*y-axis*) over trials since reversal (*x-axis*). (**d**) Recorded areas (details in **Suppl. Fig. S1**). (**e**) *Top*: Average normalized action potential waveforms of recorded neurons were narrow (*red*) or broad (*blue*). *Bottom*: Hyperpolarization ratio and repolarization duration distinguishes neurons. (**f**) Average spike-triggered multiunit modulation for narrow and broad spiking neurons (Errors are SE's). (**g**) The histogram of post-to-pre spike AUC ratios for narrow (*red*) and broad (*blue*) spiking neurons. (**h**) Scatterplot of the area under the pre-spike versus post-spike multuinut-modulation shows that narrow spiking neurons lead to reduced post-spike MUA activity. (**i**) The post-to-pre spike AUC ratio positively correlates with the local interspike-interval variability (*Local Variability*, LV) spiketrains more regular (*red*, LV<1) in narrow than in broad spiking (*blue*, LV>1) neurons (*red*).

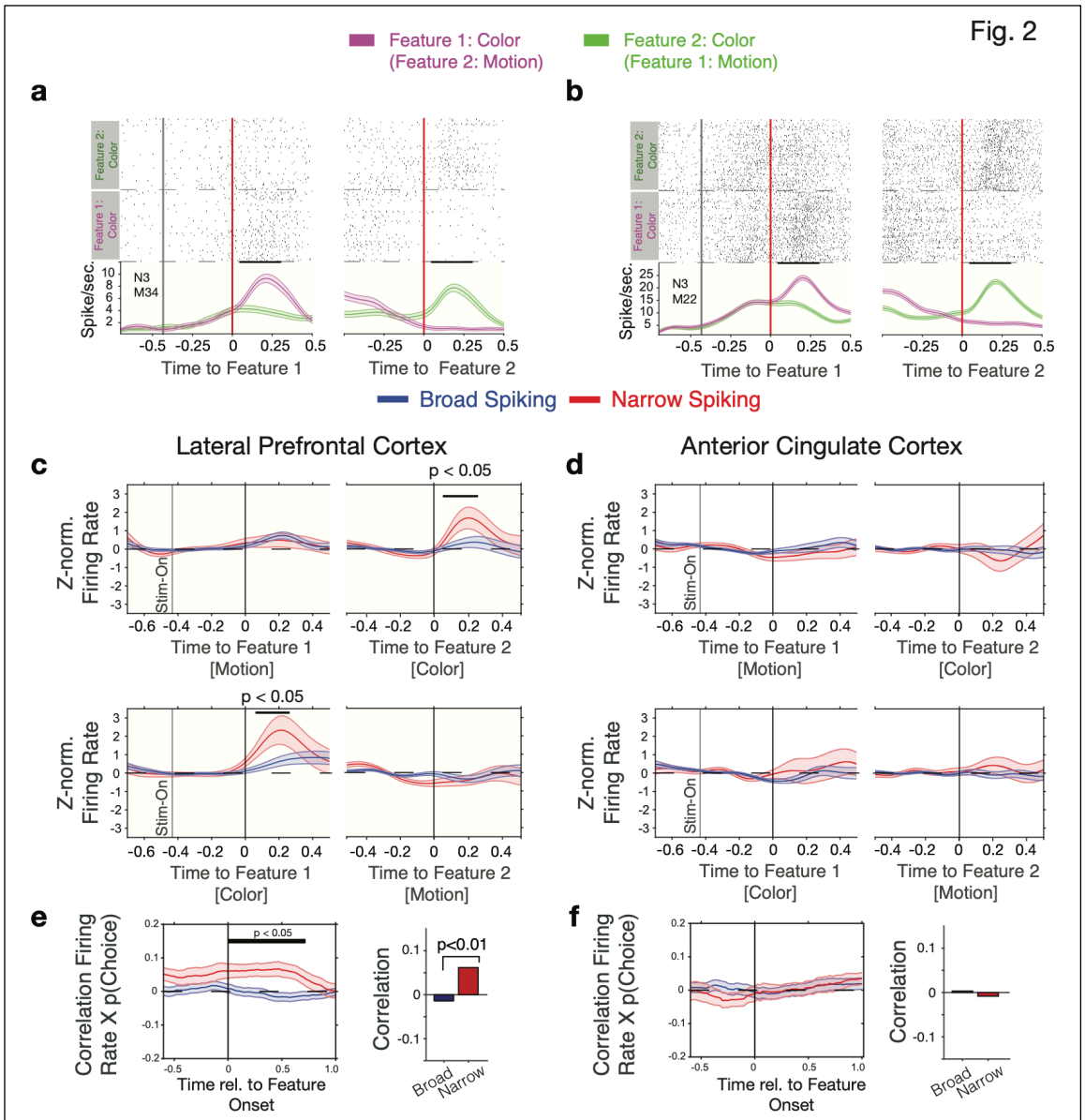

Figure 2. Firing rate modulation of narrow and broad spiking neurons to the color cue correlate with choice probability. (**a**, **b**) Spike rasters for example neurons around the onset of feature-1 and feature-2 when feature-1 was color (magenta) or motion (green). Both neurons responded stronger to the color than the motion onset irrespective of whether it was shown as first or as second feature during a trial. (**c**) Narrow spiking neurons (red) in LPFC respond to the color onset when it occurred as feature-2 (*upper panel*), or as feature-1 (*bottom panel*). (**d**) Same as *c* for the ACC shows no or weak feature onset responses. (**e**) Firing rates of narrow spiking neurons (red) in LPFC correlate with the choice probability of the to be chosen stimulus (*left*). The average Rate x Choice Probability correlation in LPFC was significantly larger in narrow than in broad spiking neurons (*right*). (**f**) Same as *e* for ACC shows no significant correlations with choice probability.

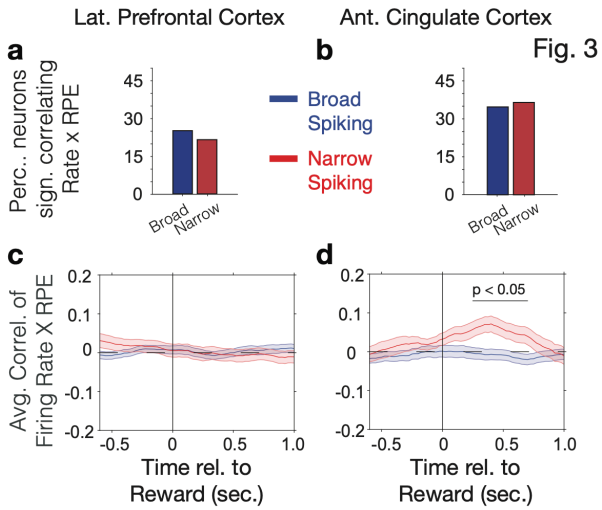

Figure 3. Firing rate modulation to trial outcomes correlate with reward prediction errors. (**a, b**) Proportion of narrow and broad spiking neurons in LPFC (*a*) and ACC (*b*) with significant firing rate X reward prediction error correlations in the [0 0.75] s after trial outcomes were received. (**c, d**) Time course of firing rate X reward prediction error correlations for narrow and broad spiking neurons in LPFC (*c*) and ACC (*d*) around the time of reward onset. Horizontal bar denotes time with significant correlations.

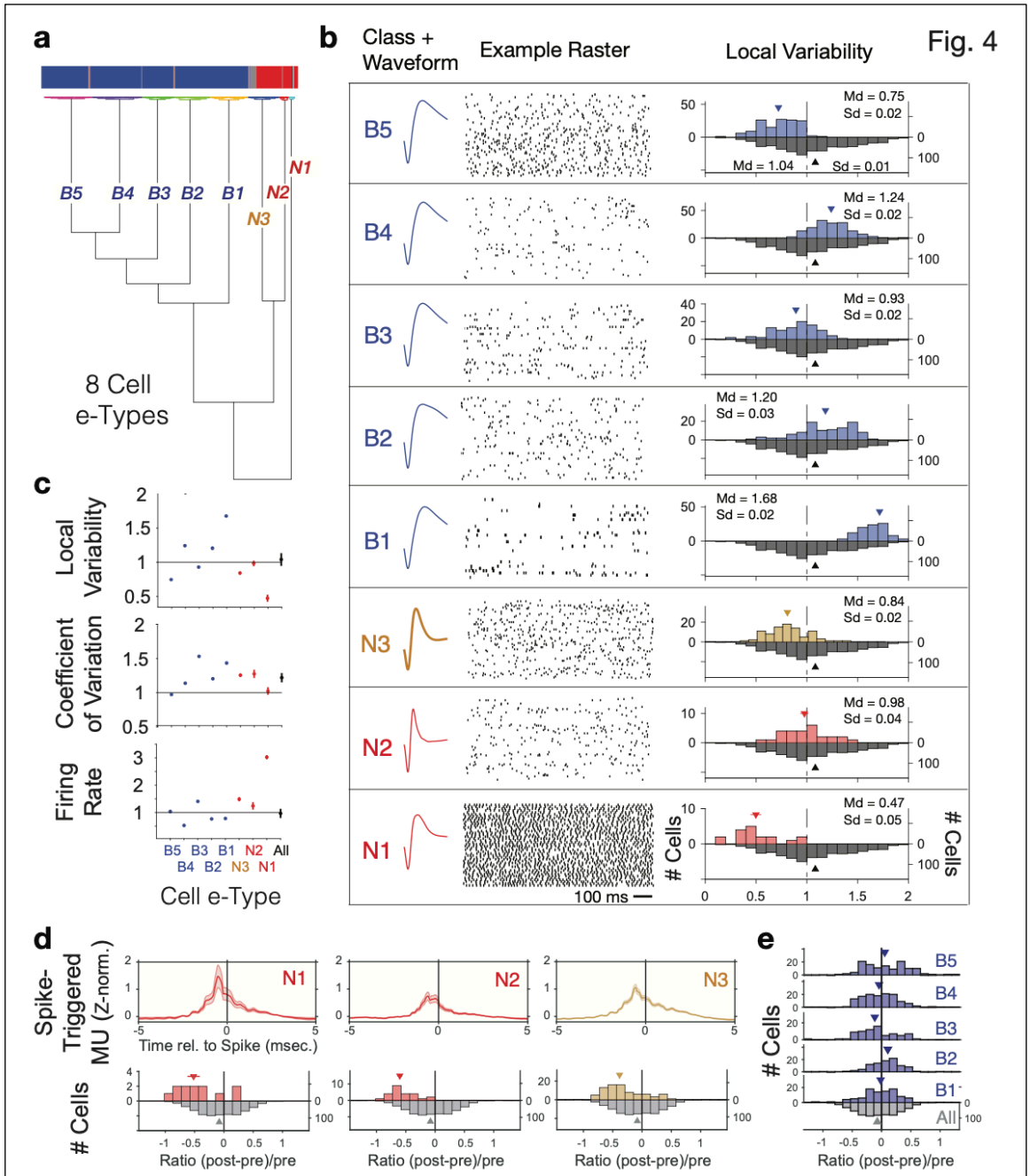

Figure 4. Clustering of *e-type* sub-classes of cells using their spike width, firing variability and rate. (**a**) Dendrogram of cluster distances for neuron classes with broad spikes (five subclasses, *blue*), and narrower spikes (three subclasses, *orange* and *red*). (**b**) Illustration of the average spike waveform, spiketrain raster example, and Local Variability (LV, *upper* histograms) for each clustered *e-type*. The bottom grey LV histogram includes all recorded cells to allow comparison of *e-type* specific distribution. (**c**) For each e-type (*x-axis*) the average LV, CV and firing rate. The rightmost point shows the average for all *e-types* combined. (**d**) The average spike-triggered multiunit modulation (*upper* panel) for *e-type* classes N1, N2 and N3. Bottom panel shows the distribution for the specific subtype (in *color*) and for all cells (in *grey*) revealing systematically reduced multiunit firing after the *e-types* fire a spike compared to before the spike. (**e**) Distribution of spike-triggered multiunit modulation for broad spiking *e-types* B1-B5 reveals symmetric modulation before and after the spike. Triangles denote medians. Error bars are SE.

Fig. 5

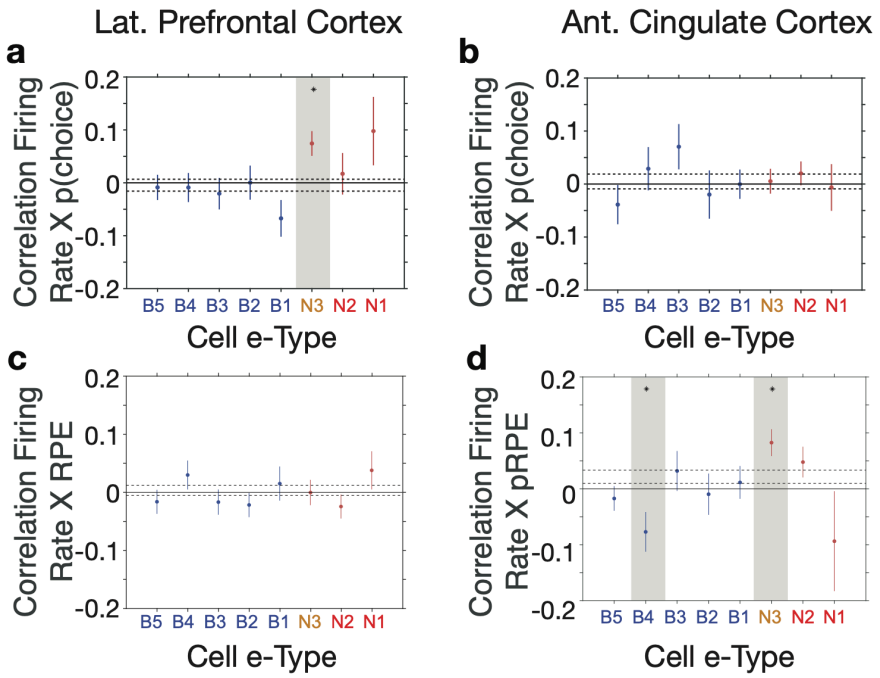

Figure 5. *E-type* specific correlations with choice probability and reward prediction error in LPFC and ACC. (a, b) Firing Rate X Choice Probability correlations for neurons of each *e-type* subclass in LPFC (*a*) and ACC (b). Only the N3 *e-type* neurons in LPFC show significant correlations. **(c, d)** Firing Rate X Reward Prediction Error correlations for neurons of each *e-type* subclass in LPFC (*c*) and ACC (*d*). The N3 *e-type* neurons in ACC show significant positive correlations, and the B3 *e-type* shows negative firing rate x RPE correlations. Grey shading denotes significance at $p<0.05$ (multiple comparison corrected). Error bars are SE's.

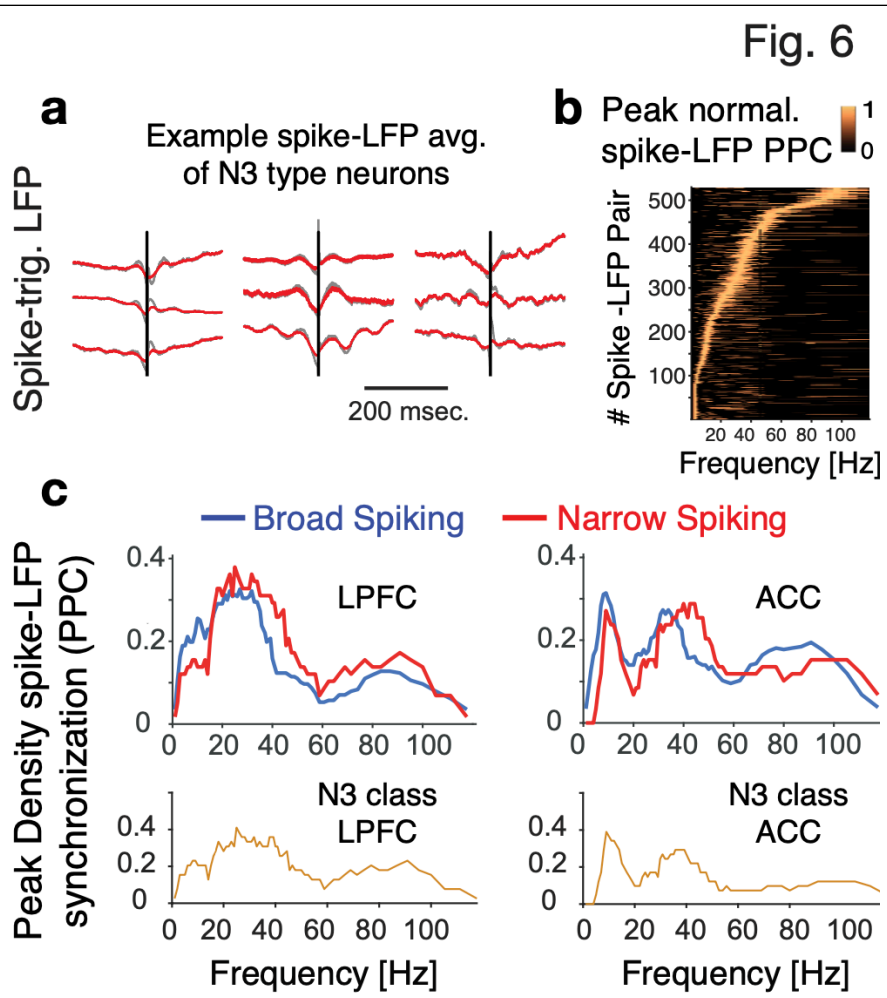

Figure 6. Spike-LFP phase synchronization. (**a**) Average spike-triggered local field potential fluctuations of nine N3 *e-type* neurons showing a transient LFP oscillations from 5 Hz up to ~30 Hz. Black vertical line is the time of the spike. The red lines denote the LPF after adaptive spike artifact removal (raw traces in grey). (**b**) Peak normalized pairwise phase consistency for each spike-LFP pair (*y-axis*) rank ordered according to the frequency (*x-axis*) with peak PPC. (**c**) Peak densities of spike-LFP synchronization for neurons in LPFC (*left*) and ACC (*right*) for narrow and broad spiking neurons (*upper rows*) and for the N3 *e-type* neurons (*bottom row*).

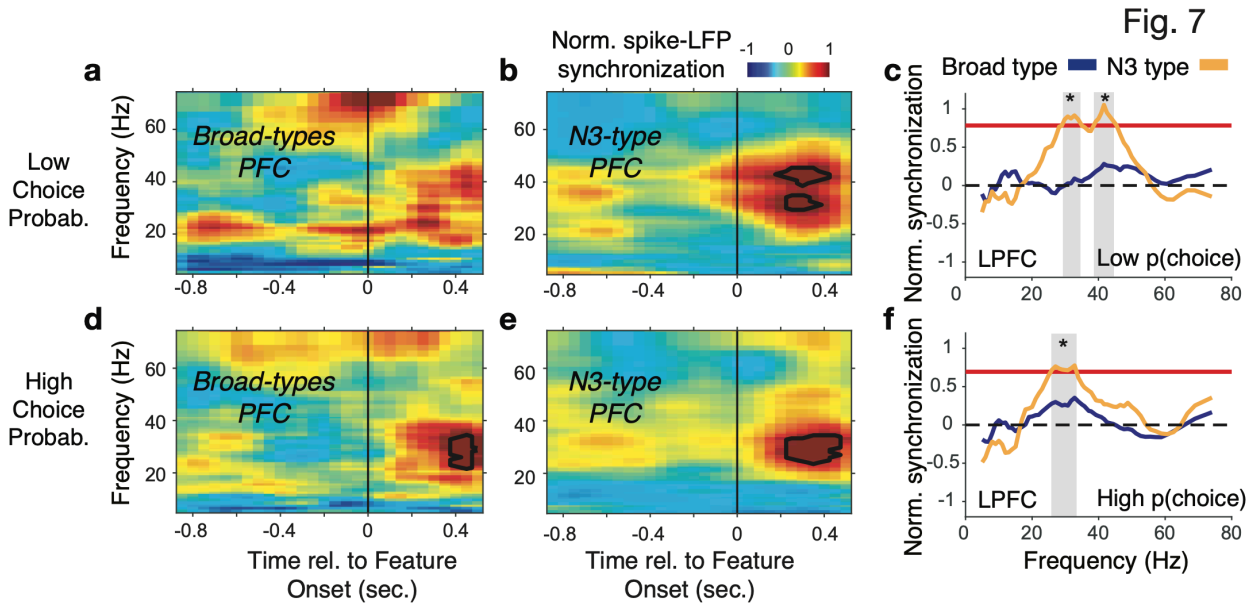

Figure 7. Spike-LFP phase synchronization in LPFC around the color onset for trials with low and high choice probability. (**a**) Spike-LFP pairwise phase consistency for broad spiking neurons in LPFC around the time of the color onset (*x-axis*) for trials with the 50% lowest choice probabilities. (b) Same as (*a*) for neurons of the N3 *e-type*. Black contour line denotes statistically significant increased phase synchrony relative to the pre-color onset period. (**c**) Statistical comparison of spike-LFP synchrony for N3 *e-type* neurons (orange) versus broad spiking neurons (blue) for low choice probability trials in LPFC. Synchrony is normalized by the pre-color onset synchrony. Grey shading denotes $p<0.05$ significant differences of broad and N3 type neurons. (*d,e,f*) Same format as (*a,b,c*) but for the 50% of trials with the highest choice probability.

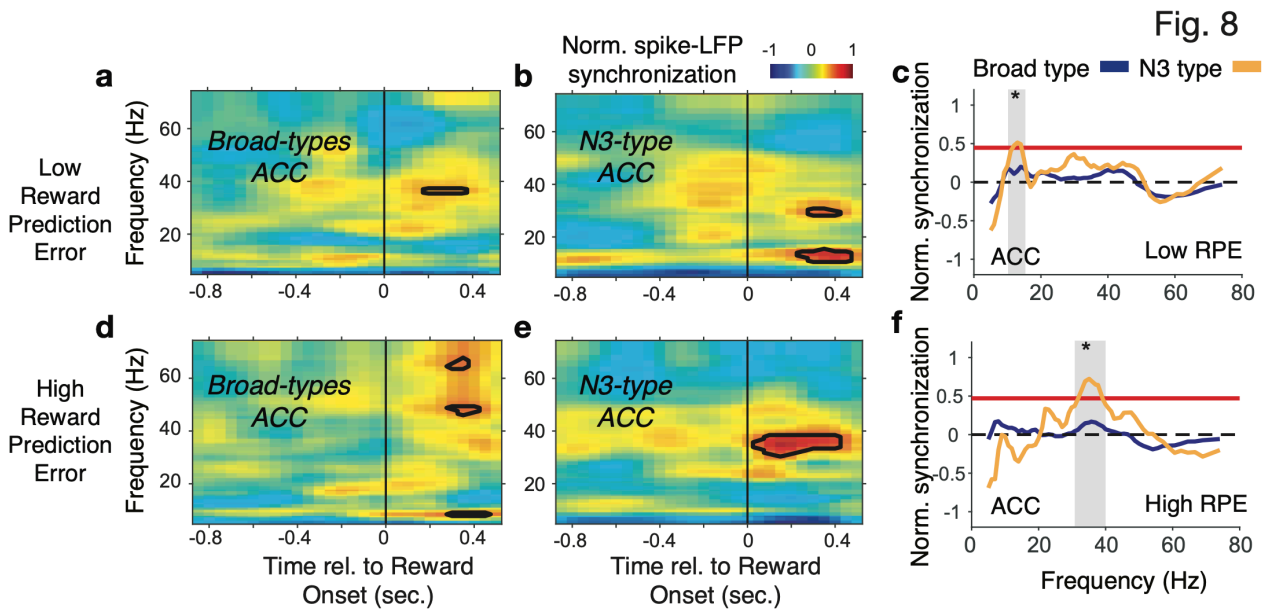

Figure 8. Spike-LFP phase synchronization in ACC during outcome processing for trials with low and high reward prediction errors. (**a**) Spike-LFP pairwise phase consistency for broad spiking neurons in ACC around reward onset (*x-axis*) for trials with the 50% lowest reward prediction errors. (**b**) Same as (*a*) for neurons of the N3 *e-type*. Black contour line denotes statistically significant increased phase synchrony relative to the pre-reward period. (**c**) Statistical comparison of the spike-LFP synchrony (normalized by the pre-reward synchrony) for N3 *e-type* neurons (orange) versus broad spiking neurons (blue) in ACC for trials ending in low reward prediction errors. Grey shading denotes frequencies with $p<0.05$ significant differences of broad spiking versus N3 *e-type* neurons. (**d,e,f**) Same format as (a,b,c) but for the 50% of trials with the highest high reward prediction error outcomes.

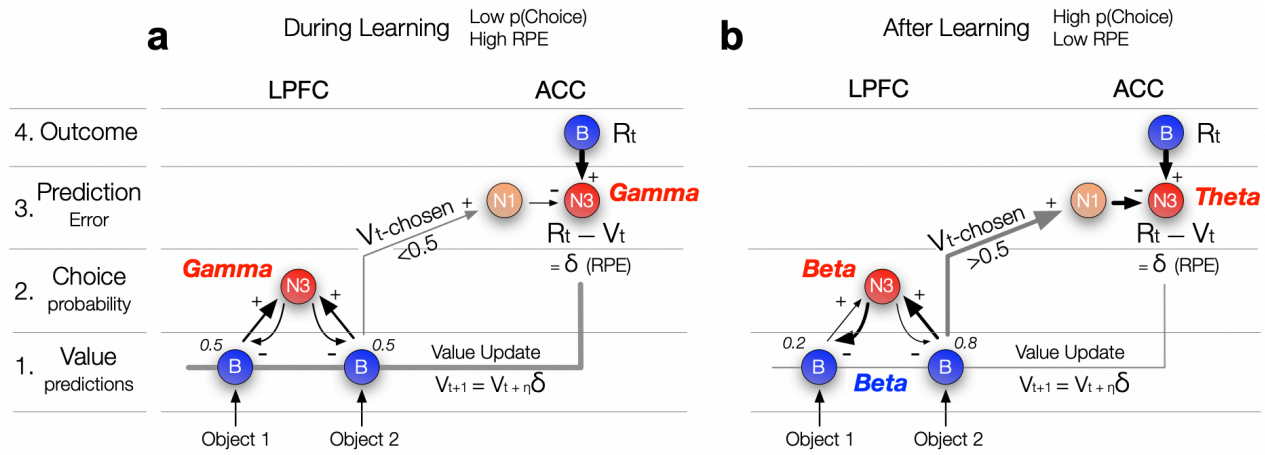

Figure 9. Circuit architecture accounting for interneuron specific synchronization. The circuit suggests that in LPFC (*1.*) object values are encoded by pyramidal cells and (2.) choice probabilities are calculated by an N3 *e-type* interneuron network. In ACC, (3.) prediction errors are calculated by a N3 *e-type* interneuron network given the value of the chosen object and (4.) the activity of pyramidal cells encodes the received reward. Value and reward outcome encoding in LPFC and ACC was shown before in (Oemisch et al., 2019). (**a**) When object values are similar (e.g. ~0.5 each) the interneuron network receives a strong drive, causing gamma synchrony and a gating of one of the values. The chosen value is then projected to an interneuron network in ACC that calculates the reward prediction error (RPE) and synchronizes at gamma when the chosen value is relatively low relative to the obtained reward, corresponding to a high RPE. This N3 e-type gamma synchronous response indicates that values need to be updated (thick grey line from ACC to LPFC). (**b**) Same network as (*a*) when one object has a high and another object a low value. In this case, the overall excitatory drive to the interneuron network is lower resulting in beta synchronization in LPFC, and in ACC a switch from N3 *e-type* gamma synchrony to theta synchrony that follows the rhythmic activity of reward activated pyramidal cells. In this case, N3 e-type cells show low firing rates indicating a low RPE, hence that no value update is needed (thin grey line from ACC to LPFC). *See* text for details.

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