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A Model of the Differential Representation of Signal Novelty in the Local Field Potentials and Spiking Activity of the Ventrolateral Prefrontal Cortex

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Abstract

Local field potentials (LFPs) and spiking activity reflect different types of information processing. For example, neurophysiological studies indicate that signal novelty in the ventrolateral prefrontal cortex is differentially represented by LFPs and spiking activity: LFPs habituate to repeated stimulus presentations, whereas spiking activity does not. The neural mechanisms that allow for this differential representation between LFPs and spiking activity are not clear. Here, we model and simulate LFPs and spiking activity of neurons in the ventrolateral prefrontal cortex in order to elucidate potential mechanisms underlying this differential representation. We demonstrate that dynamic negative-feedback loops cause LFPs to habituate in response to repeated presentations of the same stimulus while spiking activity is maintained. This disassociation between LFPs and spiking activity may be a mechanism by which LFPs code stimulus novelty, whereas spiking activity carries abstract information, such as category membership and decision-related activity.

1 Introduction

Since it is advantageous for animals to attend to informative stimuli in their environment (e.g., novel stimuli) and ignore or filter out “uninformative” stimuli (e.g., repeated presentations of this once-novel stimulus), it is reasonable to hypothesize that the nervous system differentially represents novel and repeated stimuli. Indeed, in the auditory forebrain, the firing rates of neurons habituate (i.e., decrease) to repeated presentations of the same stimulus but are enhanced by the presentation of a novel stimulus (Anderson, Christianson,

& Linden, 2009; Baldeweg, 2006; Grill-Spector, Henson, & Martin, 2006; Naatanen, 1992; Ulanovsky, Las, & Nelken, 2003).

This pattern of habituation and enhancement is ubiquitous in the sensory cortex. In addition to single-unit activity, local field potentials (LFPs) and BOLD-fMRI signals also habituate to repeated presentation of the same stimulus and are enhanced when a novel stimulus is presented (Ranganath, Johnson, & D'Esposito, 2000; Weiland, Boutros, Moran, Tepley, & Bower, 2008). However, recent work from our laboratory has demonstrated that LFPs and spiking activity in the ventrolateral prefrontal cortex (vPFC) differentially represent novel and repeated stimuli (Baker, Tsunada, Davis, Cohen, & Ghazanfar, 2009); the vPFC is part of an auditory-processing pathway that preferentially processes information about auditory objects (Recanzone & Cohen, 2010). Specifically, we found that LFPs habituate to repeated presentations of the same auditory stimulus. In contrast, the average firing rate of single neurons does not habituate to repeated presentations of a stimulus. This “insensitivity” of vPFC spiking activity to repeated-stimulus presentation is independent of both the type of auditory stimulus and the behavioral context in which the stimuli are presented (Gifford, MacLean, Hauser, & Cohen, 2005; Miller, Erickson, & Desimone, 1996; Russ, Orr, & Cohen, 2008; Saga, Iba, Tanji, & Hoshi, 2011). This differential representation of signal novelty suggests that these two types of neural responses may process different types of information.

Here, we propose that this differential representation is mediated by two independent pathways between the superior temporal gyrus (STG) and the vPFC; the STG provides one of the primary auditory inputs to the vPFC (Romanski, Bates, & Goldman-Rakic, 1999). Specifically, we hypothesize that one of these STG-vPFC pathways is modulated by dynamic negative-feedback loops, whereas the second pathway is mediated by facilitating synapses. To test this hypothesis, we created a network model of the STG and the vPFC. Our model simulations reproduced many of our empirical neurophysiological findings in the vPFC (Baker et al., 2009; Gifford et al., 2005; Russ, Orr et al., 2008): LFP power habituated following repeated-stimulus presentation, spike rate was not modulated by repeated-stimulus presentation, and spike rate increased when a novel stimulus was presented. Thus, our model simulations suggest that the differential representation of repeated and novel stimuli by LFPs and spiking activity may be due to the functional properties of the connectivity between the STG and the vPFC. This disassociation may be a mechanism by which LFPs encode stimulus novelty, whereas spiking activity carries abstract information, such as category membership (Gifford et al., 2005) and decision-related activity (Russ, Orr et al., 2008; Lee, Russ, Orr, & Cohen, 2009).

2 Neurophysiological Basis of Modeling Studies

2.1 Experiment 1: Spiking Activity in the STG and the vPFC

Details of these studies have been reported previously (Russ, Orr et al., 2008; Tsunada, Lee, & Cohen, 2011); here, we provide an overview of the key results.

Rhesus monkeys were trained to participate in an auditory-categorization task. The task began with one to four repeated presentations of a reference auditory stimulus that was

followed by the presentation of a test auditory stimulus. The firing rates of single neurons were recorded from either the STG or the vPFC while monkeys participated in this task; the STG provides one of the primary auditory inputs to the vPFC (Romanski et al., 1999). The reference and test stimuli were human spoken words (*bad* and *dad*). As discussed above, vPFC spiking activity was not reliably modulated by repeated presentations of the reference stimulus (Russ, Orr et al., 2008). However, vPFC spiking activity during the presentation of the test stimulus was enhanced when the test stimulus was novel. It is important to note that this enhancement did not simply mirror acoustic differences between the reference and test stimuli: vPFC activity was strongly modulated by the monkeys' choices (behavioral reports) indicative of a cognitive role for the vPFC in categorical judgments. In contrast, STG activity reflected the properties of the current stimulus and was not reliably modulated by the monkeys' choices. (In this study, since the reference stimulus was presented only once, we could not determine the effect that the repeated-stimulus presentations had on STG activity.) Together, these data suggest that STG neurons code the sensory evidence needed to form a decision, but the trial-by-trial decision processes that convert incoming auditory evidence into a categorical choice occur in areas afferent to the STG, such as the vPFC.

2.2 Experiment 2: Local Field Potentials in the vPFC

More recently, both LFPs and spiking activity were recorded in the vPFC while monkeys listened to repeated presentations (three to five times) of species-specific vocalizations (Baker et al., 2009). These blocks of vocalizations were interrupted by a visual-stimulus presentation, which we do not consider further. The neural signal was sampled at 24 kHz and bandpass-filtered between 2.2 Hz and 6 kHz with a preamplifier (RA16PA, Tucker-Davis Technologies). Therefore, the study focused on analyzing LFPs in the theta frequency band and higher, ranging from 4 to 50 Hz, and found that both the amplitude and the power of the LFPs habituated rapidly to repeated presentations of a vocalization.

3 Structure of the Computational Model

Our model focuses on the connectivity patterns within the STG and the vPFC, as well as the feedforward connectivity between these two areas. We do not consider feedback connections from the vPFC to the STG. The schematic of our model is displayed in Figure 1A.

3.1 External Inputs and Stimulus

Stimulus-dependent afferent activity to STG neurons was modeled using stochastic spike trains; we assumed that this activity arose from the afferent auditory input between earlier regions of the auditory cortex and the STG (Romanski et al., 1999) but do not consider it further. Each spike train was generated independently from a Poisson process at the same rate $P_{STG} = 1000$ Hz (see Figure 1A). The duration of the simulated stimulus was 500 msec, which approximated the duration of the actual stimuli used in our neurophysiological studies. For most of our simulations, we do not consider stimulus-independent inputs to the STG.

vPFC neurons received both stimulus-dependent, feedforward input from the STG neurons and stimulus-independent input. This stimulus-independent input was generated independently from a Poisson process at the rate of P_{vPFC} (see Figure 1A and section 4.1). This stimulus-independent input modeled afferent input from nonauditory cortical areas and generated a baseline level of activity for the LFPs in the vPFC.

3.2 Neuron Model

Both the STG (the dashed line box in Figure 1A) and the vPFC (neural populations to the right of the dashed line box in Figure 1A) contained excitatory (E) and inhibitory (I) neurons. These neurons are integrate- and-fire neurons and fire action potentials when their membrane potentials exceed a voltage threshold (20 mV). After firing an action potential, a neuron's membrane potential is reset to its resting-membrane potential (0 mV) with an absolute refractory period of 2 msec. E neurons are excitatory because when they synapse on a target neuron, the target neuron depolarizes. In contrast, I neurons are inhibitory because when they synapse on a target neuron, the target neuron hyperpolarizes. Except for this difference, the parameters of the E and I neurons were identical (see Table 1 for selected parameters).

The dynamics of this process are described by the following differential equation (Brunel, 2000):

$$\begin{aligned} \tau \dot{V}_i &= -V_i + RI_i, \\ RI_i &= \tau \sum_j J_{ij} \sum \delta(t - t_j^K - D), \end{aligned} \quad (3.1)$$

where V is the membrane potential, RI are neural inputs, δ is the Dirac delta function, t_K is spike time, D is the synaptic delay (1.5 msec), and τ is the time constant of the membrane. i and j index the neurons, and K is the spike index. In other words, each spike train generates a fixed-amplitude change (J) in the membrane potential V at delay D . For the majority of this study we used integrate- and-fire neurons and termed them “ δ neurons.”¹

3.3 Synapse Model

The synapses were either static or dynamic (see Figure 1A). The weights of the static synapses were independent of pre- and postsynaptic activity. These synaptic weights, once established, determined the overall architecture of the network. In contrast, the weights of the dynamic synapses were a function of the magnitude of the presynaptic spiking activity and the current synaptic state. Consequently, the weights of the dynamic synapses determined the temporal dynamics of the network.

Synapses mediating external inputs and recurrent inputs within the vPFC were always static (see the solid lines in Figure 1A). However, the synapses between STG neurons or between STG and vPFC neurons could be static or dynamic (see the dotted lines in Figure 1A). We posited that the synaptic facilitation of the dynamic synapses was solely responsible for the response properties of vPFC neurons for two reasons. First, facilitating synapses between

¹There is one exception: we used a different neuron model in section 4.2 to study an alternative model of LFPs.

pyramidal and inhibitory neurons can produce dynamic negative feedback loops (Thomson & Deuchars, 1994; Thomson, 1997; Lamsa, Heeroma, Somogyi, Rusakov, & Kullmann, 2007). Second, facilitating synapses between pyramidal neurons are found in the PFC and play a key role in working memory (Mongillo, Barak, & Tsodyks, 2008; Tsodyks, Pawelzik, & Markram, 1998; Wang et al., 2006).

In this study, a simplified synapse model was chosen for our model simulations. Specifically, the dynamic synapses were initialized to a value of 0 and updated at a fixed time step of 100 msec. That is, the weight (efficacy J_{ij}) of a synapse was facilitated (increased) by J if any presynaptic spike arrived at the synapse since the previous update: the maximum value of a synapse was $6J$. This maximum value ensured that two presentations of a stimulus provided enough presynaptic activity to saturate a synapse. This requirement was instantiated since we found that most of the habituation of the LFP power occurred during the second-stimulus presentation (Baker et al., 2009). Importantly one study has indicated that our simplified synaptic dynamics may correspond to a particular type of real synapses (Lamsa et al., 2007), at least qualitatively. Specifically, Lamsa et al. (2007) found that excitatory synapses between excitatory neurons and inhibitory neurons were updated by an anti-Hebbian rule: synapses were facilitating until inhibitory neurons, previously quiescent, became active. This property is consistent with our modeled dynamic synapse.

3.4 Types and Circuitry of STG Neurons

Our neurophysiological studies of auditory categorization, which used the spoken word *bad*, the spoken word *dad*, and morphs of these two words (see section 2.1), suggested that STG neurons can be classified into two broad categories (Tsunada et al., 2011). One class of neurons (type 1) responded preferentially to one of two different classes of stimuli: the prototype *bad* and morphs that the monkeys perceived as *bad* or the prototype *dad* and morphs that the monkeys perceived as *dad*. A second class (type 2) was not tuned and responded equally well to all stimuli. Following from this observation, our STG model had three populations of excitatory neurons: two classes of type 1 E neurons (E_1) and one class of type 2 E neurons (E_2) (see the E neurons in the dashed line box in Figure 1A). Each class of E_1 neurons was activated by one stimulus class (e.g., *bad*). The E_2 neurons were untuned and responded equally well to all stimuli (*bad* and *dad*).

Our model STG also contained I neurons (see the I neurons in the dashed line box in Figure 1A). The I neurons received weak, stimulus-dependent afferent inputs that were insufficient to depolarize these neurons to their membrane's voltage threshold. I neurons also received strong input from E neurons and had reciprocal connections with these same E neurons. There were two populations of I neurons: I_S neurons received excitatory inputs via static synapses, whereas I_D neurons received excitatory input via dynamic synapses. The reciprocal connections between E_1 (E_2) and I_S (I'_S) neurons (see Figure 1A) regulated the firing rates of E neurons. More importantly, due to the dynamic negative-feedback loops between E_1 neurons and I_D neurons, the strength of the inhibitory projections to E_1 neurons increased during repeated-stimulus presentations.

STG E neurons projected to the vPFC and had recurrent connections with other STG neurons (see the E neurons in the dashed line box in Figure 1A). E_1 neurons projected to both excitatory and inhibitory vPFC neurons, E_V and I_V (see the neural populations to the right of the dashed line box in Figure 1A). The connectivity between these neurons was all-to-all and was mediated by static synapses, $J_{E_1E_V, E_1I_V}$, respectively. The E_2 neurons also projected to both excitatory and inhibitory vPFC neurons via dynamic synapses $J_{E_2E_V, E_2I_V}$. Each vPFC neuron received inputs from a random proportion (50%) of the E_2 neurons.

The pattern of connectivity for the synaptic connections within the STG is:²

1. Each population of E_1 and E_2 neurons had recurrent excitatory feedback via static synapses ($J_{E_1E_2}$).
2. Each population of E_1 neurons projected to a unique population of I neurons (I_D) via dynamic synapses ($J_{E_1I_D}$). I_D neurons had recurrent inhibitory feedback connections via static synapses (J_{I_D}) and projected back to these E_1 neurons via static synapses ($J_{I_DE_1}$). Each I_D neuron received inputs from a random proportion (50%) of the E_1 neurons.
3. Both populations of E_1 neurons projected to a common population of I neurons (I_S) through static synapses ($J_{E_1I_S}$). I_S neurons also had recurrent inhibitory feedback via static synapses (J_{I_S}) and projected back to these E_1 neurons via static synapses ($J_{I_SE_1}$).

3.5 Types and Circuitry of vPFC Neurons

Within the vPFC, neurons were connected randomly through static synapses. Each E or I vPFC neuron (E_V or I_V) received excitatory input ($J_{E_V} = J_{E_VI_V}$) from a random population (P_C) of E_V neurons (see the neural populations to the right of the dashed line box in Figure 1A). Similarly each vPFC neuron received inhibitory inputs ($J_{I_V} = J_{I_VI_V}$) from a random population (P_C) of I_V neurons. Importantly the inhibitory connection J_{I_V} was $5\times$ bigger than the excitatory connection J_{E_V} ; this pattern of synaptic strengths was instantiated to maximize the possibility that vPFC neurons fired asynchronously (Brunel, 2000). E_V and I_V neurons also received stimulus-independent input via static synapses, J_{vPFC-E} and J_{vPFC-I} , respectively (see section 4.1 for more details).

3.6 Simulation Method

In the STG, each population of E_1 and E_2 neurons contained 200 neurons. Each population of I neurons contained 50 I neurons. In the vPFC, there were 4000 E neurons and 1000 I neurons. As noted above, afferent stimulus-driven activity to the STG was modeled with Poisson spike trains. We built 100 independent realizations of the network model and ran simulations for each realization so that bias from any one particular pattern of connectivity was minimized. For each simulation, we randomly selected 100 vPFC E neurons and tested their response properties since LFPs are mainly generated by pyramidal neurons (Mazzoni, Panzeri, Logothetis, & Brunel, 2008). We report the average spiking activity and the average

²In our terminology, synaptic connections between two populations P_1 P_2 are denoted by $J_{P_1P_2}$; see the connections in the dashed line box in Figure 1A. For convenience, recurrent connections are shown with a single index, for instance, J_{P_1} instead of $J_{P_1P_1}$.

z-scored LFPs from the 100 simulations of the 100 tested vPFC neurons; LFPs were z-scored relative to the baseline LFP power that was evoked by the stimulus-independent inputs.

Neurophysiological studies demonstrated that LFPs reflect various types of neural signals including synaptic inputs and membrane potentials (for reviews, see Buzsáki, Anastassiou, & Koch, 2012, and Logothetis & Wandell, 2004). Thus, we simulated LFPs by calculating their average membrane potential (AMP) and the absolute sum of their synaptic inputs (ASS). The AMP was calculated by averaging the membrane potentials of 100 δ neurons randomly chosen in each simulation run (Ursino & Cara, 2006; Bazhenov et al., 2001; Kudela, Franaszczuk, & Bergey, 2004; Kramer et al., 2008). Similarly, the ASS was the absolute sum of the synaptic inputs to 100 vPFC E neurons randomly chosen in each simulation. For the network of δ neurons, the synaptic events were not explicitly simulated: synapses convey spiking times to postsynaptic neurons. Thus, we used pre-synaptic spike activity to calculate the synaptic inputs to the E neurons (Mazzoni et al., 2008). Specifically, we calculated a histogram with 0.1 msec bins for weighted-spiking activity from presynaptic neurons in the both STG and vPFC. Spectral analyses were then conducted on this histogram. We also further investigated synaptic inputs as a measure of LFPs by considering the temporal dynamics of synapses with conductance-based neuron models (α neurons) that allows us to consider more realistic behavior of synapses. All of the spectral analyses were conducted using Chronux, a Matlab toolbox (Mitra & Bokil, 2008).

Simulations were instantiated using the NEST-simulation environment (Gewaltig & Diesmann, 2007). The pattern of sensory stimulation followed a protocol similar to that used in our auditory-categorization studies (see Figure 1B). Each simulation was equivalent to a trial of our neurophysiological study. Prior to starting a simulation, the dynamic synapses were initialized to have a weight value of 0, and the static synapses were set to predefined values (see Table 2). A simulation started with a null period of 1000 msec, during which stimulus-independent signals were injected into vPFC neurons; these signals simulated inputs from areas other than the STG. Baseline activity was defined as the responses of vPFC neurons during the second half of this null period (500–1000 msec).

Following the baseline period, two stimuli were presented; each had a duration of 500 msec with an interstimulus interval of 500 msec (see Figure 1B). These two stimuli simulated the reference and test stimuli in our neurophysiological studies. This interstimulus interval was shorter than that used in our neurophysiological studies; however, since our synapses could not be depressed, longer interstimulus intervals did not alter the model results.

4 Results

Section 4.1 demonstrates how the simulated LFPs were generated and modulated as a function of the stimulus-dependent and stimulus-independent inputs. In section 4.2, we explore the mechanisms underlying the disassociation between LFP and spiking habituation observed in the vPFC. In the final sections, we demonstrate how the network can model the neurophysiological results observed in our laboratory and the effect of noise on the model.

4.1 Simulation of the Baseline and Stimulus-Driven LFPs

LFPs in the vPFC can be elicited by background inputs and afferent inputs from the STG. We first asked whether these inputs can generate synchronous neural responses in the vPFC. To focus on synchrony generated locally by vPFC neurons, in this section, we measured only the average membrane potential (AMP) to simulate the LFPs (see section 3.6 for details). The spectral power of baseline AMP, which was induced by background inputs, was a function of the recurrent connections (P_C ; J_{EV} ; J_{IV} ; J_{EVI} ; J_{IVE}), the frequency of the inputs P_{vPFC} , and the efficacy of the external projections onto the vPFC E and I neurons (J_{vPFC-E} and J_{vPFC-I}).

To minimize the parameter space of the model, we took advantage of the fact that (1) our neurophysiological study indicated that the power spectrum of the baseline LFP peaks at approximately 20 Hz and (2) Brunel (2000) described the parameters needed to generate spiking activity that oscillates at 20 Hz from a randomly connected network. Specifically we set the frequency of the inputs to the vPFC to satisfy equation 4.1 (Brunel, 2000):

$$v_{ext} = C_E v_{thr} \equiv C_E \frac{\theta}{C_E J_\tau}, \quad (4.1)$$

where θ is the threshold for spiking, J is the postsynaptic potential induced by a single spike, C_E is the number of external excitatory connections from the background inputs, and τ is the membrane time constant. The number of excitatory connections in the model vPFC is given as function of P_C ; $C_E = 4000 \times P_C$, in accord with the parameter regime given by Brunel (2000).

After constraining these parameters, we explored the parameter space spanned by parameters J_{EV} and P_C (see Figure 2A) and found that a clear frequency peak was evident at about 28 Hz when $J_{EV} = 0.3$ and $P_C = 0.3$. This peak frequency was close to the peak of our neurophysiological baseline LFPs (frequency peak of about 20 Hz; see the black line in Figure 2B). However, our simulations produced a secondary peak at about 4 Hz, which we did not observe in our neurophysiological studies (see the gray line in Figure 2B). We also observed a big peak at frequencies lower than 4 Hz and found that this low-frequency power was reduced when we weakened the connectivity strength J_{vPFC-I} between the stimulus-independent inputs and the vPFC I neurons. Figure 2C illustrates this relationship between J_{vPFC-E} , J_{vPFC-I} , and low-frequency power. Since our physiological data did not contain signals in the frequency band lower than 2.2 Hz, we did not consider this secondary peak further. Importantly, we performed our simulations with various values of J_{vPFC-I} and found equivalent results as long as $J_{vPFC-I} \sim J_{vPFC-E}$. Our simulation results presented in section 4.2 were produced with $J_{vPFC-I} = J_{vPFC-E} \times 0.99$.

The stimulus-driven AMP was generated by the afferent inputs from the STG. Consequently, the AMP was modulated by the structure of the STG and the pattern of connectivity between the STG and the vPFC. We found that two key factors constrained the power of the stimulus-driven AMP: the recurrent synaptic strengths between STG E neurons and the projections between STG E neurons and the vPFC. To quantify these observations,

we calculated the synchrony between the spiking activity of STG *E* neurons. For this analysis, we used a reduced model (see Figure 3A). In this model, the STG contained only E_S and I_S neurons. E_S , which was a *E* neuron population with recurrent synaptic connections (J_S), projected onto both vPFC *E* (E_V) and *I* (I_V) neurons. The efficacy of the projections onto E_V neurons was fixed to 0.2 mV, but we tested four different projection strengths between E_S and I_V neurons. I_S neurons, a population of inhibitory neurons, were reciprocally connected with E_S neurons through static synapses only. I_D neurons, which intrinsically produce the neural temporal dynamics, were not considered here to test the steady responses of our network model. The synchrony between two spike trains was quantified using the following metric (Wang & Buzsaki, 1996),

$$\kappa_{ij} = \frac{\sum_{l=1}^K X(l)Y(l)}{\sqrt{\sum_{l=1}^K X(l) \sum_{l=1}^K Y(l)}}, \quad (4.2)$$

where $X(l)$ and $Y(l)$ are the spike trains of two neurons with 1 msec resolution.

First, as the weight values of the recurrent synapses (J_S , which characterizes $J_{E1,2}$) between STG *E* neurons (E_S neurons, which characterize both STG E_1 and E_2 neurons) increased, the firing of the STG *E* neurons became more synchronized (i.e., more neurons fired together). The average synchrony value (κ) from 100 randomly selected pairs of spike trains of E_S (see Figure 3B) increased as the strength of the recurrent synapses increased. In addition, as the synchrony increased, the LFP power also increased (see Figure 3C).

Second, AMP power was dependent on the difference between J_1 (i.e., the synaptic weight value between STG *E* neurons and vPFC *E* neurons) and J_2 (i.e., the synaptic weight value between STG *E* neurons and vPFC *I* neurons). Figure 3C displays this relationship. Specifically, as the difference between J_1 and J_2 increased, the normalized AMP power increased. In contrast, when $J_1 = J_2$, AMP power was not substantially enhanced, independent of the magnitude of J_1 and J_2 (see below and Figure 4A). Thus, vPFC AMP power was enhanced when the connections between the STG neurons and the vPFC *E* neurons were strengthened, but this increase could be negated by relative increases in the connectivity between STG *E* neurons and vPFC *I* neurons.

These observations were used to construct the synaptic connections between the STG and the vPFC. Specifically, type 1 STG *E* neurons drove vPFC *E* and *I* neurons asymmetrically ($J_{E1E_V} > J_{E1I_V}$) so that AMP power increased during stimulus presentation. In contrast, type 2 STG *E* neurons drove vPFC *E* and *I* neurons symmetrically ($J_{E2E_V} = J_{E2I_V}$) to ensure that AMP habituated with repeated-stimulus presentations. If the type 2 STG *E* neurons drove vPFC neurons asymmetrically, habituation was not possible.

4.2 Mechanisms Underlying the Differential Representation of Signal Novelty Between LFPs and Spiking Activity in the vPFC

One of the key findings from our neurophysiological vPFC studies was that LFP power reliably habituated with repeated presentations of a stimulus, whereas spiking activity did not (Baker et al., 2009). We hypothesized that this disassociation between LFP power and

spiking activity resulted from the balance between the decreased strength of the type 1 STG *E* projections and the increased strength of the type 2 STG *E* projections. More specifically, LFP habituation was due to the decreasing drive between type 1 STG *E* neurons and vPFC neurons.

Indeed, our simulations confirmed this hypothesis. We found that with repeated presentations of a stimulus, the dynamic synapses between type 1 STG *E* neurons and I_D neurons (see Figure 1A) were facilitated. This facilitation decreased the output of the type 1 STG *E* neurons. In contrast, with repeated presentations, vPFC spiking activity was maintained by increasing the synaptic weights between type 2 STG *E* neurons and the vPFC neurons. Importantly, whereas this change in efficacy affected spiking activity, it did not significantly affect AMP power when $J_{E2EV} = J_{E2IV}$ (see section 4.1 and below). These points are illustrated in the data shown in Figures 4A and 4B: when there was a connection between the type 2 STG *E* neurons and the vPFC neurons ($J_{E2V} \equiv J_{E2EV} = J_{E2IV} = 0$), AMP power was not modulated by the strength of the connectivity between the type 2 STG *E* neurons to the vPFC (see Figure 4A). In contrast, vPFC spiking activity was sensitive to the strength of this connectivity: the firing rates of vPFC neurons increased monotonically as $J_{E2EV, E2IV}$ increased (see Figure 4B).

With these two input pathways projecting onto the vPFC, our model simulations reproduced our neurophysiological findings. Figure 5A shows the time course of AMP power in the frequency bands between 4 Hz and 50 Hz in the modeled vPFC during simulations following from the protocol (see section 3.6). In order to test whether AMP power habituated, we presented the same stimulus twice. As can be seen in Figure 5A, AMP power started growing rapidly at the onset of the stimulus and decayed gradually and the peak was smaller during the second stimulus period than during the first stimulus period. Figure 5B shows the average membrane potentials of 100 vPFC *E* neurons during the reference stimulus period. More specifically the AMP power habituated following repeated presentations of the same stimulus (see Figure 6A). In contrast, the firing rate of the vPFC neurons did not habituate to repeated presentations of a stimulus (see Figure 6B). For comparison, the effect of repeated-stimulus presentations on neurophysiological (actual) vPFC LFPs and spiking activity is shown in Figures 6C and 6D, respectively. If we focus on the power spectra, we found that both the AMP (see Figure 6E) and the neurophysiological LFPs (see Figure 6F) habituated between 4 Hz and 50 Hz. We also tested the time course of the normalized AMP power during both periods and found that the simulation results (see Figure 7A) were consistent with neurophysiological data (see Figure 7B).

Mazzoni et al. (2008) showed that LFPs simulated with the absolute sum of excitatory (AMPA) and inhibitory (GABA) currents reproduced actual neurophysiological data better than averaging the membrane potentials did. Thus, we tested an alternative measure of LFPs by calculating the absolute sum of synaptic inputs (ASS) to the *E* cells (Mazzoni et al., 2008; Logothetis, 2003; Moldakarimov, Bazhenov, & Sejnowski, 2010) and determined whether our simulation results were dependent on how we approximated the LFPs. Due to the simplicity of the synaptic events in our model, we calculated synaptic inputs with weighted-spiking activities of presynaptic cells in the both STG and vPFC (see section 3.6).

As shown in Figures 7C and 7D, the power spectra and normalized power of the ASS habituated significantly (t -test, $p < 0.05$).

Finally, we considered the effect of the synaptic temporal dynamics on LFP habituation: synapses open and close over time, and they are often simulated as gating variables with the rise and decay time (Tsodyks et al., 1998; Traub et al., 2005; McCarthy, Brown, & Kopell, 2008). Since synaptic temporal dynamics cannot be considered with our network of δ neurons, we built a version of a model using a conductance-based neuron model (α neuron) that obeyed the following rules:

$$C \frac{dV}{dt} = -g_L(V - E_L) - \alpha_E(t)(V - E_E) - \alpha_I(t)(V - E_I), \quad \alpha(t) = g_{E,I} \frac{t}{\tau} \exp\left(-\frac{(t - \tau)}{\tau}\right), \quad (4.3)$$

where C is capacitance; τ is the synaptic time constant; g_L is the maximum leak conductance; g_E is the maximum conductance of the excitatory synapses; g_I is the maximum conductance for the inhibitory channel; and E_L , E_I , and E_E are the reversal potentials for the leak, inhibitory, and excitatory channels, respectively (see Table 1 for parameter values). With these α neurons, we built the same network as our original model (see Table 2 for strengths of synaptic connections) and calculated LFPs by averaging the synaptic currents that projected onto vPFC E_V neurons (Mazzoni et al., 2008; Logothetis, 2003; Moldakarimov et al., 2010). Specifically, we randomly selected 100 vPFC E_V neurons and calculated the absolute sum of the excitatory and inhibitory synaptic currents (ASS). For each simulation run, we divided this total synaptic current by 100. We simulated 100 realizations of the network using the same protocol (see section 3.6) and report the average ASS power over 100 runs.

To test whether this alternative model was capable of reproducing LFP power habituation with sustained spiking activity, the same stimulus was presented twice while the vPFC and STG received the equivalent background inputs simulated by Poisson spike trains at the rate of 1000 Hz ($P_{STG} = P_{vPFC} = 1000$ Hz). Indeed, this alternative model replicated the results of our original model (see Figures 5 and 6). That is, band-limited ASS power between 4 Hz and 50 Hz was enhanced during both stimulus periods, and the increment was smaller during the second stimulus period than during the first stimulus period (see Figure 8A). The power spectra, shown in Figure 8B, are also similar to those shown in Figure 6E. Importantly, as can be seen in Figures 8C and 8D, normalized LFP power habituated significantly (t -test, $p < 0.01$), whereas the firing rate did not habituate to repeated presentations of a stimulus (t -test, $p > 0.05$).

How dependent were our results on the specific combinations of AMPA current (I_A) and GABA current (I_G)? We found that ASS power habituation was insensitive to the specific linear combination of I_A and I_G (see Figure 8E). This result is consistent with recent findings by Mazzoni et al. (2008) who demonstrated that power spectral density is independent of the linear combination of I_A and I_G .

Since the results of our model are independent of how we approximated LFPs, we used our original δ neuron-model and the AMP measure of LFPs to further test our model in the following models.

4.3 Simulation of the Neural Responses to Repeated and Novel Stimuli

To mirror our neurophysiological studies, we examined how AMP power and spiking activity in the vPFC were modulated by repeated presentations of the reference stimulus, which was then followed by the presentation of a new (novel) test stimulus. As seen in Figure 9A, with four presentations of the same stimulus, AMP power (4 Hz–50 Hz) habituated strongly during the second presentation of reference stimulus and showed little further habituation following the third stimulus presentation. In contrast, the firing rates were not modulated by repeated presentations of the stimulus (see Figure 9B), which were in accord with our vPFC data (Baker et al., 2009).

However, when a new stimulus was presented after three presentations of the same stimulus, the AMP power was comparable to its original level (AMP power during the first presentation) and vPFC firing rates increased by about 20% (see Figures 9C and 9D). This firing rate enhancement once again mirrored our vPFC findings (Russ, Orr et al., 2008). It is important to note that the modeled restoration of AMP power is a prediction of our model since we do not have comparable neurophysiological data.

4.4 Noisy Afferent Inputs into the STG

Our simulations used noise-free afferent input to the STG. However, since real neurons receive noisy inputs, we also tested whether our network model was robust to noise. To test this question, we added nonselective Poisson spikes to all of the type 1 STG *E* neurons, independent of the actual stimulus. The strength of the noise was defined as the ratio of the rate of the nonselective Poisson spikes to the rate of the selective Poisson spikes. Figure 10A shows the AMP power during the first and second presentation of a stimulus. We found significant AMP habituation (*t*-test, $p < 0.05$) for small amounts of noise (<20%), but when the noise exceeded 20%, we could not reliably identify habituation (*t*-test, $p > 0.05$). The spiking activity, as shown in Figure 10B, was enhanced by noise during both the reference and test periods. Importantly, the spiking activity induced by a test stimulus was not significantly different (*t*-test, $p > 0.05$) from that induced by a reference stimulus. Thus, our model simulation results did not rely on noise-free afferent inputs into the STG.

5 Discussion

In our model, the disassociation between LFPs, simulated by either AMP or ASS, and spiking activity resulted from the interplay between the type 1 and type 2 STG *E* neurons and the vPFC. The repeated stimulus reduced the driving force, which originated in the type 1 STG *E* neurons. The driving force was reduced due to the enhanced negative feedback projections onto the type 1 STG *E* neurons. As a consequence, the AMP power in the vPFC was habituated (see Figure 3). In contrast, vPFC spiking activity was maintained by the facilitating projections of the type 2 *E* neurons. As shown in Figure 4, the type 2 STG *E* neurons did not enhance synchronous activity in the vPFC. Consequently, whereas inputs

from type 2 STG *E* neurons played a role in maintaining spiking activity in the vPFC, these inputs did not significantly affect AMP. The existence of these two types of STG *E* neurons should be tested carefully using empirical studies, but our simulation results proved that our hypothesis is a biophysically plausible scenario capable of reproducing neurophysiological data and makes quantitative predictions that can be tested empirically (see section 4.3).

How do type 2 STG *E* neurons enhance spiking activity without modulating the AMP power spectrum? Two properties of type 2 STG *E* allow us to answer this question through the theory that Brunel (2000) developed. First, since type 2 STG *E* neurons are connected with others by weak recurrent synapses (J_{E_2}), outputs of type 2 STG *E* neurons are not strongly correlated (see Figure 3B), which are close to uncorrelated external background inputs to the vPFC. Second, STG *E* neurons equally stimulated vPFC *E* and I neurons, as external background inputs do. Thus, the projections of type 2 STG *E* neurons can be considered equivalent to the background external inputs to the vPFC that produced the baseline in the prestimulus period. According to Brunel (2000), as the frequency of external inputs v_{ext} becomes higher, the population activity of randomly connected neurons, as in our modeled vPFC, would make a transition from a slow oscillatory activity (i.e., our baseline activity) to an asynchronous irregular activity. If vPFC neurons fire asynchronously, the spiking activity of vPFC will not affect the LFP power sensitive to the synchronous synaptic inputs (Logothetis, 2003).

5.1 LFPs as a Mechanism for Novelty Detection

Since the LFPs and spiking activity reflect different neural processes, it is likely that they encode different types of information (Logothetis & Wandell, 2004; Grill-Spector et al., 2006; Koepsell, Wang, Hirsch, & Sommer, 2010). For example, the LFPs in the auditory cortex show multisensory integration, whereas the spiking activity of most auditory-cortex sites does not show such integration (Ghazanfar, Maier, Hoffman, & Logothetis, 2005). Similarly, in the inferotemporal cortex, the topographic distribution of sites with LFPs that respond to “diagnostic” parts of visual objects is different than the topography that is based on spiking activity (Nielsen, Logothetis, & Rainer, 2006). Parietal activity also shows a dissociation: the LFPs preferentially code effector information, whereas spike rates preferentially code spatial information (Scherberger, Jarvis, & Andersen, 2005).

What roles do LFPs and spiking activity in the vPFC play? Earlier studies from our laboratory (Russ, Orr et al., 2008; Lee et al., 2009) indicated that vPFC spiking activity is predictive of the monkeys' decisions during the task that required the monkeys to report whether sequentially presented auditory stimuli were the same or different. Since this task demanded that monkeys compare sequential stimuli, we assumed that vPFC neurons should have access to a memory trace of the previous stimulus, sensory memory. However, we ruled out the possibility of sensory memory embedded in vPFC spiking activity since vPFC neurons were relatively broadly tuned and responded to several stimuli (Russ, Ackelson, Baker, & Cohen, 2008).

One implication of our model is that LFP habituation, a stimulus identity-specific event, codes information regarding the repetition of the stimulus. Specifically, if the same stimulus repeats, the total synaptic inputs would be maintained at the same level due to the sustained

spiking activity of vPFC neurons, whereas synchronous synaptic inputs would habituate due to LFP habituation. This unique pattern of neural responses will be sufficient for vPFC neurons to detect the repetition of the same stimulus, leading us to hypothesize that LFP habituation may be a neural mechanism underlying novelty detection. This hypothesis is consistent with the functional role of subthreshold oscillations suggested by Hoshino (2011).

Why does the vPFC use LFP-based mechanism to compare a reference stimulus and a test stimulus instead of persistent activity that is commonly reported in visual studies? We hypothesize that intrinsic differences between the visual and auditory systems may make systems to exploit disparate memory mechanisms. The inherent temporal nature of auditory processing may engender a habituated-based memory mechanism when listeners are discriminating stimuli presented over time. However, this mechanism may not be optimal in visual processing, which is inherently more spatial; thus, the visual system uses a different type of memory mechanism: persistent activity. Our hypothesis should be addressed in empirical studies, but studies from Amy Poremba and colleagues (personal communication, November 2011) also failed to identify the persistent activity during an auditory task demanding short-term memory, which seems to support our hypothesis.

5.2 Function of Dynamic Synapses

The functional roles of dynamic synapses have recently gained attention. For instance, Mongillo et al. (2008) proposed that facilitating synapses could serve as memory buffer and a neural substrate for working memory in the PFC. Additionally, Sugase-Miyamoto, Liu, Wiener, Optican, and Richmond (2008) argued that a matching filter could be realized by setting fast-updating synaptic weights as a function of the target stimulus (Mongillo et al., 2008).

Our model simulations suggest an additional role for these dynamic synapses: these synapses may participate in the processes underlying repetition suppression. Traditionally, firing rate adaptation and synaptic depression have been the major mechanisms underlying repetition suppression (Grill-Spector et al., 2006). Grill-Spector et al. (2006) also pointed out that long-term potentiation could underlie the repetition suppression. Indeed, in our model, we found that facilitating synapses generated repetition suppression in the LFPs by enhancing negative feedback between STG E_1 and I_D neurons.

5.3 Future Work

We plan to extend our model by incorporating more realistic vPFC structure. Specifically, we will focus on implementing various cell types and laminar structure of the vPFC. It seems natural to assume that different types of neurons participate in different computations. For example, fast-spiking and low-threshold spiking neurons could be involved in producing gamma- and beta-band cortical rhythms, respectively (Roopun et al., 2010; Traub et al., 2005). Recent studies suggest that these rhythms are critical in intercortical communications: beta rhythms are thought to carry top-down signals, whereas gamma rhythms are involved in sensory signal processing (Buschman & Miller, 2007; Wang, 2010), suggestive of roles in top-down and bottom-up processing, respectively. These ideas may apply to the computations that we see between the STG and the vPFC. In addition, Wang

(2010) argued that laminar structure could play a critical role in cortico-cortical communications. Therefore, the extended model incorporating various cell types and laminar structure could allow us to understand interactions between the STG and vPFC, a critical component of auditory cognition.

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Figure 1.

Schematic of the model. (A) Each circle represents a population of neurons. The neural populations of the STG are shown on the left of the model in the area enclosed by the dashed line box. E_1 and E_2 are type 1 and type 2 STG excitatory (E) neural populations, respectively. I_S , I'_S , and I_D are STG inhibitory (I) populations, respectively. The vPFC has two populations of neurons: a population of E neurons (E_V) and a population of I neurons (I_V). (See Table 2 for synaptic connection strengths.) (B) During a simulation, vPFC neurons were stimulated by noisy stimulus-independent input, simulated with Poisson spike trains at the rate of P_{vPFC} , and stimulus-dependent afferent inputs from the STG. In contrast, STG neurons were stimulated by presentations of a simulated auditory stimulus with Poisson spike trains at the rate of P_{STG} . In this panel, only two stimulus presentations are shown. These stimulus presentations are separated by a delay period of 500 msec. The 500 msec period prior to stimulus presentation was defined as the baseline period for the LFPs.

Figure 2.

Baseline AMP in the vPFC. (A) The power spectrum of baseline AMP as a function of recurrent synaptic strength (J_{EV}) and the probability of receiving a synaptic input from a particular neuron (P_C) in the vPFC. (B) The neurophysiological and simulated baseline AMP power spectrum in black and gray, respectively. (C) AMP power was modulated as a function of the reduction of external inputs to the vPFC/neurons. For each of the tested set of parameters, 50 simulations were performed, and the power spectrum was calculated for each simulation. The data in the figure are the average of these 50 power spectra.

Figure 3.

Responses of the STG and vPFC neurons as a function of STG structure. (A) The reduced model; see text for details. (B) The synchrony (κ) of STG neural activity is shown as a function of synaptic weight (J_S). (C) The normalized AMP power was dependent on the difference between J_1 and J_2 and the synaptic weight J_S . The mean values of standard errors of synchrony index were calculated from 100 pairs of spiking trains in the STG. In panel C, each data point is the average of 50 simulations, and the error bars indicate 1 standard error.

Figure 4. vPFC activity in response to the inputs from type 2 STG E neurons ($J_{E2V} \equiv J_{E2EV} = J_{E2IV}$). Both the AMP power spectra (A) and the firing rates (B) are shown as a function of J_{E2EV} . The data show the average value of 50 simulations. The error bars indicate 1 standard deviation.

Figure 5.

Time course of band-limited power of AMP between 4 Hz and 50 Hz (A) and the average membrane potential of 100 vPFC neurons during the reference stimulus period (B).

Figure 6.

vPFC LFPs (AMP) and firing rates as a function of stimulus presentation (repeat number). (A) AMP power habituated (t -test, $P < 0.01$), whereas (B) the firing rates did not habituate with repeated-stimulus presentations (t -test, $P > 0.1$). AMP power and firing rates were calculated from 100 simulations. Each bar graph represents the mean value, and the error bars indicate 1 standard deviation. For comparison, panels C and D show corresponding neurophysiological data collected during the first and the second presentation of a monkey vocalization (Baker et al., 2009). (E, F) The power spectrum of simulated and neurophysiological LFPs, respectively, as a function of stimulus presentation.

Figure 7.

Habituation of AMP and ASS. (A, B) Normalized power of AMP and neurophysiological LFPs, respectively. (C, D) Power spectra and normalized power of ASS, respectively.

Figure 8.

Neural responses simulated using the conductance-based (α) model. (A) Time course of ASS between 4 Hz and 50 Hz and (B) power spectrum of ASS. The B arrows in panel A indicate the stimulus periods. (C, D) The effects of stimulus presentation (i.e., repeat number) on vPFC LFPs and the firing rate, respectively. The data show the average value of 100 simulations. The error bars indicate 1 standard deviation. (E) The relationship between normalized ASS power, repeat number, and the form of the linear combination of I_A and I_G . See the figure key for the exact form of the linear combination.

Figure 9.

Neural response to multiple repetitions (i.e., repeat number) of the reference stimulus. (A) The z-scored AMP power in the simulated vPFC in response to four presentations of the reference stimulus (R1, R2, R3, and R4) and (B) spiking activity. (C, D) The effect that three presentations of the reference stimulus (R1, R2, and R3) and the novel test stimulus (T) had on AMP power and spiking activity are displayed, respectively. In these panels, the same reference stimulus was presented repeatedly three times and was then followed by a novel test stimulus presentation. The data show the average value of 100 simulations. The error bars indicate 1 standard error.

Figure 10.

The effect of noisy afferent inputs to the STG. (A) AMP power as a function of repeated-stimulus presentations (i.e., repeat number) and noise input. The scale of the y-axis is relative power. The gray scale indicates the different levels of noise added to the type 1 STG *E* neurons. (B) The effect that noisy afferent input had on vPFC firing rate.

Table 1

Parameters for Neurons.

Parameters	V_{th} (mV)	V_{reset} (mV)	V_{ref} (mV)	C_m (pF)	τ_m (ms)	E_L (mV)
δ	20	0	2.0	250	20	0
α	-55	-60	2.0	250	20	-70
Parameters	E_E (mV)	E_I (mV)	τ_E (ms)	τ_I (ms)	g_L (ns)	
α	0	-85	0.5	2.0	16.7	

Notes: We used two types of neurons: δ and α . Synapses induced a fixed-amplitude membrane potential on δ neurons, whereas they generated synaptic-current changes on α neurons.

Table 2

Efficacy Values of Network Models.

Efficacy (J)	δ (mV)	α	Efficacy (J)	δ (mV)	α (nS)
J_{E1}	0.4	0.2	$J_{\theta PC-I}$	$\times 0.99$	2.9
J_{E2}	0.24	0.02	J_{E2I_S}	0.8	0.1
J_{ID}	0.2	0.2	$J_{I_S^{E2}}$	1.8	0.42
J_{IS}	0.2	0.2	$J_{EI/ID}$	$J = 0.25$	$J = 0.9$
$J_{I_S^{I_S}}$	0.2	0.05	$J_{ID/E1}$	2.5	2.5
$J_{E1/IS}$	0.3	0.3	$J_{E1/IS}$	1.0	8.0
J_{IV}	1.5	2.0	$J_{IS/E1}$	1.8	0.5
J_{STG-IS}	0.5	1.0	$J_{E1/EV}$	0.2	0.2
$J_{STG-I_S^{I_S}}$	0.5	6.0	$J_{E1/IV}$	0.19	0.2
J_{STG-E2}	1.0	6.5	$J_{E2/EV}$	$J = 0.1$	$J = 0.025$
J_{STG-E1}	1.0	5.1	$J_{E2/IV}$	$J = 0.1$	$J = 0.025$
J_{STG-ID}	0.5	1.0	$J_{EV/IV}$	0.3	0.3
$J_{\theta PC-E}$	0.3	3.0	$J_{IV/EV}$	1.5	2.0

Notes: We report two different models here. δ is a network of δ neurons. In contrast, the α model is a network consisting of α neurons. The strength of the synapses connecting a presynaptic population P_1 with a postsynaptic population P_2 is denoted by $J_{P_1P_2}$. For recurrent connections, we used a single index; for instance, J_{P1} represents recurrent connections among P_1 neurons.