NEURAL CORRELATES OF PERCEPTUAL TRANSITIONS DURING BINOCULAR FLASH SUPPRESSION

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I hereby declare that I have produced the work entitled “neural correlates of perceptual transitions during binocular flash suppression”, submitted for the award of a doctorate, on my own (without external help), have used only the sources and aids indicated and have marked passages included from other works, whether verbatim or in content, as such. I swear upon oath that these statements are true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by a term of imprisonment of up to three years or by a fine.

Tübingen, den 03.04.2016 

Date Signature

Dedicated to my father

اسرار ازل را نه تو دانی و نه من“

وین حل معما نه تو خوانی و نه من

هست از پس پرده گفتگوی من و تو

”چون پرده برافتد نه تو مانی و نه من

—Omar Khayyam

There was a Door to which I found no Key:

There was a Veil past which I could not see:

Some little Talk awhile of ME and THEE

There seemed - and then no more of THEE and ME.

Das Rätsel dieser Welt löst weder Du noch ich,

Jene geheime Schrift liest weder Du noch ich,

Wir wüssten beide gern, was jener Schleier birgt,

Doch wenn der Schleier fällt, bist weder Du noch ich.

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Paria, nobody will know your true contribution to this work. No, not to this work: to me as what I am now; as a 'Herr Doktor', and as 'Hamed' who has now had you in nearly half of his life. Nobody will know how my life has been changed after you, with you; not even these words know, not even you know!

Mom, dad, sisi and shasha, I know what distance means. I know every single silent moment you had together when I was not there anymore for a Friday evening tea. Now this is what I did in these years far from you, and by replacing tea with coffee!

Hessam, I left you as a kid. You are a man now. I know how loneliness feels. Little bro!

Friends and colleagues at MPI, You better know how much I learnt from each of you. Not only about science, but I learnt from you how to live, laugh, drink, dance, fight, talk, travel! Simple things, very simple things that I didn't learn before!

Nikos, why should I try to list what you have done for me? But wait, I want to say one thing: I was young, the first weeks or month being abroad, the first time presenting in front of people about my work. Nervous and freaked-out. You, Nikos K. Logothetis, listened to my talk and came to me in the end, touched my shoulder, and said 'good job!'. This! I want to keep a record of this here, in my doctoral dissertation!

George, the mutual understanding between us cannot be surpassed. You supported me in every possible way in the past years as a supervisor, and as a friend, and this is not a little thing. This single sentence is for you to know that I do appreciate many things. Things that I never have told you! You taught me too many things. Thank you.

Paria, look! Your name comes here once again! For the fantastic electrodes you made with your lovely little hands. All lateral intraparietal neurons contributing to this work have the echo of your beautiful name in their spikes!

CONTENTS

ABSTRACT

Neural correlates of visual awareness have been attracting scientists' interest for decades. A central question for many students has been at which stage of brain processing the resolution of perceptual ambiguities occurs. Discovering which aspects of neural activity underlie our subjective percepts and not simply the sensory input has also fascinated many researchers for a long time. Bistable and multistable perception phenomena demonstrated great experimental potential to address this question in primary visual cortex (V1) and multiple higher cortical areas including temporal and prefrontal cortices in humans and macaques. However, the role of single neurons in parietal cortical areas in perceptual transitions has not been explored in macaques by the time of this work. Also, the role that area V1 plays in perception has been a subject of debate, as the magnitude of perceptual modulations differed substantially in single-cell and imaging studies. In this thesis, we took a step further and explored the role of parietal visual areas in perceptual transitions during binocular flash suppression (BFS). We also searched for another coding scheme in V1 in addition to firing rate modulation, which may be responsible for larger modulations observed in human studies. Furthermore, we compared the extent to which neurons in V1 modulate by perception under anesthetized conditions and compared with awake passively fixating animals during the BFS paradigm in order to highlight the possible role of task in this controversy. For the first set of experiments, we recorded extracellular activity from visual units in lateral intraparietal area (LIP) of the macaque brain under the conditions of BFS. We found that LIP neurons exhibit two type of responses to the perceptual changes, possibly responsible for two distinct underlying processes: a fast transient component that is a good candidate of feedback carrying higher order visual information to the early cortical circuits, and a tonic response, which is moderately modulated by perception and becomes selective to the visual stimuli by manipulating reward size. Next, we analyzed a large dataset of single- and multi-unit activity in V1 concurrently recorded with the local field potentials (LFP) during BFS stimulation. We found that spike-field coherence (SFC) in V1 was correlated with subjective perception. Of particular interest, this correlation was also found in the absence of significant modulations in firing rate. We conjectured that SFC plays a leading role in initiating the competition in V1. Finally, we analyzed comparable spiking data collected during anesthesia and awake passive fixation conditions from four macaque monkeys and

showed that the modulation of firing rates in V1 upon perceptual suppression during BFS is comparable in both conditions. We concluded that active engagement in a task is critical to boost firing rate modulations in V1 to the level reported in human studies. Taken together, our work confirms that a distributed network of cortical regions is responsible for the resolution of perceptual rivalry during bistable conditions. This includes areas as early as primary visual cortex and higher processing stages like fronto-parietal areas. However, the strength of these modulations may depend on the level of engagement of subjects in an active task. We demonstrated that modulation of neural activity in the firing rates during passive fixation is essentially comparable to the anesthetized condition in V1. In addition, we provided evidence that modulation of firing rate is not the only neural correlate of perception and showed that neural synchronization in V1 can reflect perceptual state even in the absence of firing rate modulations. Orchestration of coherent activity observed in V1 can be triggered by the fast feedback signals from higher visual areas like LIP. Our work, preempts fascinating studies in the future to explore the network characteristics of LIP itself, and the relationship between task engagement and SFC variations in early and higher visual areas.

1 INTRODUCTION

1.1 Neural correlates of perceptual switches in bistable phenomena

Neural correlates of visual awareness have been attracting scientists' interest for decades. The use of visual stimuli that induce ambiguous perception has been established as a classical paradigm to identify the neural circuits subserving subjective perception (Attneave 1971; Rock, Hall et al. 1994; Rock 1995; Leopold and Logothetis 1999; Logothetis 1999). Under these conditions, a single interpretation of the external world cannot be unambiguously achieved. When the brain is presented with such stimuli, typically only one possible interpretation is perceived at a time and after a few seconds the percept switches abruptly to another (Attneave 1971). Notably, such perceptual alternations occur while the sensory input is kept constant, thus offering a clear dissociation of sensory stimulation and subjective awareness (Ramachandran and Anstis 1985; Logothetis and Schall 1989; Logothetis 1998; Leopold and Logothetis 1999; Blake and Logothetis 2002; Pitts, Nerger et al. 2007). Some celebrated examples of such perceptual phenomena include binocular rivalry (BR) and binocular flash suppression (BFS) (DuTour 1760; Wheatstone 1838; Breese 1899; Breese 1909; Wolfe 1984; Blake and Logothetis 2002; Tsuchiya and Koch 2005; Tsuchiya, Koch et al. 2006). BFS ensures excellent control over the subject's perceptual state, and unlike binocular rivalry, the subjective report is not mandatory (Keliris, Logothetis et al. 2010). The first electrophysiological studies using BFS were performed in anesthetized cats (Sengpiel and Blakemore 1994; Sengpiel, Blakemore et al. 1995) and implicated that interocular interactions at the level of binocular neurons in V1 could provide a

possible neural basis for the perceptual switches experienced during BR. Later on, BFS paradigm in awake, behaving monkeys as well as humans have been successfully used in electrophysiological experiments to study the role of higher areas as well as early visual cortex in subjective perception (Sheinberg and Logothetis 1997; Kreiman, Fried et al. 2002; Maier, Logothetis et al. 2007; Keliris, Logothetis et al. 2010).

1.1.1 Perceptual modulation in ventral visual stream

Logothetis and colleagues recorded from feature selective neurons in striate and early extrastriate visual areas (V1, V2, V4, MT) (Logothetis and Schall 1989; Leopold and Logothetis 1996), and as high as inferotemporal (Shenberg and Logothetis 1997) and prefrontal (Panagiotaropoulos, Deco et al. 2012) cortices in awake monkeys experiencing BR to examine the role of these areas in the visual awareness of a stimulus. Their results confirmed that only a small proportion of striate and early extrastriate neurons discharge exclusively when the driving stimulus is seen. In contrast, the activity of majority of neurons in the lateral prefrontal cortex, inferior temporal cortex and the visual areas of the cortex of superior temporal sulcus were found to be contingent upon the perceptual dominance of an effective visual stimulus. These areas thus appear to represent a stage of processing beyond the resolution of ambiguities where neural activity reflects the brain's internal view of objects, rather than the effects of the retinal stimulus on cells encoding simple visual features or shape primitives (Sheinberg and Logothetis 1997).

1.1.2 Correlates of perceptual transitions in dorsal stream

The single cell studies mentioned above, portrayed a hierarchy of cortical processing stages, along which the fraction of neurons discharging in parallel with increases in subjective perception. However, most of this work has been done in the ventral visual stream (Logothetis 1998; Leopold and Logothetis 1999; Keliris, Logothetis et al. 2010). To date, there is no report of the neural correlates of perceptual transitions in parietal areas of non-human primates using single cell recording. Nevertheless, several imaging studies in humans have highlighted a central role of fronto-parietal network in perceptual changes during binocular rivalry and bistable views (Lumer, Friston et al. 1998; Knapen, Brascamp et al. 2011). In the first chapter of this thesis, we investigate

the possible role of the most likely homologue parietal areas in rhesus macaque in perceptual alternations in an effort to complete the global picture of cortical neural correlates of subjective visual perception.

1.1.3 Parietal cortex and lack of stimulus selectivity

The traditional approach to study the neural correlates of perceptual transitions in bistable phenomena is to capture the concurrence of activation in populations of neurons responding selectively to a particular stimulus, and the subjective perception. This approach can be easily employed in feature and object selective areas in the ventral stream (Shenberg and Logothetis 1997). However, feature and shape selectivity is weak in the dorsal stream (Lehky and Sereno 2007). This makes it much more difficult to examine the role of these areas in perceptual organization. Instead, the activity of neurons in the lateral intralparietal area (LIP) has been shown to be modulated by goal driven signals and value-based decisions (Dorris and Glimcher 2004; Sugrue, Corrado et al. 2004; Sugrue, Corrado et al. 2005; Kable and Glimcher 2009; Kubanek and Snyder 2015). Responses in LIP cells scale monotonically with the value of a planned saccade (Sugrue, Corrado et al. 2005) and encode reward-based decisions (Kubanek and Snyder 2015). LIP also encodes an abstract representation of the relative desirability of external stimuli apart from any specific motor plan (Dorris and Glimcher 2004; Leathers and Olson 2012). This research motivated us to examine the hypothesis that presenting the animals with visual stimuli associated with different reward values can demonstrate bigger modulations in LIP activity during perceptual alternations. We will discuss the results of this experiment in chapter 2.

1.2 Primary visual cortex and its controversial role in perceptual organisation

Visual information is processed across a distributed network of interconnected visual areas (Felleman and Van Essen 1991; Harris and Mrsic-Flogel 2013). The primary visual cortex (V1), being hierarchically the first cortical area receiving information from the eyes through the thalamus, constitutes a cornerstone of the visual system (Hubel and Wiesel 1962; Hubel and Wiesel 1977; Gilbert 1993; Sincich and Horton 2005; Angelucci and Bressloff 2006). Although V1 has been studied extensively and is

arguably the best-understood area in the cerebral cortex, its role in visual awareness remains controversial and has been a subject of intense debate (Crick and Koch 1995; Pollen 1995; Leopold and Logothetis 1996; Logothetis 1998; Polonsky, Blake et al. 2000; Tong and Engel 2001; Blake and Logothetis 2002). Psychophysical, single-unit and more recently fMRI studies in primates have argued both for and against V1 activity robustly reflecting perception (Blake, 1989; Leopold and Logothetis, 1996; Logothetis et al., 1996; Polonsky et al., 2000; Tong and Engel, 2001). A recent comprehensive study has investigated in detail the extent to which different electrophysiological signals recorded from V1 correlate with perception in awake, behaving monkeys (Keliris, Logothetis et al. 2010). They found that the activity of a minority (20%) of neurons, as well as the power of the local field potential (LFP) at similar percentage of sites reflect the perceived visual stimulus.

1.2.1 Synchrony code for perceptual organization in V1

Previous single-cell studies have examined the hypothesis that stimulus selection in multistable perception is achieved by the modulation of the firing rate of neurons (Logothetis 1998). This has been shown extensively in object selective cortical areas under the conditions of BR (Logothetis and Schall 1989; Leopold and Logothetis 1996; Sheinberg and Logothetis 1997). In primary visual cortex, however, the percentage of neurons that exhibited correlated activity with subjective perception during BFS was reported to be only ~20% (Keliris, Logothetis et al. 2010). On the contrary, V1 was implicated as an important candidate for the site of perceptual suppression during BR in many psychophysical studies (Abadi 1976; Lehky 1988; Blake 1989). This received further support by functional magnetic resonance imaging (fMRI) studies in humans which found that V1 is indeed modulated to a large extent by the subjective percept (Polonsky, Blake et al. 2000; Tong and Engel 2001; Lee and Blake 2002; Maier, Wilke et al. 2008) Although differences in the nature of the read-out signals could be a possible explanation for this discrepancy, it is yet possible that another coding scheme in V1 is responsible for communicating perceptual information. It has been suggested that response selection in early visual areas might be achieved by a modulation of the synchronization rather than the firing rates (Engel, Fries et al. 1999; Fries, Schroder et al. 2002; Womelsdorf, Schoffelen et al. 2007). To date, however, there is no direct

comparison between the two neuronal codes in V1 in search for neural correlates of the subjective percept. We will address this issue in chapter 3.

1.2.2 Local competition or top-down feedback: conscious state and the no-report paradigm

As discussed earlier, functional magnetic resonance imaging (fMRI) studies in humans found that V1 is indeed modulated to a large extent by the subjective percept (Polonsky, Blake et al. 2000; Tong and Engel 2001; Lee and Blake 2002; Maier, Wilke et al. 2008; Yuval-Greenberg and Heeger 2013). However, neurophysiological evidence obtained in monkeys did not corroborate this hypothesis but instead found only a small percentage of neurons that modulated their activity in parallel with the subjective perception of the animals (Logothetis and Schall 1989; Leopold and Logothetis 1996; Sheinberg and Logothetis 1997; Gail, Brinksmeyer et al. 2004; Wilke, Logothetis et al. 2006; Keliris, Logothetis et al. 2010). It is yet unclear whether these small modulations are rooted from local circuits in V1 or influenced by higher cognitive states. Possible explanations for this discrepancy include differences in the stimulus configurations, the species tested, and the experimental methodology (Boly, Seth et al. 2013; Panagiotaropoulos, Kapoor et al. 2014). In addition, a major difference between many of these studies is the extent to which the subject is involved in attending and consciously reporting the bistable alternations (Watanabe, Cheng et al. 2011; Zhang, Jamison et al. 2011; Brascamp and Blake 2012; Tsuchiya, Wilke et al. 2015; Tsuchiya, Frassle et al. 2016). Such higher cognitive processes could be based on different mechanisms from those subserving local processes and are only observable in V1 when the subject is awake and behaving (Lamme, Zipser et al. 1998; Lamme and Spekreijse 2000). In chapter 4, we will study the perceptual modulations in V1 in the absence of attentional allocation and task demands during general anaesthesia.

1.3 Aim of projects

The purpose of this thesis was to study the neural correlates of perceptual switches during the paradigm of BFS. To this end we conducted three complementary studies which are presented in the following sections. First, we explored the extent to which the firing rate of neurons in the area LIP of macaque monkey modulates with subjective

perception. We examined the transient response around the time of perceptual switches in BFS, as well as dynamics of the tonic response of those neurons concomitant with subjective perception. Secondly, we looked at another possible coding scheme in the cortex, namely neuronal synchronization, which may carry perceptual information in the absence of significant firing rate modulations. We performed experiments for this purpose in primary visual cortex during the same paradigm. Finally, we explored the role of feedback from higher cognitive processes on early visual areas and active engagement of subjects in a task compared to passive fixation during BFS. We compared the responses of V1 during awake and anesthetized conditions to highlight the potential differences in neural activity according to the conscious state.

The overall implication of this work sheds light on the mechanisms of perceptual organization in the cortex. It broadens our understanding of the sites of perceptual suppression during bistable and multistable conditions, including those of parietal cortical areas, and suggests an alternative mechanism for information transformation between multiple stages in the absence of firing rate modulation. This study also suggests a key role of active engagement in task for the paradigms of ambiguous perception and highlights the effects of feedback from higher cortical areas on the perceptual modulations observed in primary visual cortex.

2 THE ROLE OF PARIETAL VISUAL CORTEX IN PERCEPTUAL TRANSITIONS DURING BINOCULAR FLASH SUPPRESSION

2.1 Motivation

Several single cell recording and imaging studies have shown an increasing correlation between the neural activity and subjective perception during binocular rivalry (BR) while moving up in visual hierarchy. However, this has mainly been done in the ventral visual stream (Logothetis 1998; Leopold and Logothetis 1999; Keliris, Logothetis et al. 2010). To date, there is no report of neural correlates of perceptual transitions in parietal areas of non-human primates using single cell recording. Nevertheless, several imaging studies in humans have highlighted a central role of fronto-parietal network in perceptual changes during binocular rivalry and bistable views (Lumer, Friston et al. 1998; Zaretskaya, Thielscher et al. 2010; Knapen, Brascamp et al. 2011; Frassle, Sommer et al. 2014). In this chapter, we have investigated the possible role of the most

likely homologue of the reported human parietal areas in rhesus macaques, namely area LIP, in perceptual alternations.

2.2 Methods

We recorded extracellular activity from the lateral intraparietal area (LIP) of the right hemisphere of two rhesus macaques. Single cell activities were collected during the paradigm of binocular flash suppression (BFS). The subject was initially presented with congruent patterns to the two eyes. Then the stimulus was switched in either one or both eyes, resulting in a perceptual switch towards the newly presented stimulus. We quantified the neural activity during the period of stimulation and around the time of perceptual switches by obtaining the spike-density functions. In order to correlate neural activity with perceived stimulus, we required differential firing rate levels corresponding to the preference of neurons. Thus, we trained the animals with unequal rewards for different stimuli. This manipulation resulted in induced selectivity in LIP neurons towards the stimulus paired with bigger reward. We paired one of the two stimuli with tripled amount of juice, while the other stimulus resulted in normal amount. Assignment of the stimuli to the different reward sizes was on a no priori ground.

2.3 Results

We recorded from 310 single cells including 278 visual units exhibiting significant sustained activity during visual stimulation. The recorded cells typically showed an initial burst of activity at stimulus onsets as well as stimulus switches. The switch signal was present during physical alternations and, to a lesser extent, during binocular flash suppression conditions. The transient signal was followed by a tonic response of neurons in both conditions during the whole period of stimulation. After a few sessions of training the monkeys with balanced reward, we found a large differential activity in LIP neurons in favor of the stimulus paired with bigger reward. Although this effect was not as big as the preferential activity in object selective areas, but this reward-induced selectivity in LIP neurons was enough to enable us to probe the perceptual modulation of neural responses in this area. When recorded the neurons' activity during BFS, we observed significant correlation between the perceived stimulus and the firing rate in only a subset of neurons. We further studied whether the fast transient component of the

responses were also affected by the reward manipulation and found that the switch signal increased significantly in magnitude while the response to the stimulus onset did not change in size substantially. This could be explained by the importance of the second half of the stimulus presentation for monkey's expectation about the reward size.

2.4 Discussion

Previous fMRI studies in humans experiencing BR reported severely diminished activity in fronto-parietal areas during physical changes, where the perceptual switch is enforced by change in physical stimulus, as compared to rivalry (Lumer, Friston et al. 1998; Lumer and Rees 1999; Sterzer, Kleinschmidt et al. 2009). In contrast, we found strong transient activity at the single cell level during physical alternations. Our finding is consistent with the two recent fMRI studies (Knapen, Brascamp et al. 2011; Frassle, Sommer et al. 2014), which challenged the aforementioned view by highlighting the role of cognitive demands and act of reporting in studies related to the neural correlates of perceptual rivalry (Tsuchiya, Wilke et al. 2015). They reported matching fronto-parietal activity evoked by physical alternations and rivalry, upon careful controls in experimental design. In chapter 4, we investigate the effect of removing central cognitive processes on perceptual modulations, by comparing V1 activity in awake and anesthetized monkeys during no-report BFS paradigm. The sustained activity of LIP neurons in our experiments exhibited poor selectivity towards most of the visual stimuli presented to the monkeys, and was not modulated by the perceived stimulus, which is consistent with the non-selective nature of dorsal pathway neurons towards objects and shapes (Lehky and Sereno 2007). This selectivity, however, was boosted significantly by introducing differential reward sizes associated with the two stimuli presented during BFS. Interestingly, we observed this preferential activity also on the amplitude of the fast transient response after the stimulus switch, predicting the up-coming reward. We conjecture that areas at the high end of the dorsal pathway might be involved in multistable perception in a different way in comparison with feature and object selective areas of the ventral pathway. The transient signal recorded in LIP neurons during perceptual transitions could potentially trigger reorganization of activity in constellations of feature selective neurons in the ventral pathway. This can also transmit the results of cognitive operations such as prediction, attention and imagination to V1 via strong top-down feedback projections (Muckli and Petro 2013; Kok, Bains et al.

2016). In chapter 3, we will show that spike-field coherence in V1 is correlated with subjective perception. LIP can be a candidate for sending the orchestration trigger to V1 via the fast feedback signals.

3 SPIKE-FIELD COHERENCE REFLECTS PERCEPTUAL STATE IN MONKEY PRIMARY VISUAL CORTEX

3.1 Motivation

Recent studies cast doubt on the models of neural communication through firing rate modulation (Tsodyks and Markram 1997; Azouz and Gray 2003; Fries 2012; Fries 2015). Our cognitive dynamics, in particular, require a flexible communication structure across interacting neuronal groups. Recent studies suggest that this communication is mechanistically subserved by neuronal coherence (Fries 2005; Roberts, Lowet et al. 2013; Fries 2015; Zandvakili and Kohn 2015). During bistable and multi-stable perception, firing rate does not always explain the large perceptual modulations observed in different brain regions, including early visual areas (Keliris, Logothetis et al. 2010). In the previous chapter, we suggested that the area LIP may also be involved in perceptual organization in a different way in comparison with feature and object selective areas, by providing feedback to early areas. This signal could potentially provide a trigger for a communication-through-coherence (Fries 2015) structure in the

visual system to pass the output of early-stage inter-ocular competition to the higher areas. In this chapter, we examined the hypothesis that neuronal coherence could carry such perceptual information in primary visual cortex (V1). We examine this possibility in particular when the modulation of firing rates is not significant.

3.2 Methods

To directly compare the extent of firing rate modulations with changes in oscillatory activity of neurons upon perceptual transitions, we recorded V1 activity from a large number of single-units and local field potentials (LFPs) during the BFS paradigm in macaque monkeys. We calculated spike-field coherence (SFC) by measuring phase synchronization between spikes and LFP oscillations as a function of frequency (Fries, Reynolds et al. 2001). To test if the level of neuronal synchronization changes with perception, we estimated spike-field coherence for each of the visually responsive units, between their spike trains and concurrently recorded field potentials from all sites. We were particularly interested in the SFC difference during incongruent presentation, between the two conditions in which the subject was presented with the same stimuli but experienced different percept depending on the previous monocular presentation. To test whether SFC carries perceptual information in the absence of rate modulation, we identified units with no significant modulation in their firing rate during flash suppression and looked at the spike-LFP coherence associated with these units during incongruent stimulation. Moreover, we estimated the preference of each neuron across the two stimuli by using the (signed) discriminability index *d'* during the monocular stimulus presentation, and compared it with the *d'* of the SFC during the binocular presentation of both stimuli with different percepts.

3.3 Results

Roughly 22% of visually responsive units were found to exhibit significant gamma-band SFC during the incongruent stimulation with LFPs recorded from one or more simultaneously recorded sites. Our central finding across the population of all spike-LFP pairs was that the subjective perception was significantly reflected in the SFC. We tested the significance of such perceptual modulation in SFC at the peak gamma frequency across the population of 245 spike-LFP pairs. Roughly 80% of the single

units demonstrated significant difference in synchrony during incongruent stimulation with the same stimuli, albeit with different underlying perception. Firing rate of less than half of single-units which exhibited a significant differential SFC was not significantly different for comparable conditions. From the above population, 76% of them demonstrated significant difference in gamma-band SFC (28-50 Hz). Moreover, we compared the preference of neurons reflected in SFC and firing rate by the measure of *d'* index. Interestingly, 88% of above single-units showed same direction of modulation for SFC and firing rate. The values of *d'*s for the two quantities were positively correlated. Furthermore, we estimated the correlated variability between the trial-by-trial pseudo-SFC (pSFC) values and fluctuations in firing rate for every spike-LFP pair in the population of neurons with no significant BFS firing rates. We found only a moderate trial-by-trial correlations between the spike counts and pSFC (Spearman correlation 0.2939, $p<0.05$).

3.4 Discussion

We found that SFC carries significant information about perceptual suppression, even in the absence of significant rate modulation. We suggest that neuronal synchronization in early visual areas could serve as an efficient neural code to pass perceptual information on to higher processing stages, while preserving the rate code capacity for encoding physical characteristics of the stimuli. It is conceivable that neuronal populations in early visual areas maintain their activity at a base level, the putative effect of which is reversible at the arrival of a synchronization signal during perceptual switches. This sync command could be feedback from higher areas, like what we observed in LIP, and causes spikes to coincide within a short window, enhancing their impact on postsynaptic neurons and translate to an explicit firing rate change at subsequent stage.

Our results support the hypothesis that firing rate modulations observed with perceptual rivalry in higher cortical areas could be secondary to modifications of neuronal synchronization at lower processing levels. This mechanism has been implicated in a variety of sensory and cognitive processing functions including attention (Fell, Fernandez et al. 2003; Lakatos, Karmos et al. 2008), stimulus selection (Fries, Schroder et al. 2002), feature binding (Frien, Eckhorn et al. 1994; Kreiter and Singer 1996; Engel, Roelfsema et al. 1997), and resolution of perceptual and interocular rivalry (Fries, Roelfsema et al. 1997; Engel, Fries et al. 2003). It has been shown that neurons

activated by attended stimulus in monkey extrastriate cortex, exhibit stronger gamma-band synchronization compared with neighboring neurons activated by unattended stimuli (Fries, Reynolds et al. 2001; Taylor, Mandon et al. 2005). Small changes in gamma-frequency synchronization with attention may enhance the impact of neurons on their postsynaptic targets and, therefore, lead to pronounced changes in firing rate at subsequent stages (Niebur, Koch et al. 1993; Salinas and Sejnowski 2000). Similarly, we showed that gamma frequency band SFC in V1 is significantly higher for perceived stimulus during BFS. We suggest that synchronous activity of lower neuronal groups could make the entrained neurons at subsequent stages sensitive for the signal from dominant stimulus, while rendering them deaf for the signal from suppressed stimulus. Our results support the hypothesis that the general mechanism for pruning the stimulus representation is the synchrony of rhythms (Fries, Schroder et al. 2002; Fries 2005; Brunet, Bosman et al. 2014). This bottom-up communication structure for preferential routing of selected signals could transform the synchrony code to rate code throughout the visual system.

Like other electrophysiological studies in monkeys (Logothetis 1998; Leopold and Logothetis 1999), we also failed to prove the large modulation of firing rates in early visual areas during perceptual transitions. However, the subjects in our study were passively fixating and were not asked to deploy attention or report their percept. The extent to which the absence or presence of higher cognitive feedback could vary the perceptual modulations in V1 is not yet addressed in our experiments. In chapter 4, we will compare the anesthetized and awake conditions to investigate the role of local and central processes in perceptual suppression in V1.

4 BINOCULAR FLASH SUPPRESSION IN THE PRIMARY VISUAL CORTEX OF ANESTHETIZED AND AWAKE MACAQUES

4.1 Motivation

In previous chapters we discussed the importance of experimental design and act of reporting in studies related to the neural correlates of perceptual rivalry. In particular, we discussed recent evidence that discrepancies observed in fMRI and electrophysiological studies about the neural correlates of LIP in perceptual transitions could be eliminated by careful experimental design (Knapen, Brascamp et al. 2011). We also suggested the possibility in the previous chapter, that neural coherence may be the source of large modulations in V1 during a no-report paradigm. In this chapter, we would like to take a step further is studying the role of higher cognitive processes in the activity of V1 during BFS.

Primary visual cortex has been reported in numerous psychophysical and imaging studies as an important candidate for the site of perceptual suppression. However, studies in awake monkeys provided neurophysiological evidence for competition mainly between neurons in areas beyond V1 and only a moderate percentage of neurons in this area were found to modulate in parallel with perception. Also, the magnitude of such modulations was substantially smaller than the physical preference of the neurons. It is yet unclear whether these small modulations are influenced by higher cognitive states originating from areas beyond V1 or rooted from local circuits.

4.2 Methods

In order to dissociate the influence of higher cognitive states from the local processing in V1 during multistable stimulation, we performed BFS experiments in anesthetized, and awake passively fixating macaques and compared the perceptual modulation in the two conditions. We conjectured that any effects preserved under anesthesia, might reflect local interactions involved in the initiation of competition during incongruent stimulation. These effects are likely in the absence of cognitive feedback from central processes. In anesthetized experiments, monkeys were presented in the beginning of each trial with blank screen for two seconds. Subsequently, one of the two stimuli was presented alone, to either the left or the right eye for two seconds, followed by the onset of the second stimulus at the corresponding retinal location in the contralateral eye. Simultaneous presentation of incongruent stimuli last for another two seconds until the end of the trial. The two stimuli have been chosen to elicit maximal differences in neural activity based on the average responses to a battery of natural and generic images. These images were presented to the animal prior to the BFS experiment. The same paradigm was used in awake experiments. The monkeys had to passively fixate on a central fixation point to initiate the BFS trial. A fixation point appeared in the center of the screen for 300 milliseconds. It was followed by flash suppression stimulation similar to anesthetized condition but with a duration of one second for each period. Stimuli were static sinusoidal gratings with orthogonal orientations and were chosen to be optimized to elicit maximal differences between the responses to the two orientations.

4.3 Results

We found a small but significant modulation in both anesthetized and awake states during the flash suppression period. The relative amplitudes of the perceptual modulations measured by the ratio of |d′| for perceptual and sensory values were not significantly different for the two states. This was on average 28% and 25% of the sensory modulation in anesthetized and awake conditions respectively. Note that these percentages were across significantly modulating sites in both animals in each conscious state. The relative amplitude of modulations in these two conditions were closely similar which suggests similar mechanisms for these two states. We also tested if the proportion of perceptually modulating sites was significantly different in anesthetized and awake macaques. For anesthetized animals, this was on average 65%, which was higher than awake macaques which was on average 24%. Furthermore, we acquired local field potentials from 33 recording sites in three anesthetized experiments. Similar to the previous reports in awake animals, there was an increase in the power of the gamma frequency range of the LFP (24-90 Hz) shortly after the stimulus onset. Also, we observed a preference for the stimulus in 26 recording sites during congruent stimulation. During the incongruent presentation, only one third of recording sites showed a significant difference in perceptual modulation. Similar to the multi-units, this difference was substantially smaller than sensory preference of the LFPs. The power of lower frequency LFP (1-12 Hz) showed a significant increase in oscillatory activity after stimulus onset in only 14 of 33 recording sites. We observed sensory tuning to the stimulus in the same fraction of recording sites. During the dichoptic phase, this difference was significant in only 4 recording sites in one of the animals. These results indicate that perceptual modulations of the lower band of the LFP in V1 are essentially absent in anesthetized conditions, similar to the awake passively fixating animals reported previously (Keliris, Logothetis et al. 2010).

4.4 Discussion

In this chapter, we compared neural activity in V1 during binocular flash suppression in anesthetized and awake monkeys. Previous electrophysiological studies in awake monkeys reported small firing rate modulations during perceptual suppression in only a fraction of neurons, suggesting a higher origin for the perceptual competition in visual

hierarchy. We conjectured that if the small effects observed in precious studies are due to influences from central processes and not originating from local circuits, these modulations should be eliminated under anesthesia. However, we found significant modulations of the multi-unit activity recorded in V1 of anesthetized macaques during binocular flash suppression. These modulations were small but comparable to those observed in awake, passively fixating animals. Our results confirm that V1 is involved in the process of perceptual suppression during incongruent stimulation and we suggest that it plays a role in initiating the competition. Given the similarly small magnitudes of perceptual modulation during the awake passively fixating, and the anesthetized condition, we suggest that cognitive signals from task-related central processes are a key ingredient of the larger modulations that have been observed in human V1 by fMRI. Our results has inspired further investigations and has been cited in few recent studies related to the neural correlates of consciousness and perceptual rivalry (Schmid and Maier 2015; Tsuchiya, Wilke et al. 2015; Xu, Han et al. 2016).

5 DISCUSSION

5.1 Lateral intraparietal area and perceptual organization

LIP is located a few synapses away from V1 (Ferrera and Grinband 2006; Gilbert and Li 2013), and is massively interconnected with multiple visual areas including prefrontal cortex (Andersen, Asanuma et al. 1985; Cavada and Goldman-Rakic 1989; Andersen, Asanuma et al. 1990; Stanton, Bruce et al. 1995; Lewis and Van Essen 2000). We have previously shown that single-cell activity in V1 correlates with perceptual state (Keliris, Logothetis et al. 2010). The magnitude of perceptual modulations, however, is small in V1 compared to the higher visual areas (Logothetis and Schall 1989; Leopold and Logothetis 1996; Logothetis 1998; Keliris, Logothetis et al. 2010). Imaging studies in humans, on the other hand, found that perceptual suppression strongly modulates BOLD activity in primary visual cortex (Polonsky, Blake et al. 2000; Tong and Engel 2001). In a recent study, we suggested that these significantly bigger modulations may be due to the attentional demand and/or engagement of human subjects in a task (Bahmani, Logothetis et al. 2013; Bahmani, Murayama et al. 2014). Cortical neurons are, in general, subject to top-down influences of attention, expectation and perceptual tasks (Gilbert and Li 2013). These projections descending the hierarchy and targeting the primary visual cortex may play an essential role in perceptual processes (Clavagnier, Falchier et al. 2004). The ideal candidate region downstream in the visual system, which can provide immediate modulatory

cognitive feedback to primary visual cortex is LIP. It is not hard to conceive that the large perceptual modulation of V1 activity observed in humans is confounded by the massive and low-latency feedback from LIP, which is difficult to disentangle on the temporal resolution of BOLD signal.

5.1.1 Reward modulation and LIP selectivity

We showed that coupling a 'larger' reward with a particular stimulus renders LIP neurons selective to that one; the 'preferred' stimulus. They respond significantly stronger to the stimulus which leads to the bigger reward. LIP neurons were likely coding the expectation of monkeys for the amount of reward based on the second stimulus, the *flash*, while also signaling the onset of the visual stimuli in the beginning of trials regardless of their behavioral relevance. Importantly, this signal was present in a very short time after the stimulus was changed. We suggest that LIP is the first relay station in the visual system that receives the input from early visual areas with minimum delay and extracts the value of the stimulus with respect to its behavioral relevance. The reward-dependent value of the stimulus can then be distributed to other processing stages in the brain, including occulomotor cortical and subcortical structures responsible for saccadic decision and execution like frontal eye field (FEF) and superior colliculus (SC) (Gottlieb, Hayhoe et al. 2014).

LIP showed preferential activity in the absence of a task which involves action planning. Neurons became selective to the identity of objects paired with differential rewards during a passive task. In a subset of recordings, such selectivity was preserved during binocular flash suppression, similar to the neurons in the high end of the object selective pathway. This modulation of the responses in LIP is, however, not exclusively a reward effect (Gottlieb, Hayhoe et al. 2014). Many related neurophysiological experiments do not permit a clean dissociation between reward and attention (Maunsell 2004). Mere stimulus-reward associations can modify salience, or the ability of a stimulus to bias attention (Peck, Jangraw et al. 2009); an observation which is supported by psychophysical evidence in humans (Anderson, Laurent et al. 2011; Marx and Einhauser 2015). Saliency has also been already suggested as a unifying explanation for LIP activity (Bisley and Goldberg 2003; Leathers and Olson 2012). Although neural signals in LIP co-varies with the animal's final decision, but they also modulated by the quality of the sensory evidence (Shadlen and Newsome 1996; Shadlen and Newsome

2001), and informational properties of visual cue, like novelty, independent of the reward associations (Foley, Jangraw et al. 2014). Important for the current study, reward association induced necessary levels of selectivity in LIP neurons, which enabled us to look at the perceptual modulations in the parietal area.

5.2 Synchronization as a trigger for perceptual switch

Electrophysiological studies in monkeys failed to prove the large modulation of responses in early visual areas during perceptual transitions in BR (Logothetis 1998; Leopold and Logothetis 1999). In particular, only a moderate fraction of neurons in V1 showed percept-related changes in firing rate during BFS (Keliris, Logothetis et al. 2010). However, evidence from strabismic cats studies suggested that relevant variable for stimulus selection at early stages of visual processing could be the synchronicity of responses in neuronal ensembles rather than modulation of discharge rates (Fries, Roelfsema et al. 1997). We showed that synchronicity of spiking in V1 is indeed a correlate of subjective percept during BFS is macaque monkeys, even in the absence of firing rate modulation.

Neuronal synchronization has been implicated in a variety of cognitive and sensory processing functions, including attention (Fell, Fernandez et al. 2003; Lakatos, Karmos et al. 2008), stimulus selection (Fries, Schroder et al. 2002), feature binding (Frien, Eckhorn et al. 1994; Kreiter and Singer 1996; Engel, Roelfsema et al. 1997), and resolution of perceptual and interocular rivalry (Fries, Roelfsema et al. 1997; Engel, Fries et al. 2003). It has been shown that neurons activated by attended stimulus in monkey extrastriate cortex, exhibit stronger gamma-band synchronization compared with neighboring neurons activated by unattended stimuli (Fries, Reynolds et al. 2001; Taylor, Mandon et al. 2005). Small changes in gamma-frequency synchronization with attention may enhance the impact of neurons on their postsynaptic targets and, therefore, lead to pronounced changes in firing rate at subsequent stages (Niebur, Koch et al. 1993; Salinas and Sejnowski 2000). Viewing incompatible images in each eye typically produces BR in which only one image reaches conscious perception, with the other suppressed from awareness (Alais 2012). This mechanism is similar to attentional selection where behaviorally relevant stimuli gain advantage over distractors to reach awareness (Desimone and Duncan 1995). We showed that gamma frequency band spike-field coherence (SFC) in V1 is significantly higher for perceived stimulus during

BFS. We suggest that synchronous activity of lower neuronal groups could make the entrained neurons at subsequent stages sensitive for the signal from dominant stimulus, while rendering them deaf for the signal from suppressed stimulus. Our results support the hypothesis that the general mechanism for pruning the stimulus representation is the synchrony of rhythms (Fries, Schroder et al. 2002; Fries 2005; Brunet, Bosman et al. 2014). This bottom-up communication structure for preferential routing of selected signals could transform the synchrony code to rate code throughout the visual system.

We found previously that the firing rate of majority of neurons in V1 does not correlate with perception (Keliris, Logothetis et al. 2010). Firing rate also not always increases with attention (Moran and Desimone 1985; Luck, Chelazzi et al. 1997). It is conceivable that neuronal populations in early visual areas maintain their activity at a base level, the putative effect of which is reversible at the arrival of a synchronization signal during perceptual switches. This sync command causes spikes to coincide within a short window, enhancing their impact on postsynaptic neurons and translate to an explicit firing rate change at subsequent stage. Similar mechanism may subserve attentional modulation in early visual areas, where neuronal groups selective for invisible stimulus do not shut down completely, but stay active in the background and waiting for the attentional signal, to become coherent and effective. In this scenario, each individual neuron at the level of V1, does not need, and is not supposed, to change its own rate response according to the subjective percept. This hypothesis is compatible with the selective nature of V1 neurons towards physical attributes of the stimuli, which is constant in such preparations independent of the perceptual experience.

5.3 Conscious state and V1 activity during perceptual suppression

Some aspects of global processing such as the attentive and conscious analysis of a scene have been observed in V1 only in awake and perceiving animals (Lamme, Zipser et al. 1998; Lamme and Spekreijse 2000; Guo, Benson et al. 2004). We found comparable modulations in neural activity as reflected in the multi-unit activity (MUA) and local field potentials (LFPs) in both anesthetized and awake passively fixating animals. Our results suggest that the small significant modulations observed under these non-attentive conditions are arising from circuit mechanisms in early visual areas.

Local and global processing in V1 could be based on different mechanisms. Feedback signals from extrastriate visual areas modulate V1 activity extensively. The density of

such feedback projections is as much as or larger than the feedforward afferents (Douglas and Martin 1991). For example, top-down attention is a process that could be mediated via such projections and has been shown to modulate V1 activity (Corbetta, Miezin et al. 1990; Mehta, Ulbert et al. 2000; Mehta, Ulbert et al. 2000; Huk, Ress et al. 2001; Buracas and Boynton 2007). In a series of fMRI studies in human, perceptual suppression has also been found to strongly modulate BOLD activity in primary visual cortex (Polonsky, Blake et al. 2000; Tong and Engel 2001). In addition, we have shown previously that the activity of some single cells in V1 also show significant modulations during perceptual suppression induced by BFS (Keliris, Logothetis et al. 2010). However, only a small proportion of neurons in V1 showed these effects and importantly the amplitude of perceptual modulations was very small in comparison to the sensory preference. One possible explanation for the difference between the strength of modulations in area V1 of human and monkeys is the extent to which the subjects were asked to consciously attend to the stimuli (Watanabe, Cheng et al. 2011; Koch and Tsuchiya 2012). It is conceivable that the effects recorded by fMRI in humans reflect top-down modulations mediated by changes in attentional state and/or the active employment of the subject in the task instead of directly reflecting the competition happening at the level of V1 circuitry (Guo, Benson et al. 2004; Maier, Wilke et al. 2008; Watanabe, Cheng et al. 2011). On the contrary, most monkey electrophysiology studies used paradigms with animals passively fixating not directly being engaged in reporting the perceptual transitions.

5.4 Conclusions

We showed in chapter 4 that the modulation of firing rates in V1 upon perceptual suppression during BFS is comparable in anesthetized and passively fixating awake conditions and concluded that active engagement in a task is critical to boost firing rate modulations in V1 to the level which was reported in BOLD studies. In chapter 3, we showed that spike-field coherence in V1 is significantly modulated by the perceptual state, even though the single cell activity in majority of V1 neurons do not correlate with perception. We conjecture that SFC plays a leading role in initiating the competition in V1 even in the absence of a task. In chapter 2, we explored the characteristics of two possibly distinct signals in the activity of LIP neurons. The tonic response of LIP neurons is moderately modulated by perception and becomes selective

by reward manipulations. Fast transient component is a good candidate to feedback the higher order visual information to the early cortical circuits. Orchestration of coherent activity observed in V1 can be triggered by the fast feedback signals from higher visual areas like LIP. Exploring network characteristics of LIP itself, and the relationship between task engagement and SFC variations in early and higher visual areas are interesting topics to address in future studies.

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6 LIST OF AUTHOR CONTRIBUTIONS

6.1 Bahmani H., Logothetis N.K., Keliris G.A. The role of parietal visual cortex in perceptual transitions during binocular flash suppression (manuscript in submission)

Hamed Bahmani co-designed the study and conducted recordings and analyses, and wrote the manuscript. Nikos K Logothetis co-designed the study. Georgios A Keliris co-designed the study and participated in writing the manuscript.

6.2 Bahmani H., Lakshminarasimhan K., Logothetis N.K., Keliris G.A. Spike-field coherence reflects perceptual state in monkey primary visual cortex (manuscript in submission)

Hamed Bahmani co-designed the study, conducted most analyses, and wrote the manuscript. Kaushik Lakshminarasimhan wrote pieces of the analysis code. Nikos K Logothetis acquired part of the data. Georgios A Keliris collected the data, co-designed the study, and participated in writing the manuscript.

6.3 Bahmani H., Murayama Y., Logothetis N.K., Keliris G.A. (2014) Binocular Flash Suppression in the Primary Visual Cortex of Anesthetized and Awake Macaques. PLoS ONE 9(9)

Hamed Bahmani co-designed the study, conducted data analyses and wrote the manuscript. Yusuke Murayama participated in acquiring part of the data and writing the analysis code. Nikos K Logothetis participated in acquiring the data and writing the analysis code. Georgios A Keliris co-designed the study, acquired the data, and participated in writing the manuscript.

7 APPENDICES

7.1 The role of parietal visual cortex in perceptual transitions during binocular flash suppression

Neural correlates of visual awareness have been attracting scientists' interest for decades. Bistable and multistable perception phenomena demonstrated great experimental potential to address this question (*1-5*). A nice paradigm which fits perfectly to the study of perceptual organization is binocular rivalry (BR) (*6*). When dissimilar images are presented to the two eyes, perception alternates spontaneously between each monocular view, a phenomenon called binocular rivalry (*7*). Because perceptual transitions between each monocular view occur without any change in the physical stimulus, neural responses associated with perceptual processes can be distinguished from those due to stimulus characteristics. Several single cell recording and imaging studies have shown an increasing correlation between the neural activity and subjective perception during BR while moving up in visual hierarchy. However, this has mainly been done in ventral visual stream (*6-8*). To date, there is no report of neural correlates of perceptual transitions in parietal areas of non-human primates using single cell recording. Nevertheless, several imaging studies in humans have highlighted a central role of fronto-parietal network in perceptual changes during binocular rivalry and bistable views (*9, 10*). Here we investigate the possible role of the most likely homologue parietal areas in rhesus macaque in perceptual alternations.

We recorded extracellular activity from the lateral intraparietal area (LIP) of the right hemisphere of two rhesus macaques. Single cell activities were recorded during the paradigm of binocular flash suppression (BFS). The subject was initially presented with congruent patterns to the two eyes. Then the stimulus was switched in either one or both eyes, resulting in perception of the newly presented stimulus. During BFS, subject can perceive the stimulus in any of the two eyes depending on the previously shown pair of stimuli to both eyes, thus perceptual state is not dictated by the visual stimulus. BFS ensures excellent control over the subject's perceptual state (*11*), and unlike BR, the subjective report is not mandatory (*8*). We recorded from 310 single cells including 278 visual units. The recorded cells typically showed an initial burst of activity at stimulus onsets as well as stimulus switches. Previous fMRI studies in humans

reported no change in the activity of fronto-parietal areas during physical changes (*9*) (but also see (*10*)), where the perceptual switch is enforced by change in physical stimulus. In contrast, we found strong transient activity at the single cell level during physical alternations, where the stimulus in both eyes were changed to a new one (fig1a). This signal was also present, but to a lesser extent, during binocular flash suppression conditions where the stimulus in only one of the eyes was switched. The transient signal was followed by a tonic response in both conditions.

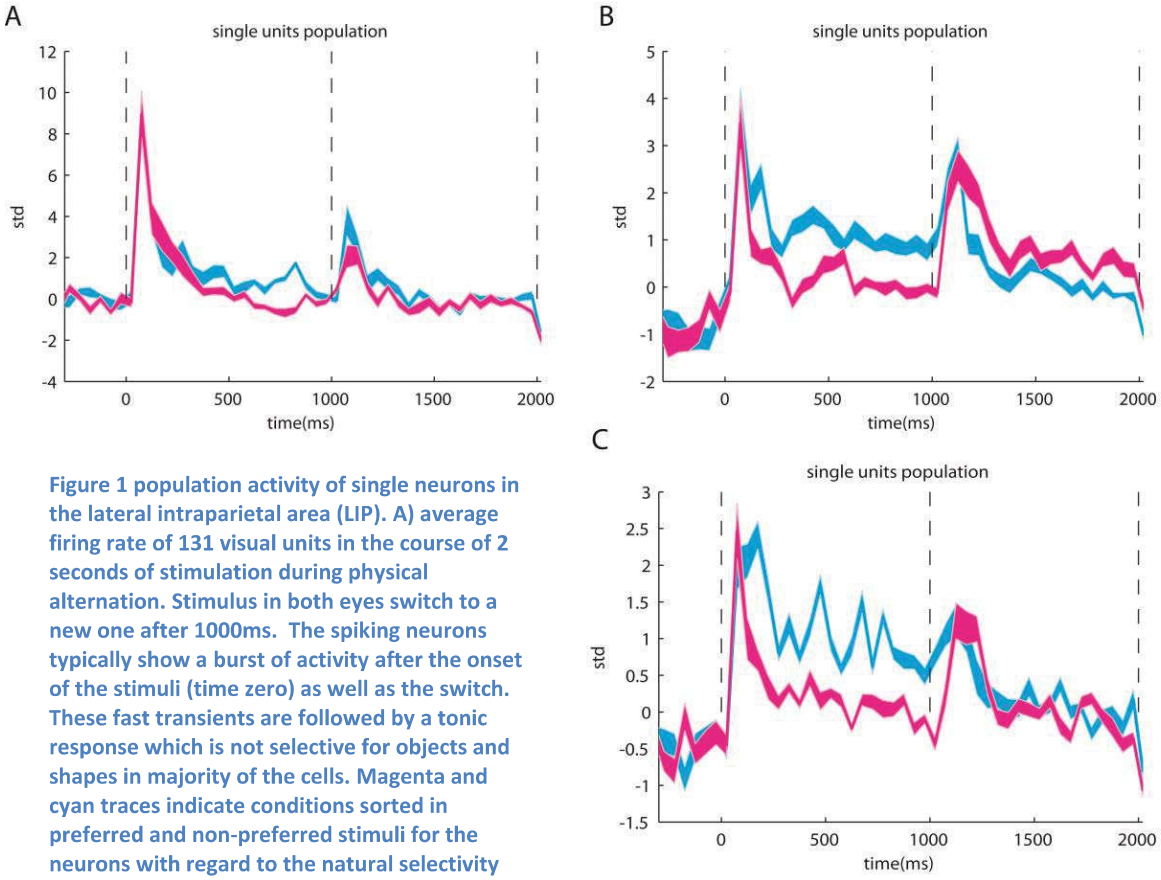

Figure 1 population activity of single neurons in the lateral intraparietal area (LIP). A) average firing rate of 131 visual units in the course of 2 seconds of stimulation during physical alternation. Stimulus in both eyes switch to a new one after 1000ms. The spiking neurons typically show a burst of activity after the onset of the stimuli (time zero) as well as the switch. These fast transients are followed by a tonic response which is not selective for objects and shapes in majority of the cells. Magenta and cyan traces indicate conditions sorted in preferred and non-preferred stimuli for the neurons with regard to the natural selectivity of recorded neurons towards objects or shapes used in the experiments. B) average firing rate of 147 visual units during the conditions of biased reward, but still during physical alternation same as (A). The cells fire more in response to the stimulus which leads to bigger reward. Two colors of the traces correspond to preferred and non-preferred stimulus induced by the associated reward to the two stimuli. C) population activity of single neurons in the lateral intraparietal area (LIP) during binocular flash suppression (BFS) with differential rewards. The two eyes are presented with the same stimulus. After 1000ms, only one of the stimuli in either of the eyes switches to a new one, resulting in BFS. Two colors indicate conditions leading to different amount of juice reward. There is significantly different firing rate for the two stimuli with different reward association. The differential activity is present in most of the cells during the first second of congruent presentation, but not prevalent in many of them during the flash suppression period. Shaded area in both panels indicates the standard error of the mean (SEM).

The traditional approach to study the neural correlates of perceptual transitions in bistable phenomena is to capture the concurrence of activation in populations of neurons responding selectively to a particular stimulus, and the subjective perception. This approach can be easily employed in feature and object selective areas in ventral stream (*12*). However, such selectivity is hardly found in dorsal stream (*13*). The tonic response of LIP neurons increased during the stimulus presentation but the level of this activity was not significantly different for the two stimuli for majority of neurons. This made it difficult to underpin the role of this area in perceptual organization. Instead, the activity of LIP neurons has been shown to be modulated by goal driven signals and value-based decisions (*14-17*). Responses in LIP cells scale monotonically with the value of a planned saccade, which suggests the neural correlates of process of choices or representation of value before a choice in this area. LIP also encodes an abstract representation of the relative desirability of external stimuli apart from any specific motor plan (*15, 18*). This motivated us to examine the hypothesis that presenting the animals with visual stimuli associated with different reward values can demonstrate bigger modulations in LIP activity during perceptual alternations. We paired one of the two stimuli with a bigger reward, while the other one resulted in normal small reward. After a few sessions of training, we found a large differential activity in favour of the stimulus paired with bigger reward (fig1b, also see supplemental figure). When recorded the neurons' activity during BFS, we observed significant physical and perceptual correlation in only a subset of neurons (fig1c). Although the effect was not as big as reports in object selective areas, but the reward association induced substantial selectivity which was necessary to probe the perceptual modulation of neural responses. The count of neurons demonstrating different properties and effects is summarized in figure 2.

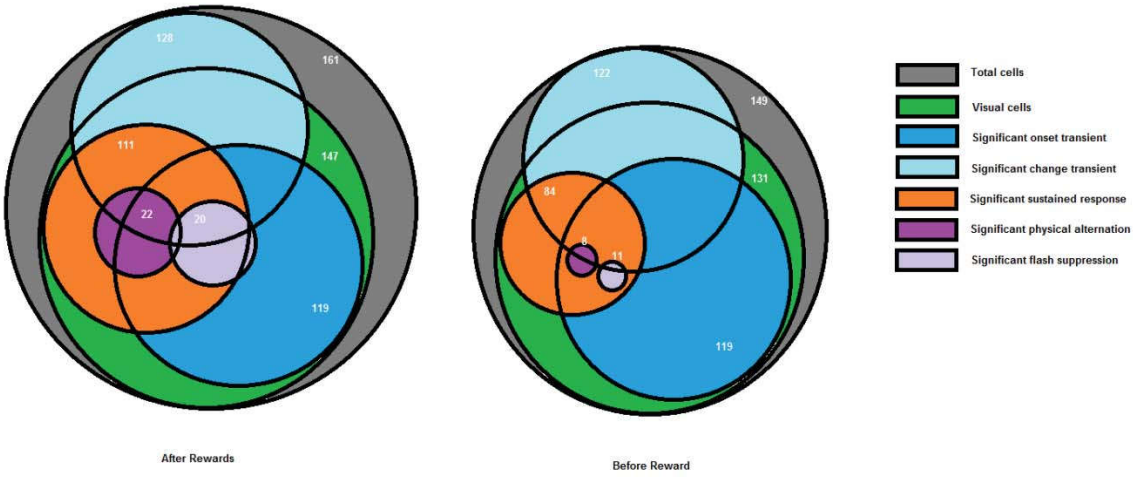

Figure 2 Count of the neurons with different properties before and after reward manipulation. Number of recorded neurons is written in each circle indicating the corresponding property. Note that the proportion of visual cells to the total recorded cells, and the cells with significant transient response at the onset and switch is similar in both population. Importantly, the number of neurons with significant sustained activity, and proportion of cells with differential activity during physical alternation and flash suppression is significantly different before and after reward effect. Only a minority of neurons demonstrated significant perceptual modulation concomitant with subjective perception. However, majority of them showed fast transient activity in both conditions.

LIP is located a few synapses away from V1 (*19*), and is massively interconnected with multiple visual areas including prefrontal cortex (*20-24*). We speculate that the transient and sustained responses in this area may reflect two separate underlying processes. The short latency response may reflect a fast sensory integration signal from early visual cortices in a bottom-up manner, while the sustained activity may represent top-down influences originating from higher areas in the prefrontal cortex. We conjecture that areas at the high end of the dorsal pathway might be involved in multistable perception in a different way in comparison with feature and object selective areas of the ventral pathway. The transient signal recorded in LIP neurons during perceptual transitions could potentially trigger reorganization of activity in constellations of feature selective neurons in the ventral pathway. We further studied whether this transient response was also affected by the reward manipulation. We pooled all conditions of the experiment and compared the magnitude of the transient signal before and after the reward association. After reward manipulation, the onset signal did not change while the switch signal

increased significantly in magnitude (fig3). We explain this observation with regards to the importance of the second half of trials, because the amount of reward was associated with the lastly seen stimulus before each trial ended. LIP neurons were likely coding the expectation of monkeys for the amount of reward based on the second stimulus, the *flash*, while also signalling the onset of the visual stimuli in the beginning of trials regardless of their behavioural relevance. Importantly, this signal was present in a very short time after the stimulus was changed. We suggest that LIP is the first relay station in the visual system that receives the input from early visual areas with minimum delay and extracts the value of the stimulus with respect to its behavioural relevance. The reward-dependent value of the stimulus can then be distributed to other processing stages in the brain, including occulomotor cortical and subcortical structures responsible for saccadic decision and execution like frontal eye field (FEF) and superior colliculus (SC) (*25*). Tonic activity of majority of LIP neurons, however, was not modulated by the perceived stimulus, which is consistent with the non-selective nature of dorsal pathway neurons towards objects and shapes (*13*). Nonetheless, this does not rule out the possibility that they correlate with subjective perception in a more complex way. We recently showed that spike-field coherence in V1 is significantly modulated by the perceptual state, even though the single cell activity in majority of V1 neurons do not correlate with perception (manuscript in submission). Orchestration of such coherent activity in V1 can be triggered by the fast feedback signals from higher visual areas like LIP. Exploring network characteristics of LIP itself is an interesting topic to address in future.

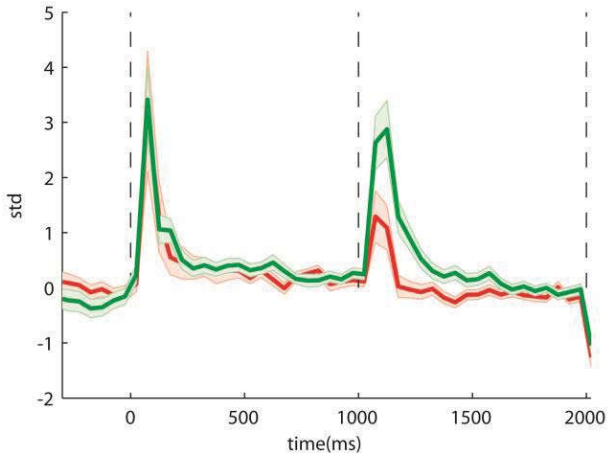

Figure 2 Different sizes of onset and switch transient response of LIP neurons before and after reward manipulation. The red trace shows the firing rate of population of neurons with significant differential response during the sustained activity, before reward manipulation. The green trace shows the population activity of neurons recorded after reward manipulation, with a significant preference towards the stimulus paired with bigger reward. The onset response after the reward manipulation becomes smaller while the switch response becomes bigger. All conditions of the experiment are pooled in both traces. Shaded areas indicate the standard error of the mean (SEM).

We previously have shown that single-cell activity in V1 correlates with perceptual state (*8*). The magnitude of perceptual modulations, however, is small in V1 compared to the higher visual areas (*6, 26, 27*). Imaging studies in humans, on the other hand, found that perceptual suppression strongly modulates BOLD activity in primary visual cortex (*28, 29*). In a recent study, we suggested that these significantly bigger modulations may be due to the attentional demand and/or engagement of human subjects in a task (*30, 31*). The ideal candidate region downstream in the visual system, which can provide immediate modulatory cognitive feedback to primary visual cortex is lateral intraparietal area. It is not hard to conceive that the large perceptual modulation of V1 activity observed in humans is confounded by the massive and low-latency feedback from LIP, which is difficult to disentangle on the temporal resolution of BOLD signal.

We showed that coupling ‘bigger’ reward with a particular stimulus renders LIP neurons selective to ‘better’ stimulus. They respond significantly stronger to the stimulus which leads to bigger reward. Importantly, such preferential activity was in the absence of action planning. LIP became selective to the identity of objects paired with differential rewards even during a passive task. In a subset of neurons, such selectivity was preserved during binocular flash suppression, similar to the neurons in the high end of the object selective pathway. This modulation of the

responses in LIP is, however, not exclusively a reward effect (*25*). Many related neurophysiological experiments do not permit a clean dissociation between reward and attention (*32*). Mere stimulus-reward associations can modify salience, or the ability of a stimulus to bias attention (*33*); an observation which is supported by psychophysical evidence in humans (*34*). Saliency has also been already suggested as a unifying explanation for LIP activity (*18, 35*). Although neural signals in LIP co-varies with the animal's final decision, but they also modulated by the quality of the sensory evidence (*36, 37*), and informational properties of visual cue, like novelty, independent of the reward associations (*38*). Important for the current study, reward association induced enough selectivity in LIP neurons to enable us to look at the perceptual modulations in the parietal area.

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Materials and Methods

Ethics Statement

The experimental and surgical procedures were performed with great care and were fully compliant with the guidelines of the local authorities (Regierungspräsidium Tübingen, protocol Nr. KY1/02), the European Community guidelines for the care and use of laboratory animals (EUVS 86/609/EEC), and the recommendations of the Weatherall report (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003440). The regional authorities (Regierungspräsidium Tübingen) approved our experimental protocol (Nr. KY1/02) and the institutional representatives for animal protection supervised all procedures. Animals were kept in large cages located adjacent to the training and experimental facilities. Space in these cages allows swinging and jumping, and enrichment equipment such as toys were changed frequently. Group housing was maintained to increase the quality of life by rich visual, olfactory, auditory and social interaction and stimulation for play. Balanced nutrition and regular veterinary care and monitoring, were provided. Chamber implantation and an anatomical scan were performed while the animals were under general anesthesia and aseptic conditions. To alleviate post-surgical pain we administered analgesics for a week after the surgery (also see surgical procedures below).

Subjects and surgical procedures

Two adult male rhesus monkeys (*Macaca mulatta*) C07 and D10, aged 8 and 6 years, weighing 9 and 11 kg respectively, took part in the experiments. Medical-grade titanium recording chambers were positioned according to stereotaxic coordinates over the intralparietal sulcus of the right hemisphere in both monkeys. This was aided by high-resolution magnetic resonance anatomical imaging. Dimensions and parameters of the skull extracted from these scans were used for designing the head-posts and the recording chambers to fit the skull surface. The anatomical scan and recording chamber implantation were done while the animals where under general anesthesia and ascetic conditions. A more detailed description of these methods can be

found elsewhere (*8*). Recording from the lateral intraprietal area was confirmed by the histology performed on one of the animals (C07) after the experiments were finished.

Data acquisition

Extracellular recordings were done non-chronically with one or two manually adjustable, custom-made microdrives and twisted-wire tetrodes with the help of a grid system. Details have been described elsewhere (*8, 39*). The recording chambers gave access to the lateral intraparietal area (LIP) by penetrating area 5 perpendicularly and passing through medial intralparietal area (MIP) and the intraparietal sulcus (IPS). We advanced the tetrodes in the brain tissue after penetrating the dura by a guide-tube. Advancing the tetrode in the guide-tube by hand enabled us to have a vivid feeling of penetrating the sulcus. The physiological responses of different areas from the cortex beneath the dura until the target area in LIP was confirmed in every recording session. We stopped advancing the tetrodes as soon as we entered the LIP right after the sulcus and left them there fixed for approximately one hour for the electrodes and the tissue to become stabilized. When a stable and reliable signal was acquired, we started the calibration procedures and data collection**.** The animals' eye movements were monitored online with non-invasive infrared eye-tracker.

Multi-unit activity was sampled at 32 kHz, digitized (12 bits), and stored using the Cheetah data acquisition system (Neuralynx) and was defined as the events that exceeded a predefined threshold (25 μV) of the filtered (600 Hz - 6 kHz) and digitized signal. Following each threshold crossing, a segment of 32 samples (1ms) was extracted from all four channels of the tetrode and these waveforms were stored for offline clustering. Single-unit spikes were then isolated from multiunit activity by a custom-built clustering system (*39*) that uses features extracted from the stored multiunit spike waveforms.

Visual stimuli

A dedicated graphics workstation (TDZ 2000; Intergraph Systems) running an OpenGL-based program was used for rendering visual stimuli, while the behavioral aspects (e.g. juice reward, trial abortion) were controlled using the QNX real-time operating system (QNX Software Systems Ltd). The display system comprised of a custom-made mirror stereoscope with an LCD monitor (resolution of 1024x768; refresh rate of 60 Hz) on each side, and allowed for dichoptic presentation of stimuli.

Each session began with a calibration procedure[52] to ensure that the monkeys could correctly overlay (fuse) the central fixation markers (0.2°) on the two displays. Thereafter, a coarse receptive field mapping was performed to position the stimuli for the experiments. The multi-unit responses were put through a sound amplifier (Grass Technologies) so that the experimenter could evaluate the gross location of the receptive fields and the preferences of the multi-unit responses towards different stimuli, locations and sizes. Details are described previously (*8*).

A battery of natural and generic images were presented to the animal and the two stimuli that have elicited maximal differences in neural activity were chosen for the experiment.

Experimental design

We used the paradigm of binocular flash suppression (BFS) to study the relationship between neural activity and perceptual modulations. The subject was initially presented with congruent patterns to the two eyes. Then the stimulus was switched in either one or both eyes (binocular flash suppression versus physical alternation), both resulting in perception of the newly presented stimulus. The paradigm ensures excellent control over the subject's perceptual state.

In order to initiate the BFS trial, the monkeys had to passively fixate on a central fixation point (0.2°) which appeared in the center of the screen for 500 milliseconds. This was followed by presentation of one of the images of the selected stimulus pair, to one of the eyes, for one second. Then the other image was added to the second eye for another second resulting in

incongruent stimulation and suppression of the previously presented stimulus/eye. The stimuli were placed within the receptive fields of the recorded sites, with a sizes of 4-6°. The animal was required to maintain fixation within a window with a radius 0.5-1° from the center of the marker throughout the duration of the trial. At the end of each successful trial, few drops of juice were delivered as a reward. For modulated reward conditions, one of the two stimuli was paired with a tripled amount of juice, while the other stimulus resulted in normal amount. The 'good' and 'not good' stimuli were chosen on a no priori ground. A failure resulted in abortion of the trial without reward. A typical recording session included 200 trials of each condition. For more details see (*8*).

Statistical and data Analysis

We used custom programs written in Matlab (The Mathworks Inc.) for data analysis. Statistical significance ($P<0.05$) of physical and perceptual modulations was assessed by using a nonparametric Wilcoxon rank sum test for equal medians. For all the comparisons, we excluded the first 500 ms after the flash to avoid transient biases after the switch. We then calculated the preference and modulation indices by using discriminability index (d'). This was defined as:

$$d' = \frac{\mu_A - \mu_B}{\sqrt{\frac{(\hat{\sigma}_A{}^2 + \hat{\sigma}_B{}^2)}{2}}}$$

where μ and σ are the mean response and the standard deviation of the conditions put in the comparison. We report d' indices for either pairs of binocularly presented identical stimuli (referred to as sensory preference d'_{sens}) or incongruent stimuli (referred to as perceptual preference d'_{perc}). Bigger values of d' indices indicate larger discriminability of responses and thus larger preference to one of the conditions being compared. Visual responsiveness of neurons were determined based on the monocular period of BFS by using the d' index. A neuron was considered visually responsive if its onset transient response or the sustained activity thereafter was significantly larger than baseline. A neuron was also counted as

physically or perceptually selective if there was a significant difference between the level of its responses to the two stimuli (during physical alternations), or two perceived stimuli (during BFS) respectively.

Supplemental figure

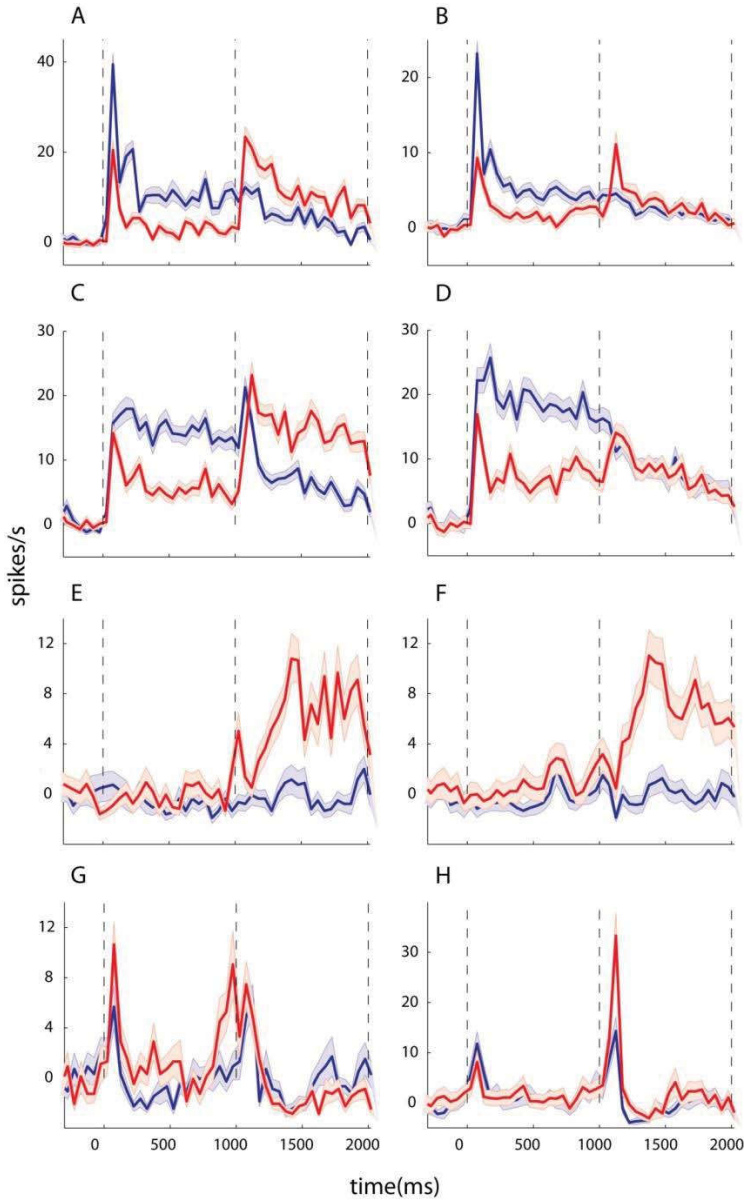

Figure Supp1 Examples of single-unit and multi-unit modulations during binocular flash suppression (BFS) (right panels) and physical alternation as control condition (left panels) after reward manipulation. The spike-density functions of three example single-units (A-D from monkey C07, E,F from monkey D10) and one example multi-unit (G,H from monkey D10) are shown. Upper diagrams on each panel demonstrate the conditions with corresponding color outlines as the spike density functions below. The conditions contrasted in each case in BFS conditions had the same stimulus during the binocular period but notably predict different percepts in awake subjects. Note the selectivity of neurons in both periods before and after the change (A,C); or only after the change leading to differential rewards for different stimuli (E). This selectivity may disappear during the incongruent presentation (B,D) or may persist (F); however the transient selectivity may persist independent of tonic activity (B,H). The shaded areas represent SEM across trials. Time zero was defined to be the onset of the monocular stimuli. The time of the switch is at 1000ms.

7.2 Spike-field coherence reflects perceptual state in monkey primary visual cortex

Summary

Recent studies cast doubt on the models of neural communication solely through firing rate modulation [1-4]. Our cognitive dynamics, in particular, require a flexible communication structure across interacting neuronal groups. Recent studies suggest that this communication is mechanistically subserved by neuronal coherence [5]. We examined the hypothesis that neuronal coherence carries perceptual information independent of neuronal firing rates in primary visual cortex (V1). We recorded extra-cellular activity from a large number of single-units and local filed potentials (LFPs) in area V1 of two rhesus macaques under conditions of binocular flash suppression (BFS). We showed that spike-field coherence (SFC) in the gamma-band frequencies was significantly modulated by subjective perception. Interestingly, the SFC modulation was significant even for the population of neurons without firing rate modulation. We suggest that neuronal synchronization in early visual areas is an effective way to transfer perceptual information to higher processing stages, while maintaining the firing rate of neurons relative to their physical preference.

Results

During incongruent stimulation using the binocular flash suppression paradigm (BFS), two sufficiently different visual stimuli are presented dichoptically and asynchronously to the two eyes; in this scenario, the stimulus appearing last becomes dominant and is perceived at the time of its onset and for a time-window of at least several hundred milliseconds depending on the stimulus properties and the interocular delay [6]; using this paradigm one can present two identical stimulus configurations and - by only

varying the interocular sequence - induce two different percepts and thus a dissociation between the input and subjective awareness (Figure 1). Previous single-cell studies have examined the hypothesis that stimulus selection in interocular competition is achieved by a modulation in the firing rates of cells according to their stimulus preferences [7]. Logothetis and colleagues recorded from feature selective neurons in early visual areas (V1, V2, V4, MT) [8, 9], and as high as the inferotemporal [10] and prefrontal cortices [11] in awake monkeys experiencing binocular rivalry (BR) [12]. They portrayed that the fraction of neurons that modulate their firing rate in parallel with perception increases as one proceeds along the cortical processing hierarchy. In a particular study, the percentage of neurons in V1 that decrease their firing rates upon perceptual suppression during BFS was reported to be only ~20% [13]. On the contrary, the primary visual cortex was implicated as an important candidate for the site of perceptual suppression during BR in many psychophysical studies [14-16]. This received further support by functional magnetic resonance imaging (fMRI) studies in humans which found that V1 is indeed modulated to a large extent by the subjective percept [17-20]. Although differences in the nature of the read-out signals could be a possible explanation for this discrepancy, it is yet possible that another coding scheme in V1 is responsible for communicating perceptual information. It has been suggested that response selection in early visual areas might be achieved by a modulation of the synchronization rather than the firing rates [21-23]. To date, however, there is no direct comparison between the two neuronal codes in V1 in search for neural correlates of the subjective percept.

To directly compare the extent of firing rate modulations with changes in oscillatory activity of neurons upon perceptual transitions, we recorded V1 activity from a large number of single-units and local filed potentials (LFPs) during the BFS paradigm in macaque monkeys. To estimate neuronal synchrony in V1, we calculated spike-field coherence (SFC) by measuring phase synchronization between spikes and LFP oscillations as a function of frequency [24] (Figure 1D). We found that SFC carries significant information about perceptual dominance/suppression, even in the absence of rate modulations. We suggest that neuronal synchronization in early visual areas is the efficient neural code to pass perceptual information on to higher processing stages, while preserving the rate code capacity for encoding physical characteristics of the stimuli.

We recorded from 474 sites from three hemispheres of two macaque monkeys (*Macaca mulatta*). A total of 803 single-units were isolated, from which about 66% (n=529/803) were visually responsive as determined by our criterion. Neuronal activity was recorded while the monkeys were presented with incongruent stimuli using the paradigm of binocular flash suppression. To test if the level of neuronal synchronization changes with perception, we estimated spike-field coherence for each of the visually responsive units, between their spike trains and concurrently recorded field potentials from all sites. Roughly 22% (n=116/529) of visually responsive units were found to exhibit significant gamma-band SFC during the incongruent stimulation ($p<0.01$; permutation test) with LFPs recorded from one or more simultaneously recorded sites. This included adequate number of units from both monkeys (87 from D98; 29 from F03). A total of 245 spike-

LFP pairs exhibiting significant gamma-band SFC were identified. We restricted the rest of our analyses to these spike-LFP pairs.

We were particularly interested in the SFC differences between the two conditions in which the subject was presented with the same stimuli but experienced a different percept (Figure 1). Each trial began with a 300 ms fixation period, followed by monocular presentation of one of the two stimuli for one second. The second stimulus, referred to as *the flash*, was presented to the contralateral eye for another second, rendering the first stimulus invisible for the rest of the trial. For details of the paradigm and stimulus presentation see Experimental Procedures. To avoid biases in our analysis caused by transient changes in firing rates around the stimulus onsets, we focused our analysis on the period between 400 and 1000 ms after the flash. An example neuron with clear preference in one of the stimuli is presented in Figure 1S (Supplemental materials).

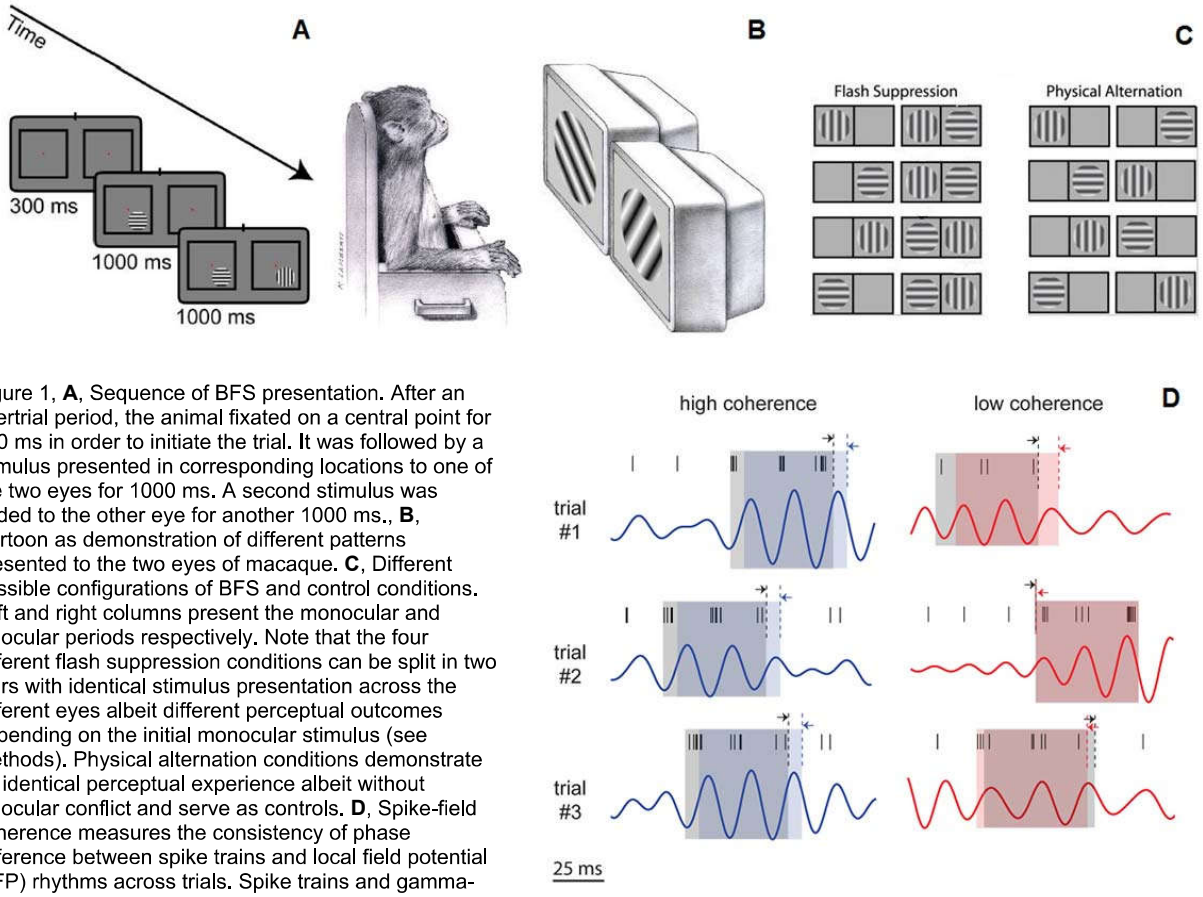

Figure 1, **A**, Sequence of BFS presentation. After an intertrial period, the animal fixated on a central point for 300 ms in order to initiate the trial. It was followed by a stimulus presented in corresponding locations to one of the two eyes for 1000 ms. A second stimulus was added to the other eye for another 1000 ms., **B**, Cartoon as demonstration of different patterns presented to the two eyes of macaque. **C**, Different possible configurations of BFS and control conditions. Left and right columns present the monocular and binocular periods respectively. Note that the four different flash suppression conditions can be split in two pairs with identical stimulus presentation across the different eyes albeit different perceptual outcomes depending on the initial monocular stimulus (see methods). Physical alternation conditions demonstrate an identical perceptual experience albeit without binocular conflict and serve as controls. **D**, Spike-field coherence measures the consistency of phase difference between spike trains and local field potential (LFP) rhythms across trials. Spike trains and gamma-band LFP rhythms corresponding to a coherent (left) and incoherent (right) spike-LFP pair from three example trials are shown. The relative phases of spike trains and LFP rhythms during the bouts of rhythmic activity are nearly identical across trials for the coherent spike-LFP pair as indicated by the separation between black and blue shaded regions, but highly variable for the incoherent pair (black and red shaded regions).

We found that changes in SFC were correlated with the perceived stimulus across the population of all spike-LFP pairs (figure 2A). We tested the significance of such perceptual modulation in SFC at the peak gamma frequency across the population of 245 spike-LFP pairs ($p = 0.0392$, Wilcoxon rank sum test). Roughly 80% of the single units (n=93/116) demonstrated significant difference in synchrony during incongruent stimulation with the same stimuli, albeit with different underlying perception.

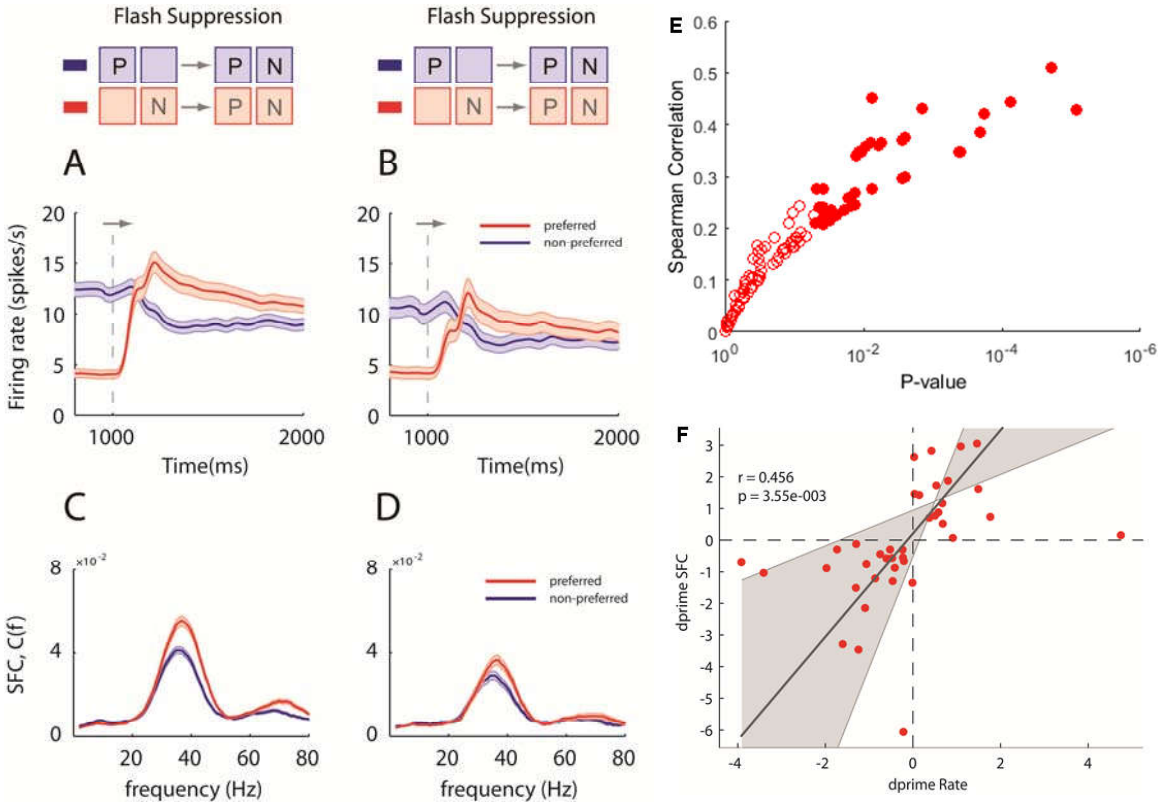

Figure 2. **A**, Average firing rate of population of all 116 single units exhibiting significant gamma-band SFC, **B**, Average firing rate of population of 42 single units with no significant perceptual modulation. **C**, SFC as a function of frequency for all single units, **D**, significant SFC modulation in the population of single units without significant perceptual modulation in firing rate. **E**, Higher correlation coefficients for lower p-values in the Spearman correlation test. Filled circles correspond to coefficients with significant p-values ($p<0.05$). **F**, *d'* index for the preference of neurons reflected in firing rate and SFC.

However, as we have shown earlier [13], ~20% of neurons in V1 show significant firing rate differences across the same conditions. To test whether SFC carries perceptual information in the absence of rate modulation, we identified units with no significant modulation in their firing rate during flash suppression. Of the total ninety-three (93) single-units that exhibited significant modulations in SFC, fourty-two (n=42/93) had no-significant changes in their firing rates. From the above population, 76% of single-units (n=32/42) demonstrated significant difference in gamma-band SFC (28-50 Hz) (Figure 2B). Although there was no significant rate modulation in the above population of neurons, we still did not know if the SFC carries additional information or reflects correlated activity with the firing rates. We showed recently that changes in SFC are

correlated with those in firing rate and gamma-band LFP (under review). We tested here if such correlation exists during BFS. For every spike-LFP pair in the population of neurons with no significant BFS firing rates, we estimated the correlated variability between the trial-by-trial pseudo-SFC (pSFC) values and fluctuations in firing rate at all frequencies (see Methods). We found on average a low to moderate trial-by-trial correlations between pSFC at the peak gamma frequency, and spike counts (Spearman correlation 0.2939, $p<0.05$). We excluded non-significant Spearman correlation coefficients to exclude relationships which may be found by chance. However, we obtained higher correlations for lower p-values which may imply a tendency for moderate correlation between pSFC and firing rates (figure 2E). Furthermore, 82% of spike-LFP pairs demonstrated positive correlations between pSFC and firing rate.

Next, we wanted to know if the modulations in SFC were consistent with the neuron's feature preferences. To this end, we estimated the preference of each neuron across the two stimuli by using the (signed) discriminability index d' during the monocular stimulus presentation (see material and methods), and compared it with the d' of the SFC during the binocular presentation of both stimuli with different percepts. Interestingly, 88% of the aforementioned single-units (n=28/32) showed modulations of SFC in the same direction as their physical preferences, which was consistent with the proportion of spike-LFP pairs which demonstrated positive correlations between pSFC and firing rate. The values of d's for the two quantities were positively correlated ($r=0.456$, $p=0.004$) (figure 2F).

We provided evidence for the modulation of synchronization in V1 as a neural correlate of stimulus selection. Our results support the hypothesis that firing rate modulations

observed with perceptual rivalry in higher cortical areas could be secondary to modifications of neuronal synchronization at lower processing levels [25].

Discussion

Electrophysiological studies in monkeys failed to prove the large modulation of responses in early visual areas during perceptual transitions in BR [7, 26]. In particular, only a moderate fraction of neurons in V1 showed percept-related changes in firing rate during BFS [13]. However, evidence from strabismic cats studies suggested that relevant variable for stimulus selection at early stages of visual processing could be the synchronicity of responses in neuronal ensembles rather than modulation of discharge rates [25]. We showed that synchronicity of spiking in V1 is indeed a correlate of subjective percept during BFS is macaque monkeys, even in the absence of firing rate modulation.

Neuronal synchronization has been implicated in a variety of cognitive and sensory processing functions, including attention [27, 28], stimulus selection [22], feature binding [29-31], and resolution of perceptual and interocular rivalry [25, 32]. It has been shown that neurons activated by attended stimulus in monkey extrastriate cortex, exhibit stronger gamma-band synchronization compared with neighboring neurons activated by unattended stimuli [24, 33]. Small changes in gamma-frequency synchronization with attention may enhance the impact of neurons on their postsynaptic targets and, therefore, lead to pronounced changes in firing rate at subsequent stages [34, 35]. During attentional selection, behaviorally relevant stimuli gain advantage over distractors to reach awareness [36]. When two stimuli are placed within the receptive

field of neurons in higher visual areas, and attention is directed to one of them, the neurons respond as if they received only the attended input [37]. Similarly, viewing incompatible images in each eye typically produces BR in which only one image reaches conscious perception, with the other suppressed from awareness [38]. We showed that gamma frequency band SFC in V1 is significantly higher for perceived stimulus during BFS. We suggest that synchronous activity of lower neuronal groups could make the entrained neurons at subsequent stages sensitive for the signal from dominant stimulus, while rendering them deaf for the signal from suppressed stimulus. Our results support the hypothesis that the general mechanism for pruning the stimulus representation is the synchrony of rhythms [5, 22, 39]. This bottom-up communication structure for preferential routing of selected signals could transform the synchrony code to rate code throughout the visual system.

We found previously that the firing rate of majority of neurons in V1 does not correlate with perception [13]. Firing rate also not always increases with attention [40, 41]. It is conceivable that neuronal populations in early visual areas maintain their activity at a base level, the putative effect of which is reversible at the arrival of a synchronization signal during perceptual switches. This sync command causes spikes to coincide within a short window, enhancing their impact on postsynaptic neurons and translate to an explicit firing rate change at subsequent stage. Similar mechanism may subserve attentional modulation in early visual areas, where neuronal groups selective for invisible stimulus do not shut down completely, but stay active in the background and waiting for the attentional signal, to become coherent and effective. In this scenario, each individual neuron at the level of V1, does not need, and is not supposed, to

change its own rate response according to the subjective percept. This hypothesis is compatible with the selective nature of V1 neurons towards physical attributes of the stimuli, which is constant in such preparations independent of the perceptual experience.

There is a long debate on the early or late mechanism of switches in perceptual reversals [12]. Is stimulus selection a bottom-up process rooted in local interaction at early stages, or higher visual areas modulate the activity of lower areas in a top-down fashion? In a recent study [42], researchers showed that auditory and tactile signals combine to influence vision during BR in humans. Interestingly, The cross-modal stimulus not only prolonged dominance when it matched the dominant visual percept but also made a perceptual switch more likely when it matched the unseen stimulus. Authors argue that even when suppressed from awareness, there is still residual neural activity related to a matching temporal frequency in two sensory brain areas which could boost the suppressed stimulus' salience and make a switch from suppression to dominance more likely, if the phase of the two groups would become aligned. Their view about the cross-modal influence on rivalry supports our suggestion that perceptual reversals are initiated by early multisensory interactions rather than feedback from higher levels. Importantly, attention cannot account for the rescue of the visual stimulus from suppression in this view, because attentional allocation to invisible objects is not thought to be possible [42].

Distribution of selected rhythms for synchronization of neuronal ensembles could be orchestrated by subcortical broadcasting centers like some thalamic nuclei [5]. Low-frequency LFPs in the visual thalamus show robust perceptual modulations when the

animals actively report their percepts during Generalized Flash Suppression [43]. These modulations are eliminated when the animals passively fixate. We showed recently [44] that the modulation of firing rates in V1 upon perceptual suppression during BFS is comparable in anesthetized and passively fixating awake conditions and concluded that active engagement in a task is critical to boost firing rate modulations in V1 to the level which was reported in BOLD studies. With the current results, we conjecture that SFC plays a leading role in initiating the competition in V1 even in the absence of a tasks; however, firing rate modulation is small under these conditions. It will be interesting for future research to investigate the relationship between task engagement and SFC variations in early and higher visual areas.

Experimental Procedures

Ethics Statement

The experimental and surgical procedures were performed with great care and in full compliance with the guidelines of the local authorities (Regierungspräsidium Tübingen, protocol Nr. KY1/02), the European Community guidelines for the care and use of laboratory animals (EUVS 86/609/EEC), and the recommendations of the Weatherall report (http://goo.gl/CVXi7e). Animals were kept in large cages located adjacent to the training and experimental facilities. Space in these cages allows swinging and jumping, and enrichment equipment such as toys were changed frequently. Group housing was maintained to increase the quality of life by rich visual, olfactory, auditory and social interaction and stimulation for play. Balanced nutrition and regular veterinary care and

monitoring, were provided. Chamber implantation and an anatomical scan were performed while the animals were under general anesthesia and aseptic conditions. To alleviate post-surgical pain we administered analgesics for a week after the surgery (Also see surgical procedures below). Animals were not sacrificed after the experiments.

Subjects and surgical procedures

Two adult monkeys (*Macaca mulatta*) D98 and F03, aged 12 and 9 years, weighing 16 and 11 kg respectively, took part in the experiments. Recording chambers were positioned according to stereotaxic coordinates over the operculum in area V1 in both hemispheres of D98 and right hemisphere of F03. This was aided by high-resolution magnetic resonance anatomical imaging. The anatomical scan and recording chamber implantation were done while the animals where under general anesthesia. A more detailed description of these methods can be found elsewhere [13]. A custom-built array of tetrodes [45] was chronically implanted in area V1 inside a form-specific titanium recording chamber implanted on the left hemisphere of the monkey D98. The tetrodes were at least 200μm apart. Recordings were also done non-chronically from the right hemisphere of both monkeys with one to four manually adjustable microdrives (Crist Instrument Co.) and custom-made twisted-wire tetrodes. The recording chambers were from either medical-grade titanium or polyether ether ketone (TECAPEEK; Ensinger GmbH). Details have been described elsewhere [13, 45]. The animals were implanted with a scleral search coil [46, 47] and their eye movements were monitored online.

Data acquisition

The raw voltage signal was passed through an analog bandpass filter (1 Hz - 475 Hz), sampled at $f_s \approx 2$ KHz, digitized (12 bits) and stored as the LFP signal. Multi-unit activity was sampled at 32 kHz, digitized (12 bits), and stored using the Cheetah data acquisition system (Neuralynx) and was defined as the events that exceeded a predefined threshold (25 μV) of the filtered (600 Hz - 6 kHz) and digitized signal. Following each threshold crossing, a segment of 32 samples (1ms) was extracted from all four channels of the tetrode and these waveforms were stored for offline clustering. Single-unit spikes were then isolated from multiunit activity by a custom-built clustering system [45] that uses features extracted from the stored multiunit spike waveforms.

Visual stimuli

Visual stimuli were sinusoidal gratings with different orientations and a typical size of 1° - 2° in diameter, displayed using a dedicated graphics workstation (TDZ 2000; Intergraph Systems) running an OpenGL-based stimulation program. The behavioral aspects like juice reward and trial abortion were controlled using the QNX real-time operating system (QNX Software Systems Ltd). The display system comprised of a custom-made mirror stereoscope with two LCD monitor (resolution of 1024x768; refresh rate of 60 Hz) on both side which allowed for dichoptic presentation of stimuli. After eye calibration and alignment of the displays, a coarse receptive field mapping was performed to position the stimulus for the experiments. Such online estimation was made possible by playing the multiunit activity through a sound amplifier (Grass Technologies) so that the experimenter could evaluate the gross location of the receptive fields and the preferences of the multi-unit responses towards different orientations and sizes. Details are described previously [13]. The pair of orthogonal

orientations that elicited maximal differential multiunit response ($\theta_{||}$ and $\theta_{\perp}$) were identified and used in the experiment.

Experimental design

To study the relationship between neural activity and perceptual modulations, we used the paradigm of binocular flash suppression (BFS). During this paradigm, a visual stimulus presented to one eye is suppressed from awareness as a result of presenting a different stimulus, flash, to the other eye at the corresponding location [6]. In order to initiate the BFS trial, the monkeys had to passively fixate on a central fixation point (0.2°) which appeared in the center of the screen for 300 milliseconds. This was followed by presentation of a static sine-wave grating of two possible orientations ($\theta_{||}$ or $\theta_{\perp}$) to one of the two eyes for one second. Then the orthogonal orientation grating was added to the second eye for another second resulting in incongruent stimulation and suppression of the previously presented stimulus/eye. The stimuli were covering the receptive fields of the recorded sites, with a sizes of 1° - 2°, spatial frequency of 3-5 cycles/s and contrast of 70%. A drop of juice was delivered to the animal if it maintained the fixation throughout the trial. A failure resulted in abortion of the trial without reward. A typical recording session included 200 trials of each condition. For more details see [13].

Data Analysis

All analyses were carried out using scripts written in Matlab (The Mathworks Inc.), together with select functions from Chronux Toolbox [48]. Unless otherwise specified, all time-domain and spectral estimates were based on responses recorded after the flash and between 1400-2000ms following stimulus onset to avoid transient biases after the

switch. Visual responsiveness of neurons as well as orientation and ocularity preferences were determined based on the monocular period of BFS (responses between 400-1000ms) by using discriminability index (d'). This was defined as:

$$d' = \frac{\mu_A - \mu_B}{\sqrt{\frac{(\hat{\sigma}_A{}^2 + \hat{\sigma}_B{}^2)}{2}}}$$

Where μ and $\hat{\sigma}$ are the mean response and the standard deviation of the conditions put in the comparison. Bigger values of d' indices indicate larger discriminability of responses and thus larger preference to one of the conditions being compared. These preferences were then sorted and labeled as preferred-eye and preferred-orientation. Details are described elsewhere [13]

To measure the extent of rhythmic synchronization between LFP and spike times at all frequencies, we estimated spike-field coherence (SFC) defined as the squared magnitude of the cross-spectrum divided by the product of the auto-spectra. For details of the SFC estimation and significance of testing see []. For every single-unit, SFCs were estimated between its spike train and LFPs obtained from each of the simultaneously recorded sites (up to 6 sites in chronic; 4 sites in non-chronic recordings). We used d' with the same definition as above, to measure the discriminability of SFCs for comparable conditions. Statistical significance of rate and SFC modulations was tested using two-sided Wilcoxon rank sum test (p=0.05).

We also tested whether firing rate exhibited correlated variability with SFC across trials. This was estimated by calculating the Spearman correlation between spike count across trials and single-trial coherence estimates. The latter was obtained by pseudo

spike-field coherence (pSFC) [49]. We calculated pFSC for any given trial as the z-transform of the SFC estimated by leaving out that trial subtracted from the original z-transformed SFC estimate, after weighting each term with the number of trials used in the estimate. A detailed procedure for calculating pSFC can be found elsewhere (under review).

Supplemental information

We analyzed the synchronization pattern for 245 spike-LFP pairs exhibiting significant gamma-band SFC, in the incongruent period of BFS paradigm. We were interested in comparing the two conditions with identical physical stimuli but different percepts.

There were two sets of such stimulus conditions (Figure 1). In the first set, we compared the incongruent stimulation followed by the presentation of preferred stimulus in the preferred eye of the neuron (pEpO), with the one followed by the presentation of non-preferred stimulus in the non-preferred eye of the neuron (npEnpO). Note that these two had identical physical stimulus but only one of the two orientations was perceived at each time. Similarly, the second set of stimulus conditions were the incongruent stimulation followed by the presentation of preferred stimulus in the non-preferred eye of the neuron (pEnpO), and the one followed by the presentation of non-preferred stimulus in the preferred eye of the neuron (npEpO).

Any difference in the firing rates or the SFCs of the two conditions in each set could be attributed to the neural correlates of perceptual suppression during BFS. We were particularly interested in the relationship between SFC modulations and the firing rate.

Figure 1S demonstrates the concomitant changes in firing rate modulation and gamma-band SFC during the incongruent stimulation for a representative neuron. As expected, amplitude of the difference in the firing rate during flash suppression is bigger for the first set of conditions since it reflects the difference between the perceptual preference of the neuron towards eyes and stimuli simultaneously. The second set of conditions, however, demonstrates the perceptual modulation related to the differential preference of the neuron toward an eye or stimulus only. Note that the SFC is estimated over the 1400-2000ms window during second second of BFS presentation. Preferred eye and orientations are sorted based on the monocular presentation preference during the first second.

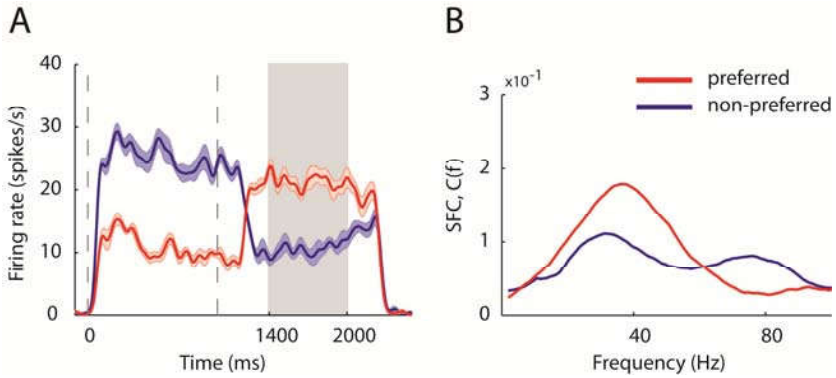

Figure 1S. **A**, spike-density function of an example neuron, **B**, Concomitant changes in spike-field coherence shows a preference of gamma-band SFC (28-50Hz) towards the preferred stimulus in the flash suppression period (1400-2000ms) as shaded in **A.**

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7.3 Binocular flash suppression in the primary visual cortex of anesthetized and awake macaques

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Binocular Flash Suppression in the Primary Visual Cortex of Anesthetized and Awake Macaques

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Abstract

Primary visual cortex (V1) was implicated as an important candidate for the site of perceptual suppression in numerous psychophysical and imaging studies. However, neurophysiological results in awake monkeys provided evidence for competition mainly between neurons in areas beyond V1. In particular, only a moderate percentage of neurons in V1 were found to modulate in parallel with perception with magnitude substantially smaller than the physical preference of these neurons. It is yet unclear whether these small modulations are rooted from local circuits in V1 or influenced by higher cognitive states. To address this question we recorded multi-unit spiking activity and local field potentials in area V1 of awake and anesthetized macaque monkeys during the paradigm of binocular flash suppression. We found that a small but significant modulation was present in both the anesthetized and awake states during the flash suppression presentation. Furthermore, the relative amplitudes of the perceptual modulations were not significantly different in the two states. We suggest that these early effects of perceptual suppression might occur locally in V1, in prior processing stages or within early visual cortical areas in the absence of top-down feedback from higher cognitive stages that are suppressed under anesthesia.

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Introduction

Visual information is processed across a distributed network of interconnected visual areas [1]. The primary visual cortex (V1), being hierarchically the first cortical area receiving information from the eyes through the thalamus, constitutes a cornerstone of the visual system [2,3,4,5,6]. Although V1 has been studied extensively and is arguably the best-understood area in the cerebral cortex, its role in visual awareness remains controversial and has been a subject of intense debate [7,8,9,10,11,12,13].

The use of visual stimuli that induce ambiguous perception has been established as a classical paradigm to identify the neural circuits subserving subjective perception [14,15,16,17,18]. Under these conditions, a single interpretation of the external world cannot be unambiguously achieved. When the brain is presented with such stimuli, typically only one possible interpretation is perceived at a time and after a few seconds the percept switches abruptly to another [18]. Notably, such perceptual alternations occur while the sensory input is kept constant, thus offering a clear dissociation of sensory stimulation and subjective awareness [9,11,14,19,20,21]. Some celebrated examples of such perceptual phenomena include binocular rivalry (BR) and binocular flash suppression (BFS) [22,23,24,25,26,27,28]. Based on many psychophysical studies over decades, the primary visual cortex (V1) was implicated as an important candidate for the site of perceptual suppression during BR [29,30,31,32,33]. However, neurophysiological evidence obtained in monkeys did not corroborate this hypothesis but instead found only a small percentage of neurons that modulated their activity in parallel with the subjective perception of the animals [10,19,34,35,36,37]. In contrast, studies using functional magnetic resonance imaging (fMRI) in humans found that V1 is indeed modulated to a large extent by the subjective percept [12,13,38,39,40].

Possible explanations for this discrepancy include differences in the stimulus configurations, the species tested, and the experimental methodology. In addition, a major difference between many of these studies is the extent to which the subject is involved in attending and consciously reporting the bistable alternations [41,42,43]. Such higher cognitive processes could be based on different mechanisms from those subserving local processes and are only observable in V1 when the subject is awake and behaving [44,45].

In order to disentangle these two processes and investigate the role of the local processing during multistable stimulation, we performed and compared BFS experiments in anesthetized and awake, passively fixating macaques. We conjectured that any effects preserved under anesthesia, in the absence of cognitive feedback from central processes, might reflect local interactions critically involved in the initiation of competition during incongruent stimulation. We found comparable modulations in neural activity as reflected in the multi-unit activity (MUA) and local field potentials (LFPs) in both anesthetized and awake passively fixating animals. Our results suggest that the small significant modulations observed under these non-attentive conditions are arising from circuit mechanisms in early visual areas. It remains to be shown if

top-down feedback to V1 engaged during active behavior would elicit larger modulations comparable to the ones previously reported by fMRI.

Materials and Methods

Ethics Statement

The experimental and surgical procedures were performed with great care and in full compliance with the German Law for the Protection of Animals, the European Community guidelines for the care and use of laboratory animals (EUVS 86/609/EEC), and the recommendations of the Weatherall report for the use of non-human primates in research (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003440). The regional authorities (Regierungspräsidium Tübingen) approved our experimental protocol (Nr. KY1/02) and the institutional representatives for animal protection supervised all procedures. Animals were kept in large cages located adjacent to the training and experimental facilities. Space in these cages allows swinging and jumping, and enrichment equipment such as toys was changed frequently. Group housing was maintained to increase the quality of life by rich visual, olfactory, auditory and social interaction and stimulation for play. Balanced nutrition and regular veterinary care and monitoring, were provided. Chamber implantation and an anatomical scan were performed while the animals were under general anesthesia and aseptic conditions. To alleviate post-surgical pain we administered analgesics for a week after the surgery (see also surgical procedures below). Animals were not sacrificed after the experiments.

Subjects

Four adult monkeys (*Macaca mulatta*) where used for anesthetized (N = 2; B01 and D01, 6 years old, weighing 10 and 8 kg respectively) and awake (N = 2; D98 and F03, aged 12 and 9 years, weighing 16 and 11 kg respectively) electrophysiological recordings.

Surgical procedures

Recording chambers were positioned over the operculum in area V1 according to stereotaxic coordinates. This was aided by high-resolution magnetic resonance anatomical imaging. The anatomical scan and recording chamber implantation were done while the animals where under general anesthesia. Details of the procedure can be found elsewhere [37,46].

Visual stimulation and data acquisition

Anesthetized experiments. Data was recorded from two monkeys (B01 and D01) in separate sessions (two sessions for monkey B01, three sessions for monkey D01) under general anesthesia. The procedure is described in detail previously [46]. Balanced anesthesia was maintained with isoflurane (end-tidal 0.3%) and fentanyl (3 μg/kg/hr). Muscle relaxation was achieved with mivacurium chloride (3–6 mg/kg/hr). Physiological parameters were monitored and maintained within the normal physiological range [46].

Visual stimuli were presented binocularly using a SVGA fiber optic system (Avotec, Silent Vision) with a resolution of 800×600 pixels at 60 Hz frame rate. To focus the eyes on the stimulus plane, animals were fitted with eye-lenses (Woehlk-Contact-Linsen). The eyepieces of the presentation system were positioned by using a modified fundus camera (Zeiss RC250) which ensures the alignment of the stimulus center with the fovea of each eye [46]. The size of stimuli varied between 6° to 9° radius in different sessions.

Intracortical recordings were conducted with the Eckhorn multielectrode arrays [47,48]. This allowed us to simultaneously monitor and record from up to 13 sites. Electrodes were $Pt_{90}W_{10}$ wire (20 μm diameter) with a glass coating (80 μm external diameter) and were guided into the brain through the overlying dura mater. During the recordings, a custom-made adaptor was used to distribute the electrodes against the dura in a 4×4 square array, with an inter-electrode spacing of 2.5 mm which separated the neighboring electrode pairs by 2.5 mm, while the pairs on opposite corners had a physical separation of 10.6 mm.

Data collection was controlled by an industrial PC (Advantech) running under the QNX operating system (QNX Software Systems). The broadband signals from each channel were amplified by a factor of 8000 and band-pass filtered between 1 Hz and 5 kHz (Alpha Omega Engineering). The signals were then individually digitized at a rate of 20.83 kHz on a 16-bit analog to digital board (PCI-6052E; National Instruments) and stored on a PC for further analysis using custom software written in MATLAB (The Mathworks Inc.).

Awake experiments. Two other animals (D98 and F03) were used in the awake sessions. We recorded spiking activity as well as local field potentials (LFP) from V1 of both monkeys by custom made tetrodes guided to the brain by manually adjustable microdrives (Crist Instrument Co.). We also recorded from a chronically implanted array of tetrodes inside a form-specific titanium chamber over the operculum of one of the monkeys (D98). The recording chambers were from either medical-grade titanium or polyether ether ketone (TECAPEEK; Ensinger GmbH). Details have been described elsewhere [37,49]. The animals were implanted with a scleral search coil [50,51] and their eye movements were monitored online.

Visual stimuli were sinusoidal gratings with different orientations and a typical size of 1°–2° in diameter, displayed using a dedicated graphics workstation (TDZ 2000; Intergraph Systems) running an OpenGL-based stimulation program. Dichoptic presentation of the visual stimuli was through a custom-made stereoscope with two LCD monitors at both sides running at a resolution of 1280×1024 and a 60 Hz refresh rate. After eye calibration and alignment of the displays, a coarse receptive field mapping was performed to position the stimulus for the experiments. The multi-unit responses were put through a sound amplifier (Grass Technologies) so that the experimenter could evaluate the gross location of the receptive fields and the preferences of the multi-unit responses towards different orientations and sizes. Details have been described previously [37].

Multi-unit activity was sampled at 32 kHz, digitized (12 bits), and stored using the Cheetah data acquisition system (Neuralynx) and was defined as the events that exceeded a predefined threshold (25 μV) of the filtered (600 Hz–6 kHz) and digitized signal. LFP signals were recorded after filtering the raw signal using analog band-pass filtering (1 Hz–475 Hz) and digitized at 2 kHz (12 bits).

Experimental design

To study the relationship between neural activity and perceptual modulations, we used the paradigm of binocular flash suppression (BFS). During this paradigm, a visual stimulus presented to one eye is suppressed from awareness as a result of presenting a different stimulus, referred to as *flash*, to the other eye at the location corresponding to the image to the first eye [26].

In anesthetized experiments, monkeys were presented with blank screen for two seconds in the beginning of each trial. Subsequently, one of the two stimuli was presented alone to either the left or the right eye for two seconds, followed by the onset (flash) of the second stimulus at the corresponding retinal location

in the contralateral eye and the simultaneous presentation of both incongruent stimuli for another two seconds until the end of the trial. The two stimuli have been chosen to elicit maximal differences in neural activity based on the average responses to a battery of natural and generic images (N = 50) that were presented to the animal prior to the BFS experiment. The time course of an example trial is depicted in Figure 1A for two stimuli used in our experiments. Figure 1C shows all four possible configurations of BFS conditions (1–4) as well as two control conditions termed physical alternation (5–6). For these conditions, the stimuli are presented congruently across the two eyes producing the same perceptual sequence (in awake conditions) and are used as controls.

The same paradigm was used in awake experiments. The monkeys had to passively fixate on a central fixation point in order to initiate the BFS trial. A fixation point (0.2°) appeared in the center of the screen for 300 milliseconds followed by flash suppression stimulation similar to anesthetized condition but with a duration of one second for each period (Fig. 1B). Stimuli were static sinusoidal gratings with orthogonal orientations optimized to elicit maximal differences between the responses to the two orientations. The sizes of the stimuli were 1°–3°, covering the receptive fields of the recorded sites. A drop of juice was delivered to the animal if it maintained the fixation throughout the trial. For more details see [37].

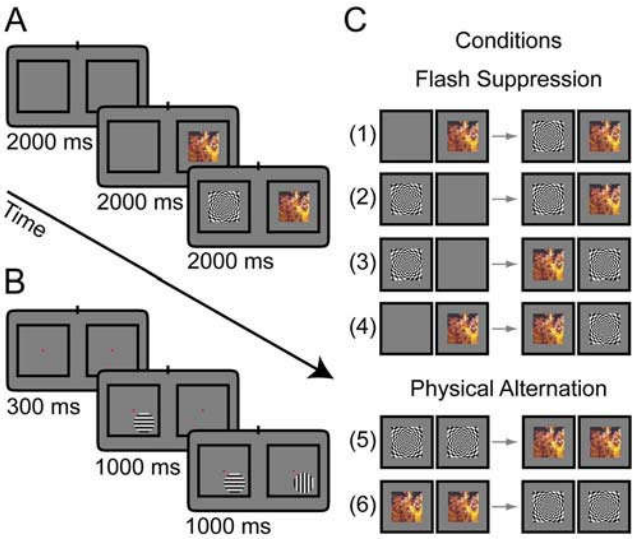

Figure 1. Illustration of the binocular flash suppression (BFS) paradigm for the anesthetized and awake experiments. (**A**) The sequence of presentation of the two stimuli to the two eyes in the anesthetized experiments. An intertrial interval of 2000 ms was followed by a stimulus presented in corresponding locations to one of the two eyes for 2000 ms. A second stimulus was added to the other eye for another 2000 ms. Stimuli have been chosen from a battery of natural and synthetic images to elicit maximal difference in the neural activity. (**B**) Sequence of BFS presentation in the awake experiments. After an intertrial period (1000–3000 ms) the animal fixated on a central point for 300 ms in order to initiate the trial and then monocular and binocular stimuli followed similar to **A**. Stimulus presentation times were 1000 ms and the stimuli were static sinusoidal gratings with orthogonal orientations optimized to elicit maximal (preferred orientation) and minimal (non-preferred orientation) responses in the recorded channels. The position of the stimuli was chosen to cover the receptive fields of the recorded sites and the sizes of the stimuli were 1°–3°. The animal fixated within a window with radius 0.5° around a small point throughout the trial to receive juice reward. Unsuccessful trials were aborted and not further analyzed. (**C**) Different possible configurations of BFS and control conditions. Left and right columns present the monocular and binocular periods respectively. Note that the four different flash suppression conditions can be split in two pairs (1–2 and 3–4) with identical stimulus presentation across the different eyes albeit different perceptual outcomes depending on the initial monocular stimulus (see methods). Physical alternation conditions (5–6) demonstrate an identical perceptual experience albeit without binocular conflict and serve as controls.
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Statistical and data analysis

We used custom programs written in Matlab (The Mathworks Inc.) for data analysis. Statistical significance ($P<0.05$) of physical and perceptual modulations was assessed by using a nonparametric Wilcoxon rank sum test for equal medians. For all the comparisons, we excluded the first 500 ms after the flash to avoid initial transient biases. We then calculated the preference and modulation indices by using discriminability index (d'). This was defined as:

$$d' = \frac{\mu_A - \mu_B}{\sqrt{\left(\sigma_A^2 + \sigma_B^2\right)/2}}$$

Where μ and σ are the mean response and the standard deviation of the conditions put in the comparison. In this paper, we report the d' indices for either pairs of binocularly presented identical stimuli (referred to as sensory preference d'_{sens}) or incongruent stimuli (referred to as perceptual preference d'_{perc}). Bigger values of d' indices indicate larger discriminability of responses and thus larger preference to one of the conditions being compared.

To estimate the time-courses of neural adaptation to prolonged presentation of the preferred stimulus we fitted exponentials of the form $y = a + b \cdot e^{-t/\tau}$ to the data of the monocular period.

Results

Perceptual modulation of multi-unit activity

We recorded neural activity from V1 of four macaques being either under general anesthesia (B01 and D01), or awake, passively fixating (D98 and F03). This allows the comparison of neural activity in the anesthetized and awake brains during the BFS task, which in awake conditions, ensures robust perceptual suppression of a monocular stimulus upon asynchronous presentation of a second stimulus to the other eye (see Materials and Methods for details). Recordings were performed with the Eckhorn multi-electrode arrays and custom made tetrodes. Unless otherwise specified, statistical tests were performed using a Wilcoxon two-sided rank sum test with a critical value of 0.05.

During anesthetized experiments, we recorded multi-unit activity from 33 electrode penetrations in two monkeys. In monkey B01, 13 electrodes were used in a single experimental session while in monkey D01, 10 electrodes were used in two separate sessions. From the total of 33 MUAs in two monkeys, 31 (94%) were visually responsive. Out of these, 29 showed significant tuning to the physical alternation conditions as measured by the d' index (see Materials and Methods). Twenty multi-unit sites (two non-tuned during physical alternation) showed significant modulations across at least one pair of binocular incongruent conditions with the same stimulus configuration. Note that these conditions elicit different percepts in awake subjects and we will refer to them as "perceptual" modulations but keep in mind that the animal was anesthetized. Some examples of significantly modulating sites are presented in Figure 2. On average, the magnitude of the perceptual modulations was substantially smaller $\bar{d}'_{perc} = 0.40 \pm 0.05 < \bar{d}'_{sens} = 1.75 \pm 0.18$

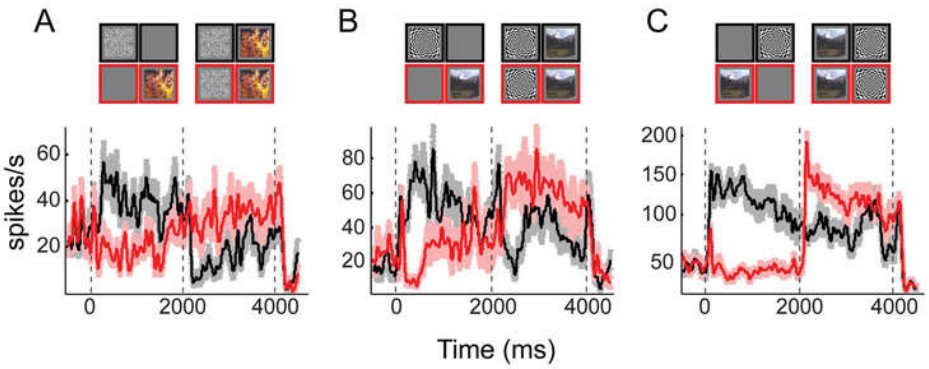

Figure 2. Examples of multi-unit modulations during binocular flash suppression in anesthetized monkeys (A–C). The spike-density functions of three example multi-units are shown (A from monkey B01, B–C from monkey D01). Upper diagrams on each panel demonstrate the conditions with corresponding color outlines as the spike density functions below. The conditions contrasted in each case had the same stimulus during the binocular period but notably predict different percepts in awake subjects. Note the significant modulations during the binocular (same stimulus) conditions that are, however, smaller than the preference during the monocular presentation. The shaded areas represent SEM across trials. Time zero was defined to be the onset of the monocular stimuli.
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[μ+SEM] in comparison to the physical alternation period ($p = 1.8\times10^{-8}$, one-tailed two-sample T-test, N = 31 visually responsive sites).

For awake experiments, we analyzed the spiking activity recorded from two other animals (D98 and F03). Analysis of the single unit activity of these two animals has been published elsewhere [37]; here we report multi-unit activity (MUA) and compare it with MUA from the anesthetized experiments. From a total of 393 multi-units, 364 were visually responsive (92%) and 275 units showed sensory tuning to the visual stimuli. Perceptual modulations were found in 88 of these sites. As in the anesthetized, the magnitude of the perceptual modulations was substantially smaller $\bar{d}'_{perc} = 0.25 \pm 0.01 < \bar{d}'_{sens} = 1.52 \pm 0.08$ [μ+SEM] in comparison to the physical alternation period ($p \approx 0$, one-tailed two-sample T-test, N = 364 visually responsive sites).

Comparison between the two conscious states

To study the effect of unconsciousness (during anesthesia) on perceptual modulations during flash suppression, we compared the spiking activity in anesthetized monkeys with those of their awake counterparts. Differences between the two conditions could potentially be also attributed to differences in experimental design and indirect influences of anesthesia (but see Discussion).

Figure 3 compares the activity for the population of multi-units across the two conscious states. A small but significant modulation was present in both the anesthetized and awake states during the flash suppression period (Fig. 3B, D). Furthermore, the relative amplitudes of the perceptual modulations as measured by the ratio of perceptual to sensory $|d'|$ were not significantly different for the two states. This was on average 28% and 25% of the sensory modulation in anesthetized and awake conditions respectively (across significantly modulating sites in both animals in each conscious state, N = 84 in awake and N = 18 in anesthetized). The close similarity between the relative amplitude of modulations in the two conditions suggests similar mechanisms for these two states.

Table 1 summarizes the numbers and percentages of significant modulations for both conscious states. We tested if the proportion of perceptually modulating sites (PM) was significantly different in anesthetized and awake macaques (two-sampled t-test between proportions, t-value 4.924, $p<10^{-5}$). This was on average 65% in anesthetized (20/31 recorded units with a 95% C.I. of 48–81%,

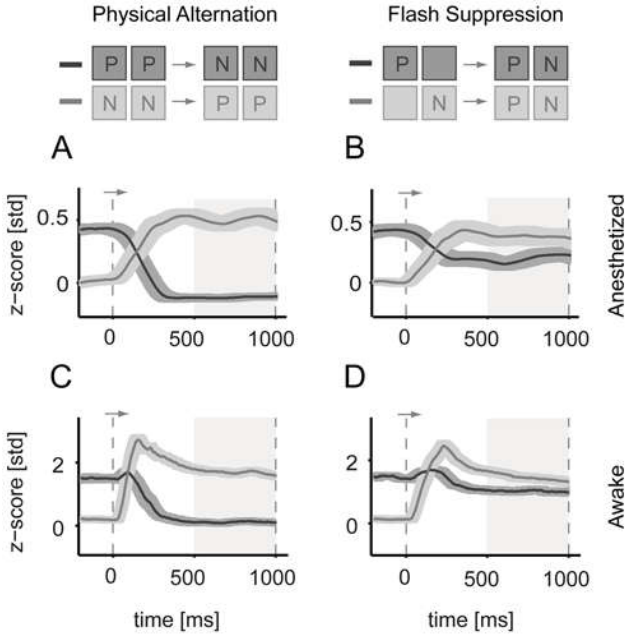

Figure 3. Population responses of neurons during physical alternation and binocular flash suppression conditions in anesthetized (A,B) and awake (C,D) monkeys. Different conditions are depicted on top of the panels with corresponding shaded outlines as the spike density functions below. Eyes are presented with preferred (P) and non-preferred (N) stimuli. Left group on the top are the two conditions of physical alternation and rightward the two flash suppression conditions eliciting the same perceptual sequence. (**A**) Population activity in z-scores during physical alternation conditions and (**B**) during binocular flash suppression in anesthetized monkey for all visually responsive multi-units (N = 31) in anesthetized experiments. Prior to averaging, conditions were sorted to preferred (P) and non-preferred (N) according to the responses during the monocular presentation. (**C,D**) the same as **A** and **B**, but in awake passively fixating monkeys. In all four panels, dark lines represent the responses to the preferred stimulus followed by non-preferred stimulus after the flash. Lighter gray lines represent the responses to the non-preferred stimulus first followed by the responses to the preferred in the second period. The shaded areas around the lines represent SEM across sites. Time zero was defined to be the time of the flash or switch of the stimuli.
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Table 1. Numbers and percentages of significant modulations.

		Anesthetized	Awake
T	Total # of multi-units/recorded sites	33	393
VR	Visually responsive (% of T)	31 (94%)	364 (92%)
SM	Sensory stimulus modulation (% VR)	29 (94%)	275 (76%)
PM	Perceptual stimulus modulation (% VR)	20 (65%)	88 (24%)
PaS	Perceptual & sensory (% PM)	18 (90%)	84 (95%)
xP	Only perceptual (% PM)	2 (10%)	4 (5%)

The absolute numbers and respective percentages of significant modulations are presented for multi-unit activities (MUA) in the two conscious states. In the first row (T) the total numbers of multi-units/recorded-sites are reported. The second row (VR) presents the number (percentage) of sites that showed significant visual responses. The third row (SM) presents the number of sites that were responding differentially two the different congruent stimuli (sensory modulation) and the fourth row (PM) the number of sites that showed differential responses under the different perceptual conditions (under the same stimulus) as a percentage of visually responsive units/sites. Note the significant difference in PM between the two conditions. In the last two rows, PaS presents the numbers of perceptually modulating sites that showed, in addition, sensory modulations and xP presents the numbers of sites that showed exclusively perceptual modulations.
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Bernoulli distribution), which was higher than the average of 24% in awake macaques (88/364 recorded units with 95% C.I. of 20–29%, Bernoulli distribution).

Flash suppression and adaptation

Neural adaptation is an inherent potential complication of the binocular flash suppression (BFS). The different history of stimulation leading to the two alternative percepts can introduce differences in the level of adaptation in the neural populations encoding the competing stimuli. However, a simple model of adaptation cannot explain the responses of V1 neurons during BFS. To examine this, we estimated the time course of adaptation of the first stimulus (preferred) for the whole duration of a trial by fitting an exponential to the data during the monocular presentation (see Materials and Methods). We found that the parallel presentation of the non-preferred stimulus during BFS introduces additional suppression compared to the estimated level of activity predicted by adaptation (Fig. 4). The time constants of adaptation (τ) were $\tau_{aw} = 225$ ms for the awake while for the anesthetized adaptation was slower with $\tau_{an} = 546$ ms. These results demonstrate that interocular and/or stimulus interactions beyond adaptation are taking place and contribute to the perceptual modulations during incongruent stimulation. Similar interactions were also present at the level of single neurons reported in a previous study (see figure 10 in [37]).

Modulations of the local field potentials

We acquired local field potentials from 33 recording sites in three anesthetized experiments. Similar to the awake results reported previously [37], the power of the gamma frequency range of the LFP (24–90 Hz) showed an increase shortly after the stimulus onset. Also, a preference for the stimulus was observed in 26 recording sites during congruent stimulation. During the incongruent presentation, however, only one third of recording sites (11/33) showed a significant difference in perceptual modulation. Similar to the MUAs, this difference was substantially smaller than sensory tuning of the LFPs (Fig. 5).

Lower frequency LFP power (1–12 Hz) showed a significant increase in oscillatory activity after stimulus onset in only 14 of 33 recording sites. Sensory tuning to the stimulus was observed in the same fraction of recording sites (14). During the dichoptic phase (perceptual suppression), this difference was significant in only 4 recording sites of one of the animals (B03). These results indicate that perceptual modulations of the lower band of the LFP in V1 are essentially absent in anesthetized conditions, similar to the awake passively fixating animals reported previously [37].

Discussion

The neural correlates of visual awareness have been attracting scientists' interest for decades. In particular, the role of primary visual cortex (V1) in perceptual rivalry has been a subject of intense debate [7,8,52]. On one hand, psychophysical data and the hierarchical position of V1 in the visual system initially suggested that perceptual suppression is resolved at the level of V1 through interocular competition between the two monocular channels [29,32,33]. Electrophysiological recordings from multiple visual areas in the brain including V1, on the other hand, provided evidence for competition happening at higher visual areas presumably between internal representations of stimuli rather than information from monocular channels in V1 [10,14,19,36]. In a comprehensive review, Blake and Logothetis discussed supporting evidence for each of these alternatives and proposed a hybrid model of rivalry which involves both mechanisms of local and global processing at different hierarchical levels [11]. This model gained further support by a number of psychophysical and computational studies [53,54,55,56].

Local and global processing in V1 could be based on different mechanisms. Feedback signals from extrastriate visual areas modulate V1 activity extensively. The density of such feedback projections is as much as or larger than the feedforward afferents [57]. For example, top-down attention is a process that could be mediated via such projections and has been shown to modulate V1 activity [58,59,60,61,62]. In a series of fMRI studies in human, perceptual suppression has also been found to strongly modulate BOLD activity in primary visual cortex [12,13]. In addition, we have shown previously that the activity of some single cells in V1 also shows significant modulations during perceptual suppression induced by BFS [37]. However, only a small proportion of neurons in V1 showed these effects and importantly the amplitude of perceptual modulations was very small in comparison to the sensory preference. One possible explanation for the difference between the strength of modulations in area V1 of human and monkeys is the extent to which the subjects were asked to consciously attend to the stimuli [41,63]. It is conceivable that the effects recorded by fMRI in humans reflect top-down modulations mediated by changes in attentional state and/or the active employment of the subject in the task instead of directly reflecting the competition happening at the level of V1 circuitry

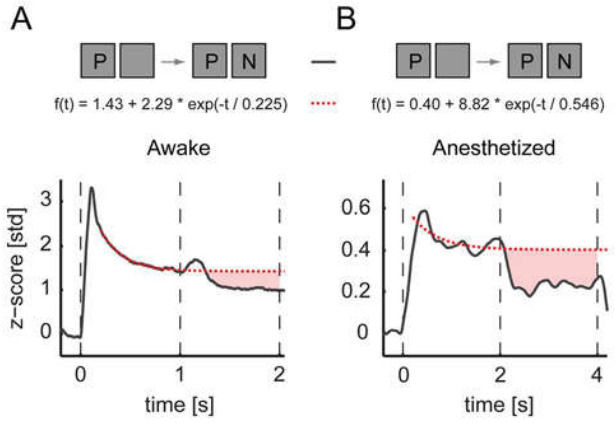

Figure 4. Effects of adaptation. (**A**) The suppression caused by the presence and perception of the non-preferred stimulus (N) compared with a modeled (red-dashed line) continuous presentation of the preferred stimulus (P) in awake experiments and (**B**) in anesthetized experiments. Shaded red areas indicate the additional suppression caused by interocular and/or stimulus interactions beyond adaptation.
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[39,41,64,65]. On the contrary, most monkey electrophysiology studies used paradigms with animals passively fixating not directly being engaged in reporting the perceptual transitions.

Two studies that did require the monkeys to report their subjective perception also reported small percentages of neurons showing spike rate modulations [10,35]. Note, however, that these studies used different stimulus paradigms and could potentially underestimate the effects. The first study by Leopold and Logothetis, 1996 used binocular rivalry (BR). Although BR has many advantages over BFS, the variability in the animal reaction times is expected to smooth the average triggered responses thereby underestimating the effect. The second study by Wilke et al., 2006 used generalized flash suppression (GFS) that notably involves no direct interocular interaction of corresponding retinal locations. Critically, the effectiveness of GFS depends on parameters like the distance of the surround stimuli to the target, the density etc. (see [66]). The authors adjusted the parameters so that the target would disappear only in about 50% of the trials. This means that the suppression-inducing stimulus was not as potent as in the case of BFS, for which suppression happens essentially in 100% of the trials [37], and therefore could also underestimate the effect.

In the present study, we compared neural activity in V1 during binocular flash suppression in anesthetized and awake monkeys to shed light on the mechanisms of perceptual suppression. Some aspects of global processing such as the attentive and conscious analysis of a scene have been observed in V1 only in awake and perceiving animals [64,67,68]. We conjectured that if the small effects observed in previous electrophysiological studies are due to influences from central processes these modulations should be eliminated under anesthesia. However, we found significant modulations of the multi-unit activity recorded in V1 of anesthetized macaques during binocular flash suppression. These modulations were small, albeit comparable to those observed in passively fixating awake animals. This suggests that these effects are arising from early processes that initiate the competition between monocular channels and do not necessarily need consciousness.

The effects of anesthesia on consciousness are controversial. Anesthesia disrupts cortical integration [69] which is associated

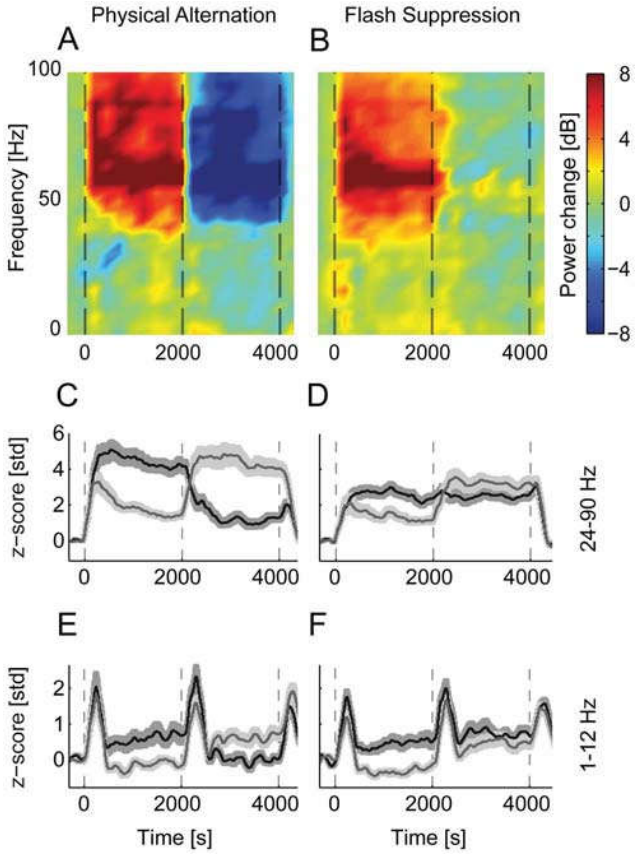

Figure 5. Population average of the local field potentials (LFP) of all visually responsive sites (anesthetized experiments). (**A**) The average difference in the spectrogram between the two conditions during physical alternation periods and (**B**) during flash suppression conditions. Spectrograms are plotted only for frequencies below 100 Hz. (**C,D**), Time domain band-passed average of the gamma-band frequencies (24–90 Hz) for physical alternation and flash suppression conditions. (**E,F**), Time domain average of the lower frequency bands (1–12 Hz), during physical and perceptual alternations, respectively.
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with unconsciousness. In particular, it abolishes contextual and attentional modulation of firing, presumably mediated by feedback connections [70]. In this study, we employed an optimized protocol for balanced anesthesia that allows robust and reproducible activation of primary visual cortex and a number of extrastriate visual areas, including areas in the superior temporal sulcus [46]; however, cognitive signals like top-down attention and post-perceptual feedback to early visual areas were presumably suppressed in this state. Given the similarly small magnitudes of perceptual modulation during the awake, passively fixating condition and the anesthetized condition, we suggest that such cognitive signals from task-related central processes are a key ingredient of the larger modulations that have been observed in human V1 by fMRI.

Furthermore, we found that the proportion of perceptually modulating sites during wakefulness was significantly lower than that under anesthesia. We note that this result should be interpreted with caution as the difference could be attributed to several potential confounds such as stimulus differences and biases in electrode positioning. Another possible explanation is that processing during awake stimulation conditions might be actively reducing perceptual modulations e.g. by decorrelating the

neuronal ensembles involved in the competition. For example, neuromodulatory processes like attention have been shown to decrease correlated variability in neuronal populations [71,72,73]. Such active gain mechanisms can largely change spiking correlations [74]. Such processes can enrich the information carried by neuronal populations in V1 and at the same time reduce bottom-up competition as reflected in perceptual modulations in multi-unit sites. Alternatively, this difference could be arising from factors that are not inherently related to perception.

In a recent study, Wilke and colleagues demonstrated that the low frequencies of the LFP in the thalamus show robust perceptual modulations only if the animals are actively reporting their percept and are eliminated when the animals passively fixate [75]. Similarly, our previous study in passively fixating animals found negligible perceptual modulations of the LFP at this frequency range [37]. Here, we found that lower frequency LFPs in anesthetized V1 were also not predictive of the percept consistent with the hypothesis that active engagement of the animal in the task might be necessary. Given the relationship between the BOLD signal and the LFP [76], it is conceivable that strong BOLD activation in V1 during binocular rivalry in humans is more likely related to the feedback from higher cognitive central stages. However, differences in the nature of the read-out signals could be still a possible explanation for these differences.

Our results confirm that V1 is involved in the process of perceptual suppression during interocular incongruent stimulation and we suggest that it plays a role in initiating the competition. This process is independent of the feedback from higher areas when the subject is not consciously involved in the task. It remains to be shown if a more pronounced and robust modulation of V1 is present during an active task, which can be eliminated under anesthesia or a no-task, passive fixation condition.

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Author Contributions

Conceived and designed the experiments: GAK NKL YM. Performed the experiments: GAK YM. Analyzed the data: HB GAK. Contributed reagents/materials/analysis tools: HB GAK YM NKL. Wrote the paper: HB GAK.

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