Local Field Potential activity associated with temporal expectations in the macaque Lateral Intraparietal area

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Oscillatory brain activity is attracting increasing interest in cognitive neuroscience. Numerous EEG-, MEG- and local field potential (LFP) measurements have related cognitive functions to different types of brain oscillations, but the functional significance of these rhythms remains poorly understood. Despite its proven value, LFP activity has not been extensively tested in the macaque lateral intraparietal area (LIP), which has been implicated in a wide variety of cognitive control processes. We recorded action potentials and LFPs in area LIP during delayed eye movement tasks and during a passive fixation task, in which the time schedule was fixed so that temporal expectations about task-relevant cues could be formed. LFP responses in the gamma band discriminated reliably between saccade targets and distractors inside the receptive field (RF). However alpha and beta responses were much less strongly affected by the presence of a saccade target but rose sharply in the waiting period before the go-signal. Surprisingly, conditions without visual stimulation of the LIP-RF evoked robust LFP responses in every frequency band – most prominently in those below 50 Hz – precisely time-locked to the expected time of stimulus onset in the RF. These results indicate that in area LIP, oscillations in the LFP, which reflect synaptic input and local network activity, are tightly coupled to the temporal expectation of task-relevant cues.

A major challenge of systems neuroscience is to relate neural activity to cognitive functions in awake, behaving animals. The majority of such studies have measured action potential activity to characterize the output of a cortical area thought to be involved in a given task. Single-unit activity (SUA), however, suffers from biases in both cell type and cell size (Stone, 1973; Towe & Harding, 1970). Multi-unit activity (MUA), on the other hand, most likely represents information from many neurons, lying within 140 - 300 μ of the

electrode tip (Logothetis, 2003), but cannot differentiate between increases in neuronal responses and increases in neuronal recruitment. Nonetheless, both MUA and SUA represent neuronal output. LFP activity, in contrast, has been thought to reflect both the input of a given cortical area and its local processing activity (Logothetis, 2003) in the population of neurons located at least 250 μ m and up to a few millimeters from the electrode tip (Katzner et al., 2009; Liu & Newsome, 2006; Mitzdorf, 1987), but see (Kajikawa & Schroeder, 2011). In recent years, LFP measurement has grown increasingly popular because of its potential for studying ensembles of neurons involved in cognitive functions such as short-term memory (Siegel, Warden, & Miller, 2009), attention (Fries, Reynolds, Rorie, & Desimone, 2001) and motor planning (Hwang & Andersen, 2009).

The macaque lateral intraparietal area (LIP) has been implicated in a broad spectrum of cognitive control processes such as saccade planning, attention, decision formation, reward expectation, timing and even categorization (Andersen & Buneo, 2002; Colby & Goldberg, 1999; Freedman & Assad, 2006; Freedman & Assad, 2011; Gnadt & Andersen, 1988; Gold & Shadlen, 2007; Leon & Shadlen, 2003; Platt & Glimcher, 1999; Wardak, Olivier, & Duhamel, 2004). Despite decades of single-cell recording in LIP, very few studies have addressed the extent to which the cognitive control processes associated with LIP spiking activity are already present in the input or local processing within LIP, and are thus reflected in the LFPs (but see Bollimunta & Ditterich, 2011). Furthermore, a systematic investigation of SUA, MUA and LFP activity in LIP is crucial for relating fMRI activations in posterior parietal cortex to single-cell studies, given that the BOLD signal correlates better with LFP than with spiking activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Finally, previous research has shown the potential of LFP power, recorded in parietal cortex, for controlling the onset of arm movements in a cortical neuroprosthesis (Hwang & Andersen, 2009).

The only study of LFP activity in area LIP during memory-guided saccades (Pesaran, Pezaris, Sahani, Mitra, & Andersen, 2002) showed that gamma-band activity (25-90 Hz) discriminated between preferred and anti-preferred saccade directions with the same accuracy as spiking activity. Furthermore, the LFP-LFP coherence between LIP and frontal areas was higher during pop-out than during visual search tasks for frequencies between 35 and 55 Hz, but the reverse pattern was observed for frequencies between 22 and 34 Hz, suggesting that coherence in different frequency bands may underlie bottom-up and top-down attention (Buschman & Miller, 2007). However, it is unknown to what extent the LFP power of various frequency bands may discriminate between saccade targets and distractors in the RF, whether the LFP power is differentially modulated by visual stimulation of the RF or by the expectancy of visual stimulation, and whether the LFP responses are affected by task context.

We recorded SUA, MUA and LFP activity in area LIP to test the effect of RF stimulation by different stimuli and the temporal expectation of RF stimulation within three different task contexts (visually-guided saccades, memory-guided saccades and passive fixation of either a grating or no visual stimulus). The onset of visual stimuli in the RF invariably evoked robust increases in LFP power in all frequency bands. The gamma power reliably discriminated between targets and distractors in the RF, and between a visual stimulus and no visual stimulus in the RF, but remained at a constant level during the waiting period preceding the saccade. In contrast, the LFP below 25 Hz was much less affected by visual stimulation but rose sharply during the waiting period before the saccade. Intriguingly, we observed pronounced modulations in LFP power in the absence of visual RF stimulation in all frequencies up to the high-gamma band, which may reflect local preparatory activity associated with the temporal expectation of salient visual stimuli.

Materials and Methods

Subjects and surgery

All experiments were performed with two male rhesus monkeys (juvenile monkey Tm, 4 kg; adult monkey Tb, 6 kg). Surgical and training procedures have been described elsewhere (Premereur, Vanduffel, & Janssen, 2011). Figure 1B shows a representative recording position for monkey Tb. In both monkeys, the recording area comprised the posterior part of the lateral bank of the IPS, corresponding to LIPd and LIPv (Lewis & Van Essen, 2000). All procedures were performed in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were approved by the Ethical Committee at the Katholieke Universiteit Leuven Medical School.

Stimuli and tests

The stimuli and tasks were described in Premereur et al. (2011). In the *visually-guided saccade task* with multiple distractors, monkeys had to hold fixation within a window of 2 x 2 degrees around a small red spot in the center of the display for a fixed duration of 450 ms, after which a single green saccade target and four grey distractors appeared (Fig. 1A). Target and distractors were equal in size (0.25°) and luminance (6 cd/m^2). The saccade target appeared either inside the LIP RF (Target-In condition) or at the opposite position ipsilateral to the recording cylinder (Target-Out condition). The distractors appeared in the upper and lower hemifield ipsi- and contralateral to the RF, with one of them always located inside the RF. Note that in the Target-In conditions, both the saccade target and a distractor are presented inside the RF. After a variable delay (between 500 and 2000 ms), the luminance of one of the distractors (selected at random) increased by 300%, indicating to the animal to make a saccade towards the green target. The monkey was rewarded for making a saccade towards the target within 500 ms after the go-signal and holding fixation in a window (max 4x4 degrees) around the target for 250 ms. We will use the term

‘distractors’ to indicate the four grey stimuli that could become the go-signal (with a probability of 0.25). To encourage rapid responses, reward size was governed by an exponential function of reaction time between 150 and 500 ms after the go-signal. The time between target onset and the go-signal was a random variable drawn from a unimodal Weibull distribution delayed by 500 ms (Janssen & Shadlen, 2005):

$$(1) U(t) = \begin{cases} 3\alpha(t - \frac{1}{2})^2 e^{-\alpha(t - \frac{1}{2})^3} & \text{for } t > \frac{1}{2} \\ 0 & \text{Otherwise} \end{cases}$$

In the visually-guided saccade task with a single distractor all parameters were identical to the multiple distractor task, except that a single (green) target stimulus and a single (grey) distractor appeared either in or outside the LIP RF. Therefore the single-distractor task consisted of four conditions: target and distractor in RF, target in RF and distractor outside RF, target outside RF and distractor in RF, and target and distractor outside the RF.

In the *memory-guided saccade task* a green saccade target appeared either inside or outside the RF for 200 ms after a 450 ms period of fixation. After disappearance of the target, the monkey had to maintain central fixation until the fixation point dimmed, hereby cueing the monkey to saccade to the remembered target position. We used the same distribution of random go-times as in the visually-guided saccade task.

The *passive fixation task* consisted of a fixed 800 ms period of fixation, after which a static colored grating (1.5 degrees in diameter, spatial frequency: 1 cycle/deg, red-blue sine wave gratings, mean luminance of red: 30 cd/m², mean luminance of blue: 100 cd/m²) was presented for 600 ms inside the RF on 80% of the trials. In the other 20% of the randomly interleaved trials a bitmap figure with the same luminance and color as the background of the monitor (and therefore invisible to the animal: equal to no stimulus presentation) was

presented in the RF of the neuron. This trial structure was used to obtain the exact same timing parameters in both conditions (Grating-In vs No-Grating). The animal was rewarded for maintaining fixation until 500 ms after stimulus offset.

Recording procedure

We employed standard recording procedures as described in Premereur et al. (2011). A photocell was attached to the monitor to detect the onset of a white square in the lower right corner of the screen (covered with black tape to obscure it from the monkeys' view), that appeared in the first video frame containing a stimulus (distractor, saccade target or go-signal). LFP and spiking activity were recorded with the same tungsten electrode. LFP signals were amplified and filtered between 1 and 170 Hz (Frequency Devices, IL, USA). Eye position signals (EyeLink 1000, SR Research, Ontario), neural activity, and photocell pulses were digitized and processed on a digital signal processor (DSP) at 20 kHz (C6000 series; Texas Instruments, TX, USA). We searched for responses in MUA by placing saccade targets at various locations in the contralateral hemifield. Formal testing started once a spatially selective multi- or single-unit target response was observed. Thus the selection of LIP neurons was based on the presence of spatially-selective target responses, but sites with significant memory delay-period activity were found at nearby locations, consistent with previous LIP studies (e.g. Falkner, Krishna, & Goldberg, 2010). The tasks were presented in a sequence with, if possible, multiple repetitions, always in the same order: visually-guided saccade task with multiple distractors (120 trials), passive fixation task (100 trials), and memory saccade task (80 trials). In 14 sites the task sequence also contained the single-distractor saccade task after the memory saccade task.

Data analysis

All data analysis (unless mentioned otherwise) was performed using custom-written Matlab (the MathWorks, MA, USA) programs.

LFP analysis. For every trial, the time-frequency power spectrum was calculated using Morlet's wavelet analysis techniques (Tallon-Baudry & Bertrand, 1999), with spectro-temporal resolution equal to 7, after filtering with a 50 Hz notch filter (FieldTrip Toolbox, Donders Institute, The Netherlands). Power was normalized per trial by dividing the power trace per frequency by the average power for this frequency in the 300 ms interval before stimulus onset. To exclude trials containing possible artifacts in the LFP recordings, maximum and minimum values of the continuous LFP signal and of the time-frequency spectrum were calculated per trial, and trials with minimum signal values below the 5th percentile or maximum values above the 95th percentile were removed. Furthermore, the data set was split in two and all population analyses were repeated for both halves of the population of recording sites to check for consistency. If inconsistent findings were found, due to one trial or recording site with extreme values, this trial/recording site was removed. We analyzed the LFP power in standard frequency bands: high-gamma (80-170 Hz), medium-gamma (50-80 Hz), low-gamma (25-50 Hz), beta (12-25 Hz) and alpha (8-12 Hz). Lower frequencies were excluded from our analyses, as our trials were on average only 1.5 s in length. LFP power was averaged across trials and over frequencies to extract the average power per frequency band over time. LFP data were not corrected for average visually evoked potentials (VEPs), but removing the VEP yielded similar response patterns. LFP analyses using multi-taper methods also revealed similar response patterns. All statistics on LFP data were obtained using permutation tests, where real data were randomly distributed over all the different conditions 10000 times, and the differences between two conditions were then calculated for every permutation for comparison with the actual difference between conditions. Differences between conditions were calculated based on the response in the 0-500 ms interval after stimulus (target or distractor) onset. Presaccadic enhancement in LFP power was assessed by comparing power in the 100 ms interval before the saccade with power in the interval 200-100 ms before the saccade.

To assess the temporal modulation of the LFP activity during the delay period in a visually-guided saccade task, the average LFP power was fitted with a weighted sum of two functions: the subjective hazard rate associated with a unimodal distribution of go-times ($A_u(t)$), and an exponential distribution with a mean of 0.2 ($E(t)$) (Premereur et al., 2011):

$$(2) R(t) = w_c + w_{Uni}A_u(t-\tau) + w_{Exp}E(t) + \varepsilon$$

where R is the neural response, w_c is a constant term, w_{Uni} and w_{Exp} are the weights for the unimodal anticipation function and the exponential function, respectively, with A_u delayed by time shift τ , which was fixed at -0.1 sec. The variable ε represents noise, which is assumed to be Gaussian with an uncertainty derived from the sample means. The combination of these two functions was chosen because of their distinct patterns: while the exponential function [$E(t)$] decreases over time, the unimodal hazard rate function [$A_u(t)$] increases. The mean LFP activity was fitted from 280 to 920 ms after target onset. The exponential function in this interval was normalized to its maximum value, so that the function ranged from 0 to 1. The subjective hazard rate associated with the unimodal time schedule was calculated as in (Janssen & Shadlen, 2005), and normalized to its highest value. The coefficient of variation, Φ , is the Weber fraction for time estimation, and was set at 0.25. We used a maximum-likelihood fitting procedure to obtain the fits, parameters estimates and their standard errors. Standard errors of parameters were estimated from the Hessian matrix of second partial derivatives of the log likelihood.

Correlation neural activity / RT. We calculated the trial-by-trial correlation between RT and LFP power per frequency band around the time of the go-signal (-150 before until 50 ms after go-time). Because both neural activity and RT can increase or decrease over time and can therefore exhibit spurious correlations, we ‘detrended’ the power in each frequency band by trialwise subtracting the average power in that frequency band across trials in the interval from 150 ms before until 50 ms after the time of the go-cue. The same detrending procedure was employed for RT by trialwise subtraction of the average RT for

that go-time. Thus the correlations were computed on the residuals of LFP power and RT after subtraction of the means.

Spike-field coherence. Spike-field coherence (SFC) was calculated between spiking (SUA or MUA) and LFP activity using the Chronux toolbox (<http://chronux.org>), (Bokil, Andrews, Kulkarni, Mehta, & Mitra, 2010). LFP-data were corrected for the average visually-evoked potential (VEP) by trialwise subtraction of the average VEP for a given site and condition. We calculated the temporal dynamics of the average SFC after target onset in the same frequency bands as for the LFPs, in time bins of 350 ms with a 10 ms step width. Because of the large bin width used to calculate the SFC, only trials with a go-time of 900 ms or longer were included, and significant differences between conditions were tested using permutation tests in the entire interval 0-900 ms. Increases in coherence after stimulus onset were tested for significance with non-parametric permutation tests by comparing baseline coherence (-300-0 ms) with coherence in the 0-200 ms interval. Time bandwidth product and number of tapers were set at 3 and 5, respectively. We randomly extracted the same number of trials for every condition. An extra control analysis was performed to eliminate any possible influence of firing rate differences upon observed differences in spike-field coherence. Therefore, we equalized firing rates over time using a procedure similar to the one proposed by (Gregoriou, Gotts, Zhou, & Desimone, 2009). Spike trains in both Target-In and Target-Out conditions were binned in 1 ms segments, convolved with a Gaussian kernel ($\sigma = 10$ ms), and averaged across trials for each condition. Average baseline activity was calculated as the average spike rate in the 300 ms before target-onset. We calculated the difference in spike rates between each time bin and the baseline activity, and divided this value by the maximum rate for this time bin. This normalization allowed us to estimate for each bin the probability that spikes would need to be removed from the higher firing rate signal. Spikes in the original spike trains were randomly removed based on this calculated probability value. Equalizing spikes over time in this way typically

resulted in a reduction in absolute coherence values by 1-12%. Note that spike rates not only differ over time but also between conditions (Target-In vs Target-Out). By equalizing the firing rates towards baseline activity, we also corrected for spike rate differences between conditions.

Microsaccades. We calculated the number of microsaccades as a function of time after stimulus onset. A microsaccade was defined as an increase in the velocity of the eye trace exceeding 3 times the standard deviation of the velocity in the delay period (typically in the range of 50 degrees per second) within the electronically defined fixation window.

Results

We recorded LFP activity at 114 responsive LIP sites (26 in monkey Tm, 88 in monkey Tb) showing spatially-selective activity in either SUA or MUA during visually-guided saccades. Single-unit activity (SUA) was recorded in 66/114 sites (26 in monkey Tm, 40 in monkey Tb), and multi-unit activity (MUA) in 48/114 (all in monkey Tb) sites. Both monkeys anticipated the dimming of the go-signal: the mean RT for long trials (> 1.2 s) was significantly shorter (on average 50 ms) than for short trials (0.5 s) (Fig. 1C), in agreement with previous studies (Janssen & Shadlen, 2005).

Visually-guided saccade task with multiple distractors

We recorded the LFP signal from the same electrode that was used for spike recordings. The time frequency spectrum of one example site (aligned on stimulus onset and excluding activity after the go-signal) is shown in Figure 2A. The onset of visual stimuli (both target and distractor) evoked strong LFP responses in every frequency band ($p < 0.01$). The power in the gamma band (> 25 Hz) was clearly stronger for Target-In compared to Target-Out trials (permutation test, $p < 0.05$), whereas the alpha and beta bands did not discriminate between Target-In and Target-Out trials ($p > 0.3$). Furthermore the power in the higher frequencies (> 50 Hz) clearly decreased after the visual transient despite the

continuous presence of the stimuli in the RF, whereas the power in the lower frequencies (< 25 Hz) increased markedly in the waiting period before the go-signal. For more detailed analyses, we calculated the average SUA and MUA, and the average power for every frequency band as a function of time across all recording sites (Fig. 2B & C). In both animals visual stimulation of the LIP RF (by the onset of either a distractor alone or a distractor together with a saccade target) evoked robust responses in all frequency bands in the first 150 ms after stimulus onset (Fig. 2B & C), but the temporal dynamics of the LFP-responses after the visual transient differed in the high (> 50 Hz) and low (< 25 Hz) frequency bands. The high-frequency bands (high-gamma: 80-170 Hz, and medium-gamma: 50-80 Hz) showed a decline in power after 150 ms, falling to a sustained level of activity around 500 ms after target onset. Throughout the waiting period and up to the time of the saccade, the mean high-, medium- and low-gamma power was significantly higher for Target-In trials compared to Target-Out trials ($p < 0.001$, permutation test). Note that the high- and medium-gamma response to target and distractor onset strongly resembled the SUA and MUA response up to the time of the saccade (Fig. 2B & C).

In contrast, the average power below 25 Hz discriminated much less between target and distractor in the RF ($p > 0.03$; only the beta band power in monkey Tb showed a significant difference between Target-In and Target-Out trials, $p < 0.001$). Both beta and alpha power increased shortly after stimulus onset, declined briefly and then grew steadily during the waiting period: at 800 ms after target onset, the activity reached 153.39 % (beta) and 188.84 % (alpha) of the mean activity [160-240 ms] after target-onset. Importantly, the increase in power over time in lower frequency bands was not related to the number of microsaccades during the delay period, which remained constant during this period (on average 2.7 microsaccades/sec; data not shown). In the 100 ms before the saccade a significant decrease in LFP power in all frequency bands below 50 Hz was present ($p < 0.01$) in both monkeys. The low-gamma band (25-50 Hz) also discriminated between

Target-In and Target-Out trials ($p < 0.001$, Fig. 2B & C) throughout the waiting period. However in contrast to the alpha and beta bands the low-gamma power remained fairly constant (a slight drop after 500 ms in monkey Tm and a small rise in low-gamma power in monkey Tb) during the waiting period before the go-signal appeared. As our trials were on average only 1.2 s long, we did not focus on lower frequency bands (theta: 4-8 Hz). However theta-band power showed a response pattern similar to that of alpha: theta power gradually increased over time without distinguishing between Target-In Vs Target-Out trials (permutation test, $p = 0.74$).

The temporal dynamics of the LFP power were well-captured by fitting the neural data with a weighted sum of an anticipation function and an exponential distribution (black lines in Fig. 2B; $R^2 = 0.76 - 0.99$ for the different frequency bands; regression analysis: $p < 0.01$ for all frequency bands). For the alpha and beta bands, the unimodal weights were consistently larger than the exponential weights in both monkeys ($w_{\text{exp}} < w_{\text{uni}} + 2 \times \text{SEM}$, Fig. 3), indicating climbing activity (Premereur et al., 2011). For the high- and medium-gamma - bands, in contrast, the exponential weights were higher: in monkey Tm the exponential weights were positive and not significantly different from the unimodal weights ($w_{\text{exp}} < w_{\text{uni}} + 2 \times \text{SEM}$, Fig. 3A), indicating a decrease in activity followed by a slight increase, whereas in monkey Tb the exponential weights were positive and significantly larger than the unimodal weights ($w_{\text{exp}} > w_{\text{uni}} + 2 \times \text{SEM}$, Fig. 3B), indicating a decrease in activity over time.

For each recording site, we calculated the trial-by-trial correlation between RT and LFP power around the time of the go-signal (150 ms before until 50 ms after the go-signal) for the various frequency bands. For the Target-In trials, only the alpha power correlated weakly with RT (median $r = 0.03$, Wilcoxon signed rank test: $p = 0.04$) after detrending both LFP power and RT for time-varying modulations. Thus trials in which the alpha power around the go-signal was lower than average were associated with faster RTs. For Target-

Out conditions, high-gamma correlated significantly with RT (median $r = 0.06$; Wilcoxon signed rank test: $p = 0.006$).

To investigate whether the firing of LIP neurons becomes synchronized with particular frequency bands in the LFP, we calculated the coherence (SFC) between the spikes and the LFP recorded with the same electrode. In Target-In trials, an elevation in the gamma SFC emerged shortly after the target appeared in the RF (Fig. 4A, left panel). The SFC then declined until sub-pre-stimulus levels were reached in the interval [400-600 ms] after target onset. The decline in the SFC was not a result of the decreased average firing rate within the 200-500 ms interval, since the decline remained even after correcting for time-varying spike rate (see Methods, data not shown). Target-Out trials, in contrast, showed almost no elevation in SFC after stimulus onset (permutation test, $p > 0.3$ for all frequency bands, Fig. 4A, right panel). The difference in SFC between Target-In and Target-Out trials was largest for the low-gamma band in the interval [100-400 ms] after stimulus onset (Fig. 4B). However the elevated SFC for Target-in trials was caused by the higher firing rate for Target-in compared to Target-out trials, since no additional elevation was present when correcting for the different spike rates in both conditions. Note that the apparent elevation of the medium and high-gamma SFC before stimulus onset was caused by the relatively large analysis window (350 ms). Thus the increased target-response of clusters of LIP neurons was transiently synchronized with the low-gamma oscillations of the LFP.

Our results show that during visually-guided saccades the gamma power in area LIP encodes the location of the saccade target but does not rise in the waiting period, whereas the lower frequencies (< 25 Hz) show climbing activity during the waiting period but are less sensitive to the location of the saccade target.

Single-distractor task

The multiple-distractor experiment used four distractors inside the visual field (one of which always appeared within the RF), so that Target-Out trials (a single distractor in the RF) were not visually identical to Target-In trials (distractor + target inside the RF). To assess the LFP-responses to a single saccade target and a single distractor appearing inside the RF, we recorded spiking and LFP activity (N = 14) in monkey Tb during the single-distractor task, in a manner similar to the experiment described in Janssen and Shadlen (Janssen & Shadlen, 2005). Furthermore the single-distractor task also allowed assessing the LFP responses when no visual stimulus appeared in the RF (Target-Out/Distractor-Out condition). The average spiking activity (SUA: N = 8, MUA: N = 6) in the single-distractor experiment was quite similar to the neural activity in the multiple-distractor experiment (Fig. 2B&C). Importantly, LIP neurons did not discriminate between trials in which only the saccade target appeared in the RF and trials in which both the saccade target and distractor appeared in the RF (t-test, $p < 0.001$), consistent with previous findings (Janssen & Shadlen, 2005).

The temporal modulation of the LFP power in the single-distractor experiment (Fig. 5C-G) strongly resembled that of the multiple-distractor experiment: after the initial transient response, Target-In/Distractor-In trials showed declining activity in the high- and medium-gamma bands, but robust increases in power over time for low-gamma (+11%), beta (+108%) and alpha (+31%) bands in the interval [160-800 ms] after stimulus onset. The average power in the high- and medium-gamma band [200-800 ms] after target onset reliably discriminated between a single target and a single distractor in the RF (Fig. 5C-D, for Target-In/Distractor-Out versus Target-Out/Distractor-In trials: permutation test, $p < 0.05$), but not the low-gamma and beta bands; the latter only signaled the location of the saccade target when both the target and the distractor appeared inside the RF ($p < 0.05$, Fig. 5E-G). Similar to the multiple-distractor task the alpha power did not discriminate between

saccades towards the RF and saccades away from the RF (Fig. 5G). Furthermore, we fitted the LFP-frequency bands with the weighted combination of a unimodal anticipation function and an exponential function (black lines in Fig. 5D-G), and obtained weights that were highly similar to those of the multiple-distractor saccade task (Fig. 5H). Overall, the results of the single-distractor experiment were comparable to those of the multiple-distractor experiment.

Remarkably, trials in which no visual stimulus appeared in the RF (Target-Out/Distractor-Out trials, purple traces in Fig. 5) also evoked significant increases in LFP power in every frequency band ($p < 0.001$), even reaching the levels of Target-In/Distractor-Out trials for the beta and alpha bands ($p > 0.49$). The high-, medium- and low-gamma power distinguished reliably between Target-Out/Distractor-Out trials and the three other types of trials, but even the high-gamma power – which is strongly associated with spiking activity (Ray & Maunsell, 2011) – showed a noticeable increase when target and distractor appeared in the opposite hemifield but no stimulus appeared in the RF (Fig. 5C). Although the gamma responses during Target-Out/Distractor-Out trials evolved more slowly than trials with visual stimulation of the RF (Fig. 5C-E), the increase in gamma power seemed to be locked to the moment that both target and distractor appeared contralateral to the RF. The spiking activity of the same recording sites did not show any significant increase when the LIP RF was not stimulated (t-test, $p = 0.32$, Fig. 5B; SUA and MUA separately: $p > 0.38$), consistent with the known contralateral location of LIP RFs (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991). These results indicate that in area LIP pronounced modulations in the LFP power up to the high-gamma band can occur in the absence of visual stimulation of the RF. The functional significance of these LFP responses will be examined in more detail in the next sections.

Suppressive LIP responses

To test the generality of the LFP responses we recorded in a subset of LIP sites (SUA: N = 14, MUA: N = 4) which did not show excitatory responses during visually-guided saccades to any position on the display. These non-excitatory recording sites were either nonresponsive or suppressed by target onset, but still located in area LIP because sites with target-selective S/MUA responses were found at neighboring positions (at a distance of typically < 1000 micron). Targets were placed at positions that evoked responses in these neighboring recording positions. The example site in Figure 6A responded to stimulus onset mainly in the low-gamma, beta and the alpha band, the latter reaching a level comparable to the responsive sites (Fig. 2A). However even in the higher frequencies (50-170 Hz) we measured a weak but significant response (permutation test, $p < 0.05$) to stimulus onset although no response was present in spike rate (data not shown). Across all our non-excitatory sites the average spike rate (both SUA and MUA) showed suppression, since the response rate decreased significantly after target onset (Fig. 6B & C), reaching a level of 25% of baseline activity after 200 ms (t-test, activity [-200-0 ms] compared to activity [200-400 ms]: SUA: $p < 0.001$; MUA: Target-Contralateral n.s., Target-Ipsilateral: $p < 0.01$). In contrast, the LFP power increased in both Contralateral-Target and Ipsilateral-Target conditions in all frequency bands (Fig. 6D-H, permutation test, $p < 0.001$). Below 50 Hz, the temporal pattern of the LFP power was similar to data obtained at responsive LIP sites (compare Fig. 6E-H with Fig. 2B & C), with climbing activity during the waiting period ([160-800 ms] after stimulus onset) in the beta (+146%) and alpha (+228%) bands. In contrast to responsive LIP sites, only the low-gamma ($p = 0.03$) and beta ($p < 0.001$) power distinguished contralateral from ipsilateral saccades. High- and medium-gamma bands – which are widely assumed to reflect spiking activity (Liu & Newsome, 2006) – were significantly elevated ($p < 0.01$) but did not discriminate between target locations ($p > 0.08$). Hence, below 50 Hz the LFP modulations in nonresponsive LIP sites were highly similar to those in responsive LIP sites. Significant suppressive responses in the SUA and

MUA were obtained in 10 out of 18 (56 %) recording sites, and 7 of the latter sites were accompanied by significant excitatory responses in the high- and medium-gamma bands (permutation test, $p < 0.01$). We cannot rule out the possibility that the LIP-neurons showing suppressive responses had a receptive field which was outside the visual range we tested. In the latter case, the suppression in spike rate could reflect surround suppression. However, the main finding here is the dissociation between spiking activity and high/medium-gamma responses. Furthermore, the data confirm the aspecific nature of the frequencies below 25 Hz, which show increases in power over time in the absence of spike rate responses.

Memory-Guided Saccade Task

To test the task-dependency and the importance of continuous visual RF stimulation for the LFP responses in LIP we recorded in 84 sites during memory-guided saccades. Memory saccades towards the RF elicited strong gamma responses in LIP, as illustrated by the example site in Figure 7A. More surprisingly, memory saccades towards the opposite hemifield, leaving the RF empty, also evoked significant LFP responses in every frequency band (permutation test, $p < 0.01$), albeit to a lesser degree than during Target-In trials. Notice that the gamma response in Target-In trials was remarkably transient in the first 400 ms after Target onset. Figures 7B & C show the average SUA ($N = 32$) and MUA ($N = 52$) recorded during memory-guided saccades. Since we did not select LIP sites based on memory-delay period activity, the average SUA and MUA did not show persistent delay activity: after a transient response to target onset the activity declined to baseline within the interval 300-600 ms after target onset (Premereur et al., 2011). A subset of LIP recording sites showed persistent delay activity (delay period / visual activity > 0.6 , $N = 21$), but the population response was dominated by the prevailing decrease in activity found in the majority of LIP sites ($N = 63$, the same recording sites as in (Premereur et al., 2011)). Interestingly, we measured a significant MUA response (t-test, $p < 0.01$) shortly after

target-onset in the ipsilateral hemifield, leaving the RF empty. These excitatory MUA responses in Target-Out trials were significant in 14 out of 52 recording sites (27%). Furthermore, another 16 recording sites (31%, 7 SUA, 9 MUA) showed significant decreases in spike rate ($p < 0.05$) compared to baseline in the interval 200-400 ms after target-onset in the opposite hemifield.

The average LFP power in the memory-guided saccade task appeared similar to the power in the multiple-distractor visually-guided saccade task: a pronounced decay after the visual transient for the high- and medium-gamma power, and a constant level (low-gamma power) or robust climbing activity (beta and alpha power) for the lower frequency bands (Fig. 7D-H). In the first 500 ms after stimulus onset, Target-In trials elicited significantly stronger increases than Target-Out trials in the beta and high-, medium- and low-gamma power (permutation test, $p < 0.001$), but not in the alpha power ($p = 0.21$). However the decay in the medium and high-gamma power was much stronger in the memory-saccade task compared to the multiple distractor visually-guided saccade task (compare Fig. 7D & E with Fig. 2B & C), illustrating that these higher LFP frequencies were modulated by visual RF stimulation.

Interestingly, Target-Out trials evoked significant responses in all frequency bands (permutation test, $p < 0.001$) compared to baseline, but most strongly so in the low-gamma, beta and alpha bands. For these lower frequency bands the power for Target-Out trials even reached Target-In levels around 500 ms after target onset. These stimulus-locked responses were very robust: the trend was present in both monkeys independently ($p < 0.08$); when LFP power was calculated from sites with SUA (which showed no spike rate response in Target-Out trials, $N = 32$, $p < 0.001$); and when the LFP power was calculated using only MUA sites that did not respond to Target-Out trials ($N = 38$, $p < 0.001$). We also verified that stimulus-locked responses were also present when multi-taper analyses were used for calculating power, and when the average VEP was subtracted from the LFP traces. The

sustained increase in LFP power in Target-Out trials might reflect cross-hemispheric interactions initiated by stimuli appearing in the ipsilateral hemifield. Alternatively, such pronounced modulations in LFP power in the absence of any visual stimulation in the RF could be related to the monkeys' expectation of a target appearing at a fixed time in the RF (which was the case in 50% of the trials). The latter hypothesis was tested in the passive fixation task.

Passive Fixation Task

We tested 84 responsive LIP sites in a passive fixation task (SUA: N = 38, MUA: N = 46), in which either a sine-wave grating was presented in the RF (in 80% of the trials, Grating-In condition) or no visual stimulus was presented (20% of the trials, No-Grating condition), in interleaved trials. The example site in Figure 8A showed strong gamma responses to the onset of the grating in the RF ($p < 0.01$ for high-, medium and low-gamma). Remarkably, trials without visual stimulation (No-Grating condition) also evoked significant gamma responses that were time-locked to the expected time of stimulus onset. Averaged over the entire interval of stimulus presentation, the low-gamma, beta and alpha band responses did not even discriminate between trials with and without visual stimulation of the RF. Averaged across all recording sites, the SUA showed a significant response to the grating onset (t-test, $p < 0.01$), but not in the No-Grating condition ($p = 0.16$, Fig. 8B). The MUA, in contrast, responded to the onset of the grating ($p < 0.01$) but also – though only weakly – in the No-Grating condition around the time at which the grating would normally have appeared ($p = 0.03$, Fig. 8C). Note that this increase in MUA response was significant for only one recording site. Distinct time-locked responses in the No-Grating condition were even more apparent in the average LFP activity across all sites. All frequency bands showed significant and sustained increases in power in the absence of visual RF stimulation (permutation test, $p < 0.001$, Fig. 8D-H). More specifically, the low-gamma power rose by 25% compared to baseline in No-Grating trials, which was only slightly less than in trials in

which a highly salient grating appeared in the RF (+36%, permutation test, $p < 0.01$). For comparison, the low-gamma power during visually-guided saccades towards the RF rose by +53% compared to the pre-stimulus baseline. The response in beta and alpha activity in No-Grating trials was even comparable to presentations of the grating ($p > 0.60$). As in the memory-guided saccade task, these LFP-responses were present for each monkey independently ($p < 0.01$), as well as in the LFP recordings averaged across the SUA sites (which did not respond in the No-Grating condition, $p < 0.01$). Thus, the results of the passive fixation task argue against the possibility that the responses in the memory saccade/Target-Out condition were caused by the target appearance in the ipsilateral hemifield. The strong LFP responses in the No-Grating condition – in which the only visual stimulus on the display was the fixation point – also suggest that even in the gamma band a considerable part of the LFP responses in LIP is not driven by visual inputs.

The increase in power observed in the absence of visual stimulation might be a consequence of a decrease in the variance of the raw LFP-trace in anticipation of stimulus-onset, followed by a return to the original level of variance when the expected stimulus does not appear (rebound response). The root mean square of the LFP trace indeed decreased slightly before the expected point of stimulus onset, but then remained constant in the first 500 ms after stimulus onset (data not shown). Furthermore, the number of microsaccades did not increase at the time at which the stimulus would appear (data not shown). Hence the results of the passive fixation task strongly suggest that time-locked MUA and LFP-responses in the no-stimulus condition are related to the monkeys' expectation of stimulus onset in the RF.

The results of the passive fixation task also indicate that the rise in alpha and beta power during the waiting period in the visually-guided saccade task with multiple distractors was much stronger compared to the passive fixation task even though the animals were rewarded identically at the end of the trial: in the interval between 200 and

600 ms after target-onset, alpha and beta power increased more than two times more in the multiple distractor task (alpha: +110 %, beta: +80%) compared to the no visual stimulus condition of the passive fixation task (alpha: +45%, beta: +16%). The unimodal weights were significantly higher for the Target-In conditions in the multiple-distractor saccade task compared to the Grating conditions for both the beta (Target-In: 0.298 ± 0.068 , Grating-In: -0.069 ± 0.052) and alpha (Target-In: 0.966 ± 0.127 , Grating-In: -0.209 ± 0.125) band.

Could reward expectation explain the strong increases in alpha and beta power around the expected time of stimulus onset in the passive fixation task, or the increase in alpha and beta power during the delay interval in the saccade tasks? In this case, one would expect to see an additional rise in alpha and beta power immediately before the reward was delivered. To address this possibility we analyzed the LFP power in the interval immediately before the reward was administered (Fig. 9), starting at stimulus offset (passive fixation task) or 250 ms before the eye trace entered the electronically-defined window around the target (multiple-distractor task). Both the alpha and beta band power remained relatively constant (passive fixation task) or even declined to baseline levels (multiple-distractor task) before the reward arrived, arguing against a role for reward expectation. Surprisingly we observed strong increases in low-, medium-, and high-gamma power in the 100 ms before the reward, which might be related to reward anticipation. However around the expected time of stimulus onset in the no-Grating condition the high and medium gamma responses were relatively weak. In any case the decline in alpha and beta power in the multiple-distractor task preceding reward delivery suggests that reward expectation cannot be the only factor driving the alpha and beta responses. However, we cannot exclude the possibility that an explicit manipulation of reward size could be reflected in the LFP in LIP, similar to the results obtained by Platt & Glimcher (1999) on the LIP spike rates. Future studies will have to address the functional significance of the pre-reward gamma increases we observed in LIP.

Taken together, a parsimonious interpretation of the alpha and beta modulations we measured in LIP could entail temporal anticipation in two distinct ways. Firstly, alpha and beta showed an increase in power around the expected time of stimulus onset, even in conditions without visual stimulation of the RF, suggesting anticipation of stimulus onset. Due to the limited temporal resolution of the Morlet wavelet analysis we cannot be certain that the increase in alpha and beta power did not already start before the expected time of stimulus onset. Secondly, the additional rise in LFP power in the frequencies below 25 Hz during the delay (400-1000 ms after stimulus onset) in the saccade tasks was associated with the anticipation of the dimming of the go-cue (see Fig 1C: faster RTs for longer trial durations). Both types of anticipation appear to be present in the saccade tasks (notice the bimodal response pattern of alpha and beta power in Fig 2B, 5E, 7G-H). Consistent with this interpretation the first rise in alpha and beta power (anticipation of stimulus onset) was similar in the passive fixation task and the saccade tasks, whereas the second rise of alpha and beta power (during the delay period, anticipation of the go-signal) was much stronger in saccade tasks than in passive fixation trials.

Summary of results

Figure 10 shows the average power for all frequency bands and all tasks (visually guided saccade, memory guided saccade and passive fixation) in two intervals: an early interval (visual transient) [50-150 ms] after stimulus onset (Fig. 10A-E), and a late interval (waiting period) [400-600 ms] after stimulus onset (Fig. 10F-J). (Qualitatively similar results were obtained when only those sites were included where all three tasks were recorded, data not shown.) High- and medium-gamma power was strongly influenced by visual stimulation in both the early (50-150 ms) and the later (400-600 ms) intervals (Fig. 10A & F and B & G: VisSacc Target-In > Target-Out; Memory Target-In > Target-Out; Grating-In > No-Grating). Beta and alpha power, in contrast, were not strongly modulated by visual stimulation in the early interval, but increased significantly in the later interval

(Fig. 10 D-E and I-J). Note that the alpha response in the No-Grating condition was even stronger than during memory saccades and comparable to the response in the visually-guided saccade task.

Based on its response properties, the low-gamma band occupied an intermediate position between the high- and the low LFP frequencies. In the first 150 ms after stimulus onset, the increase in low-gamma power was modulated by visual stimulation (VisSacc Target-In/Out, Memory Target-In, Grating-In > No-Grating, Memory Target-Out, Fig. 10C). However, in the later epoch the average low-gamma power converged to the same level (+30% compared to pre-stimulus baseline) for conditions with or without visual stimulation and with or without a saccade planned in the direction of the RF. Only Target-In trials of the multiple-distractor task (VisSacc Target-In) showed a stronger increase in low-gamma power over all other trial types (Fig. 10H), reaching +53% compared to baseline towards the end of the waiting period. Therefore the additional increase in low-gamma power during the waiting period was specifically associated with the presence of a highly-salient visual stimulus in the RF that would become the target of the saccade.

Discussion

We observed strong LFP responses in area LIP during visually-guided and memory-guided saccades in every frequency band. Although the attentional component may have differed between our three saccade tasks in view of the differences in the location of the go-signal, we observed highly similar LFP responses: the gamma band encoded the location of the saccade target but decreased in the waiting period before the saccade, whereas the alpha and beta powers were much less sensitive to target location but showed strong climbing activity in the waiting period before the go-signal. Remarkably, robust time-locked LFP and MUA responses occurred in area LIP in the absence of any visual stimulation of the

RF. These results demonstrate for the first time that LFP responses in area LIP may at least partially reflect the temporal expectation of visual stimulation.

Recent research has shown that in some cases the LFP can be measured many millimeters distant to the active neuronal tissue in which it is generated (Kajikawa & Schroeder, 2011), leaving open the possibility that the LFPs recorded in area LIP were actually generated in neighboring areas. In contrast, LFPs in area LIP carry relevant information for perceptual decisions, which suggests that more local information is represented in the LFP (Bollimunta & Ditterich, 2011). Although we cannot exclude an influence of neighboring areas, we therefore hypothesize that the majority of our signal originated in area LIP itself.

As in other extrastriate areas (Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Liu & Newsome, 2006), gamma band activity in LIP was stimulus-selective (in our case, target-selective) whereas alpha and beta band activity were generally not. Consistent with previous findings (Henrie & Shapley, 2005; Liu & Newsome, 2006; Niessing et al., 2005; Pesaran et al., 2002; Ray & Maunsell, 2011; Siegel & Konig, 2003) the overall response pattern of the LFP frequencies above 50 Hz largely mimicked the response patterns of the SUA and MUA recorded in the same trials. However, a clear dissociation between high- and medium-gamma power and spiking activity was present in trials without visual RF stimulation (discussed below). Furthermore, recording sites that were suppressed by the onset of visual stimuli also showed significant medium/high-gamma responses, albeit weaker than in sites with excitatory spiking responses. It is unlikely that nearby responsive LIP sites were the source of the increased gamma responses at the non-responsive sites, since the medium- and high-gamma responses at non-responsive sites were not selective for target location, whereas the nearby responsive sites were clearly spatially-selective. Most likely LIP neurons with suppressive responses may have had an RF outside the display, such that our stimuli were presented in the suppressive surround of the RF

(Falkner et al., 2010). Overall, the combination of suppressive SUA and MUA responses and increases in high/medium-gamma power suggests that at least part of the medium/high-gamma responses in LIP may be related to inhibitory interneuron activity (Falkner et al., 2010). The gamma responses we measured in area LIP may therefore reflect a combination of excitation and inhibition, in a manner similar to the BOLD signal (Logothetis, 2003).

During the waiting period before the go-signal, the dynamics of the LFP power differed conspicuously between the high frequencies (medium/high-gamma) and the lower frequencies (beta and alpha): Although both high- and low-frequency oscillations rose shortly after stimulus onset, the medium- and high-gamma power declined after the initial visual transient whereas alpha and beta power showed a strong increase in the epoch [200-1000ms] after stimulus onset preceding the go-signal. Although we employed only a single schedule of go-times, both animals clearly exploited knowledge of the distribution of go-times, as evidenced by the shorter RTs for longer trial durations (see also Janssen & Shadlen (2005); Premereur et al., (2011)). Therefore the temporal expectation of the go-signal was associated with a decrease in gamma power and with a strong increase in beta and alpha power in posterior parietal cortex. These results are consistent with data obtained from human EEG studies, which demonstrate that slow brain potentials ramp up gradually during temporal expectation (Cravo, Rohenkohl, Wyart, & Nobre, 2011; Miniussi, Wilding, Coull, & Nobre, 1999). [Note, however, that in the LIP recording sites showing rising spike rates, the gamma power also rose during the waiting period (data not shown); the increase in alpha and beta power was present regardless of the temporal pattern of the spiking activity of the recording site.]

To our knowledge, our data are the first to show MUA and LFP responses in the absence of visual stimulation of the RF in area LIP. LFP responses in the absence of visual RF stimulation occurred in all LFP frequency bands (up to the high-gamma-band) in Target-Out trials of the memory-guided saccade task and in the No-Grating condition of the passive

fixation task. All experimental conditions with ipsilateral or no visual stimulation also showed slight but significant increases in MUA but not SUA, which suggests that small neurons - possibly interneurons - were responding in these conditions and were captured in our MUA but not in SUA recordings. Undoubtedly, the fixed time structure of our tasks combined with the extensive training period allowed the animals to develop temporal expectations about the conditional probability of the go-time, but also about the time of stimulus onset, which could explain the precisely-timed LFP responses and the small but significant increase in MUA in the No-Grating condition. Note that anticipation of stimulus onset reflected in baseline activity has been observed in area LIP (Colby, Duhamel, & Goldberg, 1996), and fMRI activations have been observed in human parietal cortex in the absence of visual stimulation (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). Furthermore, the haemodynamic signal may consist of two components, one of which showing predictive timing with increases in cerebral blood volume in anticipation of trial onset (Sirotin & Das, 2009). Inferior parietal activations have been consistently observed in fMRI studies of temporal expectation (reviewed in Coull & Nobre (2008). Furthermore, Nobre, Correa, & Coull (2007) hypothesized that implicit timing mechanisms subserving temporal expectations may be rooted in oscillatory activity and synchronization of activity in ensembles of neurons. Analogous to the LFP responses in suppressive LIP sites, the LFP responses in the absence of RF stimulation may reflect anticipatory inhibitory activity (Chalk et al., 2010), since the animals were required to suppress eye movements towards salient stimuli that could appear in the RF until the appearance of the go-signal.

Our findings are critical for interpreting the LFP responses in area LIP, specifically with regard to the frequency bands below 50 Hz. To a very high degree, the beta and alpha power increased regardless of the visual stimulation of the RF. Beta oscillations are frequently observed in the motor system and have been related to the maintenance of the status quo in the absence of salient events (Engel & Fries, 2010). In primary motor cortex,

beta oscillations increase during an enforced delay period in anticipation of task-relevant cues (Saleh, Reimer, Penn, Ojakangas, & Hatsopoulos, 2010), which is consistent with our observations. Furthermore climbing beta band activity and perisaccadic beta band suppression have been reported for LIP (Pesaran et al., 2002) during memory saccades. We even observed pronounced increases in beta power during passive fixation in the absence of visual stimulation around the expected time of stimulus onset. The rise in beta power within the later trial epoch (the waiting period) was specific for saccade tasks, since it did not occur during passive fixation.

Decreases in alpha power have been associated with the deployment of spatial attention (Thut, Nietzel, Brandt, & Pascual-Leone, 2006), whereas increases in alpha band activity occur over the hemisphere contralateral to unattended locations (Worden, Foxe, Wang, & Simpson, 2000). In our experiments, alpha power increased in the no-stimulus condition almost as strongly as during visually-guided saccades. Moreover, the alpha power rose markedly before the go-signal, and decreased immediately before the saccade, and higher alpha power around the go-signal was associated with slower RTs. The latter observations are more compatible with the view that event-related alpha oscillations play a role in withholding a response in areas that operate under, or exert, top-down control (Hummel, Andres, Altenmuller, Dichgans, & Gerloff, 2002; Klimesch, Sauseng, & Hanslmayr, 2007). In contrast to our results, EEG recordings over the occipital cortex of human subjects show *decreases* in alpha power before the expected reappearance of a target (Rohenkohl & Nobre, 2011), and in the primary visual cortex of monkeys, the expectation of an event in time is associated with an increase in gamma power and a suppression of alpha (Lima, Singer, & Neuenschwander, 2011). Thus the dynamics of alpha oscillations during temporal expectation may be radically different in the posterior parietal cortex and in the early visual areas. More generally, alpha oscillations may play a functional role in high-level extrastriate visual areas different from that in earlier visual areas (Mo, Schroeder, & Ding, 2011).

We also measured low-gamma responses in the absence of visual RF stimulation. During the waiting period before the go-signal, an additional increase in low-gamma activity, exceeding that in the No-Grating condition, occurred only in the Target-In condition of the multiple-distractor saccade task. Hence this particular increase in low-gamma was specific for the condition where a salient saccade target appeared and remained present in the RF, equivalent to a pop-out condition. Taken together, the diversity of effects among the different frequency bands in LIP – a prototypical visuomotor area – may reflect a variety of processes at the level of the LFP, activities which have been shown to represent input and local processing. Future studies will have to investigate the extent to which the low-gamma power in LIP reflects cognitive processes such as spatial attention (Fries et al., 2001) and/or inhibitory drive (Chalk et al., 2010).

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