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Oculomotor inhibition reflects temporal expectations

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ABSTRACT

The accurate extraction of signals out of noisy environments is a major challenge of the perceptual system. Forming temporal expectations and continuously matching them with perceptual input can facilitate this process. In humans, temporal expectations are typically assessed using behavioral measures, which provide only retrospective but no real-time estimates during target anticipation, or by using electrophysiological measures, which require extensive preprocessing and are difficult to interpret. Here we show a new correlate of temporal expectations based on oculomotor behavior. Observers performed an orientation-discrimination task on a central grating target, while their gaze position and EEG were monitored. In each trial, a cue preceded the target by a varying interval ("foreperiod"). In separate blocks, the cue was either predictive or non-predictive regarding the timing of the target. Results showed that saccades and blinks were inhibited more prior to an anticipated regular target than a less-anticipated irregular one. This consistent oculomotor inhibition effect enabled a trial-by-trial classification according to interval-regularity. Additionally, in the regular condition the slope of saccade-rate and drift were shallower for longer than shorter foreperiods, indicating their adjustment according to temporal expectations. Comparing the sensitivity of this oculomotor marker with those of other common predictability markers (e.g. alpha-suppression) showed that it is a sensitive marker for cue-related anticipation. In contrast, temporal changes in conditional probabilities (hazard-rate) modulated alpha-suppression more than cue-related anticipation. We conclude that pre-target oculomotor inhibition is a correlate of temporal predictions induced by cue-target associations, whereas alpha-suppression is more sensitive to conditional probabilities across time.

1. Introduction

A major challenge of the perceptual system is to accurately extract signals out of their noisy environment (Friston, 2005; Morillon and Schroeder, 2015). One way this is achieved is by constructing top-down predictions and continuously matching them with bottom-up input. *Temporal prediction* is the ability to construct expectations regarding the timing of events, based on previously-experienced temporal regularities.

Several types of temporal regularities enable anticipation of an event: (1) when events occur rhythmically, anticipation may arise from the periodicity of previous ones (rhythmic regularity; Large and Jones, 1999; Barnes and Jones, 2000; Dankner et al., 2017); (2) prediction may be based on learning temporal associations between a pair of consecutive events, such as a warning signal (cue) and target appearing at regular intervals (associative regularity; Baumeister and Joubert, 1969; Niemi and Näätänen, 1981, Coull and Nobre, 1998; Breska and Deouell, 2017); (3) statistical factors; even without additional information anticipations may rely on the "hazard-rate" – the conditional probability of an event occurring at a certain time given that it has not yet occurred (statistical regularity; Trillenberg et al., 2000; Nobre et al., 2007; Lima et al., 2011).

Associative and statistical regularities are often studied by manipulating characteristics of the intervals between cue and target. The durations of these "foreperiods" could be either regular across trials and consequently predictive regarding the time of target onset, or they can be irregular and non-predictive. Regular foreperiods typically result in higher performance (e.g. shorter reaction times), but this effect is modulated by the duration of the foreperiod. Specifically, when foreperiods are regular, their duration is *positively* correlated with reaction times (RTs): performance is slower with longer intervals between cue and target (Niemi and Näätänen, 1981). In contrast, when the foreperiods are irregular, their duration is *negatively* correlated with RT: performance is faster with longer intervals between cue and target (Niemi and Näätänen, 1981). Both effects are thought to reflect modulations in temporal uncertainty. The first effect –positive correlations for regular foreperiods–

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reflects an *increase* in uncertainty with interval duration, due to less accurate estimation of longer regular intervals. When cue-target intervals are too long to be accurately estimated, associative regularities between cue and target become less effective for constructing expectations. The second effect –negative correlations for irregular foreperiods– reflects a *decrease* in uncertainty with interval duration, due to the hazard-rate function – the conditional temporal information acquired with time. With increasingly longer intervals following the cue, more statistical information regarding the possible time appearance is acquired and expectations are gradually enhanced. Manipulations of both the foreperiod's regularity and duration are often used to assess associative and statistical temporal expectations (Breska and Deouell, 2017; Praamstra et al., 2006; Trillenberg et al., 2000).

Classical behavioral measurements, such as RTs and accuracy rates, are commonly used as markers for temporal expectations in humans (Niemi and Näätänen, 1981; Trillenberg et al., 2000). However, as they are measured only after the target has appeared, they are limited to retrospective estimation of prediction processes, after stimulus offset. Alternatively, physiological measurements can be informative even prior to target-onset. A few such measurements have been reported in human scalp-EEG, including the contingent negative variation (CNV) component (Walter et al., 1964) and alpha-band suppression (Breska and Deouell, 2017; Praamstra et al., 2006; Rohenkohl and Nobre, 2011; van Diepen et al., 2015). Such electrophysiological correlates provide information on temporal expectations while they are being constructed (prior to target onset), but have the disadvantage of being indirect and difficult to interpret functionally and physiologically.

In this study we present a new approach for indexing temporal expectations, with oculomotor behavior (saccades, ocular drift and blinks) prior to the target. Such oculomotor markers have the advantage of being both direct and easy to measure, like other behavioral measurements, and measured prior to target onset while expectations are being formed, like the neurophysiological measures. Predictability was manipulated, as in previous studies, by modulating the regularity and durations of the foreperiods (Breska and Deouell, 2017; Trillenberg et al., 2000), and linked, for the first time, with oculomotor responses.

A few studies have provided initial support for the link between pre-target oculomotion and anticipation, by showing reduced saccade-rates before a predictable target (Betta and Massimo, 2006; Fried et al., 2014; Hafed et al., 2011; Olmos-Solis et al., 2017). These studies, however, did not manipulate predictability directly as they included no unpredictable targets. In a recent study (Dankner et al., 2017), we found pronounced saccadic inhibition prior to stimuli which appeared within a rhythmic stream (fixed inter-stimulus-intervals), relative to those that were part of a non-rhythmic stream (random inter-stimulus-intervals). This effect was correlated with participants' ability to sustain attention over-time. However, when expectations are modulated through rhythmicity it is impossible to tease-apart the effects of predictability from those of neural entrainment (Breska and Deouell, 2017). When events appear rhythmically, low frequency neural oscillations become synchronized to the external rhythm (Schroeder and Lakatos, 2009), and this entrainment could be the source of the observed inhibition effect, rather than predictability. To rule out entrainment as the source of the pre-target inhibition of saccades and blinks, in the present study we manipulated expectations via a non-rhythmic temporal regularity, and thus examine for the first time the direct link between target's predictability and pre-target oculomotor inhibition.

We co-registered gaze positions and EEG while human participants performed an orientation-discrimination task on targets that occurred at predictable and unpredictable times. Presenting temporal cues, which were either indicative or non-indicative of the timing of a consecutive target, modulated associative temporal regularities. Varying the duration of the foreperiod modulated statistical regularities. We examined three types of oculomotor behaviors: saccades, blinks and drift in a short time interval prior to target onset. Pronounced oculomotor inhibition was found prior to the onset of an anticipated target, and was modulated by target's predictability. This oculomotor marker was found to be more sensitive to associative regularities than other common behavioral and electrophysiological markers: RTs, CNV and alpha-suppression. In contrast, alpha-suppression was robustly modulated by conditional probabilities, and thus more sensitive to statistical regularities than the other markers.

2. Materials and methods

2.1. Subjects

Twenty-one students of Tel-Aviv University participated in the experiment for course credit or monetary compensation. One participant was discarded from all analysis due to poor eye-tracking data and excessive blinking. Another participant was excluded from EEG analysis due to poor recording. Consequently, eye tracking and behavioral analysis were based on a total of 20 participants (13 females; Mean age 22.5 ± 2.7) and EEG analysis was based on a total of 19 participants (12 females; Mean age 22.8 ± 2.7). All participants reported normal (uncorrected) vision and no history of neurological disorders. All were naïve to the purpose of this study. The ethical committees of Tel Aviv University and the School of Psychological Sciences approved the study. All participants signed an informed consent.

2.2. Procedure

Participants sat, head placed on a headrest in a dimly-lit sound-attenuated chamber, at a distance of 97 cm from a display monitor (ASUS VG248QE, 120 Hz refresh rate) covering 30° of the horizontal visual field. Fig. 1 depicts the experimental procedure. In each trial, a black fixation cross (0.4°) was centrally presented on a mid-gray background. After achieving 0.5s of stable fixation (<0.5° off center) as verified by a gaze contingent procedure and a random interval of 0.2–0.7s, the fixation cross changed color to blue marking the onset of the foreperiod (1, 1.5, 2, 2.5, or 3 s), after which a full-contrast slightly-tilted Gabor grating was presented in the center of the screen for 33 ms (visible diameter 1°, spatial frequency 3 cpd). Participants were then asked to perform a 2AFC discrimination task: report the tilt orientation of the grating (clockwise or counter-clockwise) by pressing one of two buttons. They were not informed as to any regularity; therefore, all temporal expectations were incidentally learned.

The foreperiod was either constant throughout the block (regular condition), or sampled randomly in each trial from the five possible foreperiods (irregular condition). With this protocol, the change of color of the fixation cross acted as a 100% valid temporal cue in the regular condition but was uninformative regarding target timing in the irregular condition. Importantly, the stimuli were identical in the two conditions, and differed only in the validity of the temporal cue in predicting the time of the target. Although a random foreperiod would have resulted in greater temporal uncertainty than using 5 possible foreperiods, we chose the latter to enable comparison of the same foreperiods across the regular and irregular conditions. This would have not been possible if we had used random foreperiods.

The experimental session was divided into 10 blocks of approximately 4.5 min each, half of which were of the regular condition and half of the irregular condition. The order of the blocks was counterbalanced across participants.

A short pretest was conducted to set the tilt angle of the Gabor patch individually per-participant. Using a 1-up/2-down staircase procedure (García-Pérez, 1998), we aimed to obtain 78% accuracy rate. The tilt-angle remained unchanged throughout the experiment. A long break (8 min) was given after 5 blocks and short (<2 min) breaks were usually given between blocks.

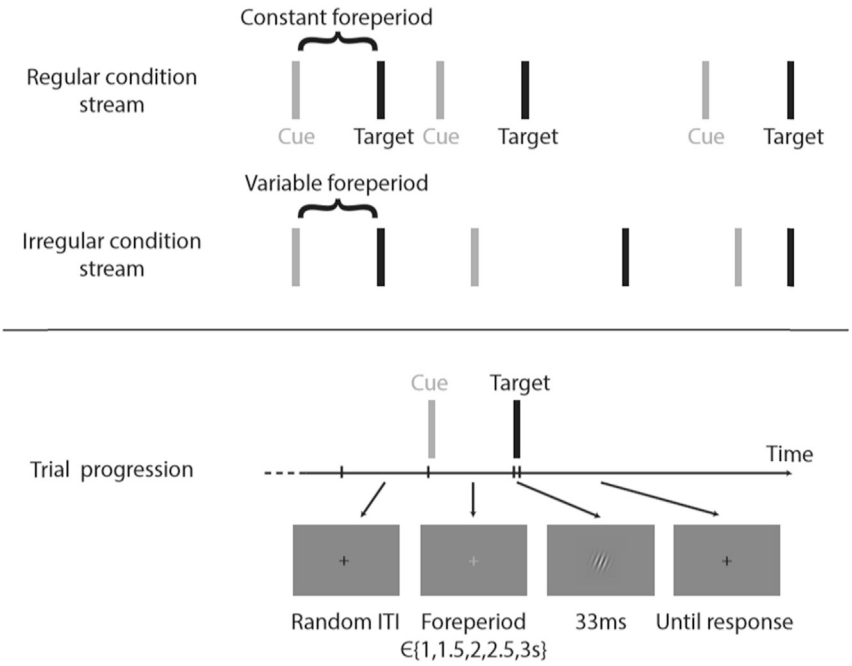

Fig. 1. *Experimental procedure*. Top: The intervals between cue and target (foreperiods) were constant in the regular condition and varied among five options in the irregular condition. Bottom: A tilted Gabor patch was presented after the temporal cue, which was either 100% valid (regular condition) or uninformative (irregular condition) regarding the foreperiod duration. In each trial, participants reported the tilt orientation of the Gabor. A change of the fixation color to blue (marked here in gray) marked the onset of the foreperiod.

2.3. Behavioral data analysis

Accuracy and reaction times (RT) were calculated separately for each participant, condition and foreperiod. Only correct trials were included in the RT analysis. Outlier RTs deviating by more than 2.5 standard deviations from the mean RT were excluded from analysis.

2.4. Eye tracking acquisition and analysis

Binocular gaze position was monitored using a remote infrared video-oculographic system (Eyelink 1000 Plus; SR Research, Canada), with a spatial resolution $\leq 0.01^{\circ}$ and average accuracy of 0.25^{o}-0.5° when using a head-rest (as reported by the manufacturer). Raw gaze positions were converted into degrees of visual angle using the 9-point-grid calibration, performed at the start of each experimental block and sampled at 1000 Hz.

Blinks were detected using Eyelink's automatic blink-detection. This blink detection procedure could be criticized for producing false alarms (Hershman et al., 2018). We therefore repeated all analysis using an alternative pupil-size based detection algorithm (Methods in Supplementary Material S1) and found qualitatively similar findings (Results in Supplementary Material S1). Saccades were detected using a modification of a published algorithm (Engbert and Mergenthaler, 2006) which was applied on filtered gaze position data (low-pass IIR Butterworth filter; cutoff 60 Hz) as in (Amit et al., 2017). An elliptic threshold criterion for microsaccade detection was determined in 2D velocity space based on the horizontal and the vertical velocities of the eye-movement. Specifically, we set the threshold to be six times the standard deviation (SD) of the eye-movement velocity, using a median-based estimate of the SD (Engbert and Mergenthaler, 2006). The SD estimate was set based on entire recording blocks. A saccade onset was defined when six or more consecutive velocity samples were outside the ellipse, in both eyes.

Saccades offsets are sometimes accompanied by an "overshoot" which may be erroneously detected as a new saccade. Therefore, per standard procedure (Dimigen et al., 2012; Kornrumpf et al., 2016; Kovalenko and Busch, 2016), we imposed a minimum criterion of 50 ms for the interval between two consecutive saccade and kept only the first saccade in cases where two saccades were detected within such interval. Additionally, as blinks are accompanied by fast vertical eye movement, we also imposed a minimum criterion of 100 ms between a saccade and a blink, keeping only the blink in cases where both were detected within such interval. Saccades of all sizes were included in the analysis, but due to the instruction to keep sustained fixation, most saccades were small (in the range of microsaccades, $<1^{\circ}$). The correlation between logs of saccade amplitude and peak velocity ("main sequence") (Zuber et al., 1965) was $r > 0.9$ for all participants, ensuring low false alarm rate in detection.

The time series of saccade-rate and blink-rate were constructed for each participant by counting the number of saccade/blink events he/she performed in each time-point across trials, separately for each condition and foreperiod. These values were then divided by the number of trials. The saccade time series was then smoothed using a causal filter (Rolfs et al., 2008) with an α parameter of 20 ms, and multiplied by the sampling rate, converting the measure to Hz. Following our previous study (Dankner et al., 2017), mean saccade rate in the time window of -100-0 ms relative to stimulus onset was taken as the dependent variable for statistical analysis of pre-target saccade-rate. Since blink events are scarce and last longer, the blink-rate time series was smoothed using a boxcar window of 100 ms and averaged across a longer window of 500–0 ms relative to stimulus onset, and multiplied by the sampling rate. Saccade rate slope was calculated as the difference between saccade rate at the PSR window (-100-0 ms) and the post cue window (400–500 ms post cue, after saccade rate returns to baseline – see Fig. 3A), divided by the time difference between the two windows (which was different for each foreperiod duration). Note that these analyses included oculomotor behaviors that were initiated prior to target onset, although some of them lasted even after the target appeared (for example a saccade that was initiated at −10 ms, is likely to last after target onset). This is consistent with our goal to examine behaviors that were planned exclusively based on expectations and not on physical stimulation.

Ocular drift was quantified using the "Box counting" method (Engbert and Mergenthaler, 2006). We used a sliding window of 50 ms, moving in steps of 25 ms. For each time window we counted the number of rectangular boxes of size 0.0318° needed to cover the eye's trajectory. Gaze position was determined as an average of the two eyes' position. If a saccade onset or a blink occurred within the analyzed window or during the 50 ms interval before it, this window was not included in the analysis. The result was baseline corrected for each trial by taking the change in percent from the mean box-count in the 300 ms pre-cue interval.

2.5. Single trial classification by oculomotor events

The timings of saccades and blinks were used to classify single trials as regular vs. irregular. We applied a similar approach to that of a Bayesian classifier (White and Rolfs, 2016), which was used on saccade data to classify trials according to their visibility.

We started by calculating the prior probabilities for saccades and blinks occurrences for each participant and foreperiod, on a "training set" containing 80% of the original data. Due to the sparseness of the saccades/blinks data sets, they were downsampled to bins of 100 ms starting from −1000 ms and until 0 ms relative to target onset (10 bins). We constructed two binary vectors (saccades and blinks) representing sequential bins of 100 ms: a vector cell contained 0 unless there was a saccade/blink in its corresponding time-bin. For the training, trials were divided into "regular" (R) and "irregular" (I) trials. We express the prior probability that there would be an event (saccade or blink) in time-bin t (of 100 ms) of a regular trial as: p[E(t)|R] and the probability that there would be an event in time t of an irregular trial as: p(E(t)|I). The probabilities p(R) and p(I) were always 0.5. We also calculated the overall probability p(E(t)) that there was a saccade or a blink in time-bin t of the segment, regardless of condition. We then computed for each time-bin t_i (i = 1,2,..,10), a predictor p(R|E(t_i)) of the probability a trial was "regular" given the observed saccades and blinks in the segment.

$$p[R|E(t_i)] = p[\mathrm{E}(t_i)|\mathrm{R}] \times \mathrm{p}(\mathrm{R})/\mathrm{p}[\mathrm{E}(\mathrm{ti})]$$

We then multiplied the vector P[R|E(t_i)] (created using the train set) by the observed events of an independent set of test trials (20% of the data). This analysis resulted in a score X for each trial. We then classified each trial as "regular" or "irregular" by comparing its score X to a criterion C. We varied C across the full range, computing hit rate and false alarms rate and then calculated the area under this receiver operating characteristics (ROC) curve. This area is the classification accuracy A'. To avoid a sampling bias, we repeated this procedure of training and testing 100 times to get a mean A′ for each observer and foreperiod (Quiroga et al., 2008).

2.6. EEG acquisition and analysis

EEG data were collected using a Biosemi 10–20 system with 64 active Ag/AgCl scalp electrodes and 7 external electrodes (2 on the mastoids, 2 vertical EOG, 2 horizontal EOG and one on the tip of the nose). The EEG signal was sampled at a rate of 1024 Hz (24 bits/channel) with an online anti-aliasing 204 Hz low-pass filter. As in recent studies measuring CNV and alpha band power (Breska and Deouell, 2017; Cheung et al., 2016; Jang et al., 2016), data were referenced offline to the average of the mastoid electrodes and filtered by a zero-phase 0.1–40 Hz bandpass FIR filter (6 db reduction at 0.05 and 40.05 Hz). The EEG data were analyzed with the EEGLab Matlab-based toolbox (Delorme and Makeig, 2004). Saccades and blinks artifacts were removed from the EEG signal with independent component analysis (ICA), based on the components' typical scalp topography and time course (Delorme and Makeig, 2004).

Data were segmented at −200 ms pre-cue to 1000 ms post-target and baseline-corrected by subtracting the mean of the pre-cue interval. Artifacts remaining after ICA were removed using a semi-automatic procedure, rejecting segments where the absolute voltage was greater than ±100 μV or the voltage fluctuated by more than ±100 μV within an interval of 200 ms. This procedure resulted in the rejection of 10.92% trials on average (Range across participants 3.3%–33.1%, SD = 7.28). The average number of trials remaining per participant was 891 (SD = 72.8).

2.6.1. CNV analysis

Target-locked ERP was calculated by averaging all segments of each condition and forperiod. The CNV component was estimated by averaging a cluster of parietal electrodes (CP1, CPz, CP2, P1, Pz, P2, PO3, POz, PO4), where the pre-target negativity was found to be maximal. Following Praamstra et al. (2006), we used the mean amplitude of the CNV signal in the -100-0 ms interval as the dependent measurement for statistical analysis of pre-target CNV and derived its slope from the mean amplitudes at 600–700 ms relative to cue onset and -100-0 ms relative to target onset.

2.6.2. Alpha amplitude analysis

EEG alpha power was obtained by filtering the data at 8–13hz using a zero-phase bandpass FIR filter (6 db reduction at 8 and 13 Hz, transition bandwidth of 0.5 Hz at each side) and applying Hilbert transform. We then segmented the data to the same intervals as for the CNV analysis. Segments rejected from analysis in the CNV data were removed here as well. Amplitude of Alpha-band activity was calculated for each timepoint by taking the absolute value of the complex number achieved. The alpha amplitude at each segment and electrode was baseline corrected by subtracting the mean power in the pre-cue baseline window. Alpha amplitudes were then averaged across an occipital electrode cluster (PO3/4,PO7/8,O1/2), along the -300-0 ms pre-target interval (following Breska and Deouell, 2017) and across trials. Slope was calculated between this value and mean amplitude at −300 to 0 ms relative to cue onset.

2.7. Statistical analysis

Most statistical analysis in this study was based on repeated measures ANOVAs with factors Predictability (regular/irregular) and Foreperiod (1, 1.5, 2, 2.5, 3s). The assumption of sphericity was tested, when applicable, using Mauchly's test. When Mauchly's test was significant ($p < 0.05$) the Greenhouse-Geisser corrected p values are reported, along with the original degrees of freedom and the epsilon value. T-tests and trend analyses were conducted to interpret interactions. When several t-tests were applied, the p-value was corrected for multiple comparisons using "FDR p-value adjustment" (Yekutieli and Benjamini, 1999). All statistical tests performed were two-tailed.

Correlations were calculated individually for each participant, and then the r coefficients were Fisher transformed. These z-scores of correlations were then averaged across participants and the inverse Fisher's transform was applied on their average to obtain an average r coefficient (Trillenberg et al., 2000). Likewise, when comparing r correlation coefficients, the comparison was made on the Fisher transformed coefficients.

3. Results

To test both associative and statistical regularities, participants (n = 21) performed an orientation-discrimination task on slightly-tilted grating targets, which followed a cue (fixation changing color) in two different conditions. In the regular condition, the foreperiod (the interval between the cue and target) was fixed at either 1, 1.5, 2, 2.5, 3 s within a block. In the irregular condition, the foreperiod duration was randomly drawn with equal probability at each trial from the same set of durations. All stimuli were presented centrally and participants were instructed to maintain central fixation throughout each trial.

3.1. Behavioral performance: reaction times and accuracy-rates

We analyzed accuracy-rates and RTs using a two-way repeated measures ANOVA with factors Predictability (regular/irregular) and Foreperiod (1, 1.5, 2, 2.5, 3 s). Consistent with previous findings (e.g. Rohenkohl and Nobre, 2011), there was no evidence for differences in accuracy-rates between predictability conditions ($F(1,19) = 1.37$, $p = 0.25$) or foreperiods ($F(4,76) = 1.72$, $p = 0.15$), and no significant interaction between the two factors ($F(4,76)<1$). RTs revealed no main effect of Predictability ($F(1,19) = 1.96$, $p = 0.17$) or Foreperiod ($F(4, 76) = 1.7$,$p = 0.155$), but these two factors significantly interacted ($F(4, 76) = 3.83$, $p = 0.014$, $\varepsilon = 0.745$; Fig. 2). To interpret this interaction, we

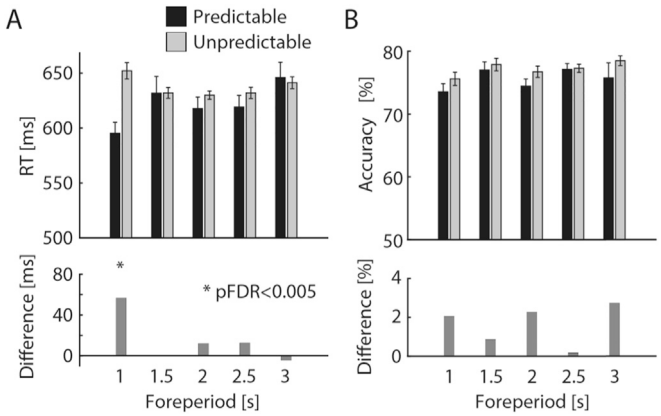

Fig. 2. *Reaction times (RTs) and accuracy by predictability and foreperiod.* A) Top: *Reaction times* in regular (black bars) and irregular (gray bars) conditions; Bottom: RT difference between irregular and regular conditions. B) Top: Accuracy rates in regular (black bars) and irregular (gray bars) conditions; Bottom: accuracy difference between irregular and regular conditions.

conducted 5 separate t-tests for each foreperiod between the two predictability conditions, and corrected the results for multiple comparisons (Yekutieli and Benjamini, 1999). There was a significant predictability effect in the shortest foreperiod of 1s ($t(19) = 3.9$, $p < 0.005$ FDR-adjusted): RTs were slower for the irregular relative to the regular condition. There was no significant predictability effect in any of the other foreperiod intervals (all adjusted $p > 0.4$). This pattern is consistent with previous findings showing that RT predictability effects are diminished for long foreperiods (e.g. Niemi and Näätänen, 1981; Mattes and Ulrich, 1997; Griffin et al., 2001; Anderson and Sheinberg, 2008; Correa and Nobre, 2008). Trend analysis conducted separately for the regular condition revealed a marginally significant positive linear trend in the regular condition with longer RTs for longer foreperiods ($F(1, 19) = 3.90$, $p = 0.063$), which is consistent with previous studies showing higher RTs for regular longer foreperiods (Niemi and Näätänen, 1981; Teichner, 1954). No similar trend was found for the irregular condition ($F(1,19) = 1.19, p = 0.28$).

3.2. Saccades

3.2.1. Pre-target saccade rate (PSR)

A repeated measures ANOVA was performed on the average pre-target saccade rate (PSR) at the -100-0 ms interval, with factors Predictability (regular/Irregular) and Foreperiod (1–3s). There was a significant effect of Predictability ($F(1,19) = 26.47$, $p < 10^{-4}$), arising from stronger inhibition of saccades for the regular relative to the irregular condition (Fig. 3A–C). This predictability effect indicates that, overall, saccade-inhibition was a marker for the ability to anticipate the occurrence of an expected event. This finding is consistent with our recent study (Dankner et al., 2017). A significant interaction between Predictability and Foreperiod)$F(4,76) = 8.60$, $p < 10^{-5}$ (indicated that this predictability effect was modulated by the foreperiod. The predictability

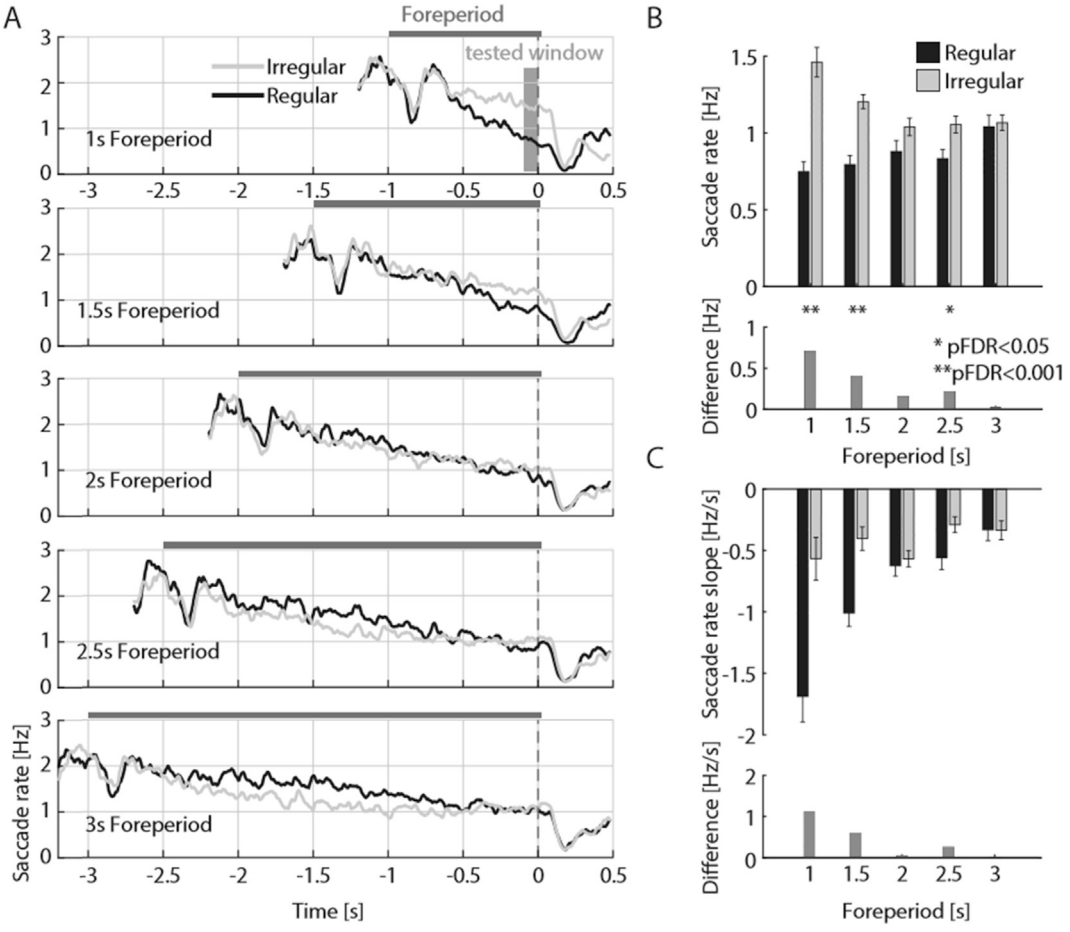

Fig. 3. *Saccade rates by predictability and foreperiod.* A) Grand average ($N = 20$) saccade rate traces in the regular (black) and irregular (gray) condition in each foreperiod duration. B) Top: Grand average pre-target saccade rate in the regular (black bars) and irregular (gray bars) conditions at -100-0 ms relative to target onset; Bottom: difference between irregular and regular pre-target saccade rates. D) Top: Saccade rate slope; Bottom: difference between irregular and regular saccade rate slope.

effect was significant for foreperiods 1, 1.5 and 2.5s but not for 2 and 3s (1s: $t(19) = 5.18$, $p = 0.0002$; 1.5s: $t(19) = 4.90$, $p = 0.0002$; 2s: $t(19) = 1.58$, $p = 0.16$; 2.5s: $t(19) = 2.44$, $p = 0.041$; 3s ($t(19) = 0.33$, $p = 0.74$ p-values are FDR-adjusted). The difference between saccade rates for the regular and irregular conditions yielded a negative linear trend ($F(1,19) = 20.95$, $p < 0.001$), indicating that the predictability effect diminished as the foreperiod increased (Fig. 3B).

To further explore the source of the predictability effect, we examined the effect of foreperiod on PSR shortly before the target, separately for the two conditions. In the regular condition there was a significant positive linear trend ($F(1,19) = 13.39$, $p = 0.0016$; Fig. 3B, black bars): PSR increased with longer foreperiods. This positive trend parallels results showing that RT increases with foreperiod duration in constant foreperiod protocols (Mattes and Ulrich, 1997). In the irregular condition, there was a significant negative linear trend ($F(1,19) = 10.98$, $p = 0.0036$; Fig. 3B, gray bars): PSR decreased with longer foreperiods. This negative trend parallels results showing that RT decreases with foreperiod duration in irregular foreperiod protocols (Niemi and Näätänen, 1981). This trend may be hypothesized to reflect the effect of conditional probabilities (the hazard rate).

3.2.2. Hazard rate analysis of the PSR

In the irregular condition, the five foreperiods (1, 1.5, 2, 2.5, 3s) could appear with equal probability (0.2). However, as time passes, the conditional probability of each interval changes: if no target has appeared by the time of the shortest possible interval (after 1s), the probabilities of each of the remaining four intervals increase from 0.2 to 0.25; If no target has yet appeared by the time of the second interval (after 1.5s), the probabilities of the three remaining foreperiods are increased to 0.33; and so on. The conditional probabilities of each of the five foreperiods to occur given that they have not yet occurred are 0.2, 0.25, 0.33, 0.5, 1. This is called the hazard-rate function.

We assessed whether the PSR correlated with the hazard-rate function across foreperiods. We examined the PSR in the irregular condition across the foreperiods and tested whether it fit the hazard function better than the linear function, which we used as a baseline for comparison. To do so, we used three analyses: First, trend analysis was applied to examine the data fit with linear compared to a hazard-rate trend. This analysis was equivalent to correlating the data across the 5 foreperiods with both sets of weights (hazard: 0.2, 0.25, 0.33, 0.5, 1; and linear 0.2, 0.4, 0.6, 0.8, 1). There were significantly higher individual correlations ($t(19) = 2.56$, $p = 0.018$) across foreperiods for the mean PSR with the linear trend (Mean r across participants $= -0.43$, different than zero: $t(19) = 3.41$, $p = 0.0029$) than with the hazard-rate (Mean r across participants $= -0.27$, different than zero: $t(19) = 2.8$, $p = 0.0098$). This analysis showed that the data correlated better with a linear trend than with a hazard trend, lending no support for the involvement of the hazard-rate function in explaining saccade rate across the foreperiods in the irregular condition.

Given that the hazard and the linear weights were highly intercorrelated, we performed a complimentary analysis for each participant comparing the two partial correlations across the foreperiods between the PSR and a) the hazard probability values (0.2, 0.25, 0.33, 0.5, 1) while controlling for the linear trend; and b) the linear trend (0.2, 0.4, 0.6, 0.8, 1) while controlling for the hazard-rate. The mean correlation coefficient across participants reflecting the contribution of the hazard function (calculated in analysis a), was $r = 0.38$, only marginally significantly different from zero ($t(19) = 2.04$, $p = 0.054$). In contrast, the mean correlation coefficient reflecting the contribution of the linear function (calculated in analysis b), was $r = 0.53$, significantly higher than zero ($t(19) = 2.72$, $p = 0.013$) and higher than the hazard-related coefficient ($t(19) = 2.72$, $p = 0.013$). Consistently with the simple correlations, partial correlations indicated that the linear trend provided a better fit than the hazard-rate trend, suggesting that conditional probabilities are not involved in determining the modulation of the PSR across time.

3.2.3. Saccade rate slope

Previous analyses focused on saccade rate shortly prior to the presentation of the stimulus. These effects reflected the end result of a long process of saccadic inhibition that started around 2s before the target. To examine these longer inhibition processes we examined the slope of saccade rate across time. A similar analysis, previously performed with the amplitude slope of the CNV component (Praamstra et al., 2006), demonstrated that it is steeper for shorter foreperiods. This finding was taken to indicate that the CNV slope is adjusted according to predictions and with the goal of reaching a similar final amplitude at target onset, regardless of the foreperiod duration (Pfeuty et al., 2005; Praamstra et al., 2006).

The slope of saccade rate (PSR minus post cue rate, divided by time difference between the two windows; see Methods) in the regular condition showed a significant negative linear trend across foreperiods: the slope was steeper for shorter foreperiods and shallower for longer foreperiods ($F(4,76) = 23.11$, $p = 0.00012$, Fig. 3C, black bars). This finding suggests that preparation for the predicted stimulus started early on by adjusting the slope of saccade rate throughout the interval.

In the irregular condition, the saccade rate slopes did not differ significantly across foreperiods ($F(4,76) = 1.25$, $p = 0.29$; Fig. 3C, gray bars) and there was no evidence for a linear trend ($F(1,18) = 1.35$, $p = 0.25$). With a non-linear rate modulation, such as the hazard-rate, we would have expected to find steeper slopes with increasing foreperiod duration. The lack of evidence for such a trend was consistent with the previous conclusion that there no evidence for a better fit for the hazard-rate relative to the linear function.

3.2.4. Blink rate

Similar analyses were performed on the average pre-target blink rate (PBR) at -500-0 ms. A repeated measures ANOVA with factors Predictability and Foreperiod revealed a main effect of Predictability ($F(1,19) = 10.76$, $p = 0.004$; Fig. 4A), a marginal effect of Foreperiod ($F(4,76) = 2.63$, $p = 0.067$, $\varepsilon = 0.66$) and a significant interaction of Foreperiod and Predictability ($F(4,76) = 5.66$, $p = 0.011$ $\varepsilon = 0.41$). Five separate t-tests performed for each foreperiod between predictability conditions revealed significant differences in two foreperiods: 1 and 1.5 (1s: $t(19) = 3.34$, $p = 0.015$; 1.5s: $t(19) = 3.08$, $p = 0.015$; 2s: $t(19) = 1.69$, $p = 0.16$; 2.5s: $t(19) = 0.46$, $p = 0.647$; 3s: $t(19) = 0.5$, $p = 0.6$ all p's FDR-adjusted). The difference between blink rates of the irregular and the regular conditions yielded a negative linear trend ($F(1,19) = 7.73$, $p = 0.012$), indicating that the effect of predictability diminished for longer foreperiods (Fig. 4A).

Trend analyses of PBR across the different foreperiods were performed separately for the two predictability conditions. For the regular condition, there was a significant positive linear trend: blinks increased for longer foreperiods ($F(1,19) = 6.20$, $P = 0.022$; Fig. 4A, black bars). But for the Irregular condition, there was a negative linear trend: blinks decreased for longer foreperiods ($F(1,19) = 5.00$, $p = 0.037$; Fig. 4A, gray bars).

To examine the fit of the PBR with the hazard-rate, we correlated the irregular condition blinks rates with the linear weights and with the hazard-rate weights. Two participants were excluded from this analysis because they performed no blinks in at least two foreperiod conditions. For the remaining 18 participants, mean correlations with the linear weights (Mean r across participants $= -0.53$, $t(17) = 3.73$, $p = 0.0017$) and with hazard-rate (Mean r across participants $= -0.31$, $t(17) = 2.3$, $p = 0.03$) significantly differed from 0, but the former was higher than the latter ($t(17) = 3.39$, $p = 0.0035$). As with the saccade-rate, this analysis showed that the data correlated better with a linear trend than with a hazard trend.

We further performed a complementary analysis using partial correlations. Both mean partial correlations of the PBR with the linear trend weights, while controlling for the hazard-rate (Mean r across participants $= 0.68$, $t(17) = 3.90$, $p = 0.0011$), and mean partial correlations of the PBR with the hazard-rate, while controlling for the linear trend

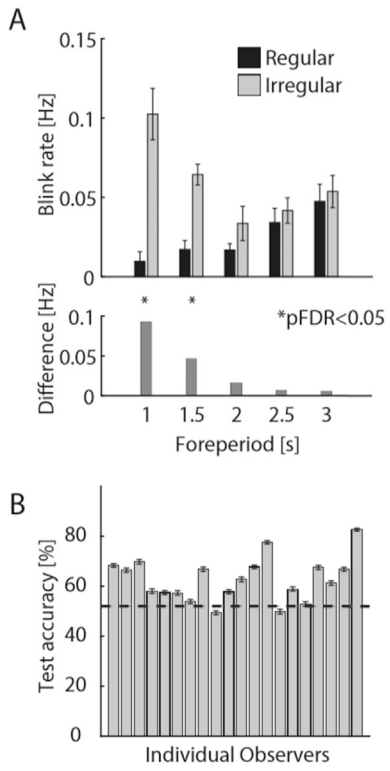

Fig. 4. *Blink rate by predictability and foreperiod.* A) Top: Grand average (N = 20) blink rate (BR) in regular (black bars) and irregular (gray bars) conditions in each foreperiod duration at -500-0 ms relative to target onset; Bottom: Difference between regular and irregular BR. B) Classification accuracy (regular/irregular) for the test trials of individual participants, based on blinks and saccades occurrences. Dashed line represents the accuracy significance threshold.

(Mean r across participants = 0.52; $t(17) = 2.82$, $p = 0.011$) were significant, but the former was higher than the latter ($t(17) = 3.43$, $p = 0.0032$). Consistently with the simple correlations this analysis indicated that the linear trend provided a better fit than the hazard-rate trend, lending no support to the involvement of conditional probabilities in determining the modulation of the PBR across time.

Blink rate slopes were not analyzed because the blink data was too sparse for this analysis.

3.3. Single trial analysis: predictability classification according to saccades and blinks

Single trials of the 1s foreperiod were classified to either regular or irregular conditions based on saccade and blink occurrences. A Bayesian classifier was trained for each participant and foreperiod, based on 80% of trials. Accuracy was then measured on the remaining 20% independent trials. This was repeated 100 times and the mean accuracy A′ of classification (AUC) was calculated (see Methods). Mean classification accuracy was 62.6 ± 8.67% (Mean ± SD) across participants (range 49.4–82.6). In 18/20 participants classification was above chance (Fig. 4B). This indicates that the link between predictability and oculomotor responses is strong enough to allow classification of single-trials.

3.3.1. Ocular drift rate

Ocular drift was measured using the Box-counting approach (Engbert and Mergenthaler, 2006) to assess whether drift is also modulated by predictability. The interpretation of this analysis should be taken with caution, as the question of whether drift could be accurately measured with video eye trackers is still under debate (Engbert and Mergenthaler, 2006; Kimmel et al., 2012; McCamy et al., 2015).

A repeated measures ANOVA with factors Predictability and Foreperiod was performed on the ocular drift. This analysis revealed no main effect of Predictability ($F(1,19) = 0.34$, $p = 0.58$), a significant effect of Foreperiod ($F(4,76) = 8.81$, $p < 10^{-5}$) and its interaction with Predictability ($F(4,76) = 3.26$, $p = 0.016$; Fig. 5A–B). Separate analyses performed on the 5 foreperiods revealed no significant predictability effect in any of the foreperiods after correcting for multiple comparisons (1s: $t(19) = 2.40$, $p = 0.13$; 1.5s: $t(19) = 2.06$, $p = 0.13$; 2s: $t(19) = 0.16$, $p = 0.87$; 2.5s: $t(19) = 0.72$, $p = 0.59$; 3s: $t(19) = 1.14$, $p = 0.44$ FDR-adjusted). The difference between the drift rates of the irregular and the regular conditions yielded a negative linear trend ($F(1,19) = 11.40$, $p = 0.0031$); the difference decreased for longer foreperiods (Fig. 5A).

Trend analysis was performed separately for the regular and the irregular conditions. There was a negative linear trend for the irregular condition, reflecting a reduction in drift for longer foreperiods ($F(1,19) = 38.65$, $p < 10^{-5}$), but that was not the case for the regular condition ($F(1,19) = 1.46$, $p = 0.24$).

To examine the involvement of conditional anticipation by hazard-rate in the irregular condition, we correlated for each participant his/her mean drift values with the linear weights and, separately, with the hazard weights across the foreperiods. Both correlations significantly differed from zero (linear: Mean r across participants = −0.76, $t(19) = 5.56$, $p < 10^{-4}$; hazard: Mean r across participants = −0.55, $t(19) = 5.05$, $p < 10^{-4}$). The correlation with the linear function was higher than that with the hazard function ($t(19) = 3.09$, $p = 0.0060$). We calculated the partial correlations between the drift values of each foreperiod with each set of weights, while controlling for the other set of weights. The mean correlation coefficient across participants reflecting the contribution of the linear function while controlling for the hazard function was r = −0.68 and significantly different than zero ($t(19) = 2.44$, $p = 0.024$). In contrast, the mean correlation coefficient reflecting the contribution of the hazard function while controlling for the linear function, was r = 0.32 and not significantly larger than zero ($t(19) = 1.04$, $p = 0.31$). The first correlation was marginally higher than the second ($t(19) = 1.78$, $p = 0.090$). Consistently with the simple correlations, partial correlations indicated that the linear trend provided a better fit than the hazard-rate trend, suggesting that conditional probabilities are not involved in determining the modulation of the drift across time.

3.3.2. Drift slope

A repeated measures ANOVA performed on the slopes of the regular condition drift rates in the different foreperiods revealed a significant effect ($F(4,76) = 4.61$, $p = 0.002$; Fig. 5C) with a significant negative linear trend ($F(1,19) = 12.37$, $p = 0.002$). This result indicates that drift behavior, similar to saccade rate, was modulated by expectations: drift slope was adjusted according to expected foreperiod duration. The irregular condition revealed no significant effect ($F(4,76) = 1.92$, $p = 0.11$). Taken together with the correlation analysis above, we conclude that there is no evidence that drift is modulated by the hazard function, more than it is by a simple linear trend.

3.3.3. Correlation between drift and saccades and blinks

Given a temporal relation between drift and saccades (Engbert and Mergenthaler, 2006), we tested the hypothesis that our drift findings are a mere manifestation of saccade or blink-related effects. To do so, we correlated drift data with saccade and blink data across participants. For each combination of conditions (predictability and foreperiod; 10 combinations overall), we correlated the PSR and the pre-target drift rates across participants. Out of 10 correlations, all FDR-adjusted p-values were >0.82, and all uncorrected p-values were >0.08. Similarly, we correlated the differences between regular and irregular conditions: out of 5 correlations, all uncorrected p-values were >0.6. For drift and blinks, out of 10 correlations, all uncorrected p-values were >0.12, FDR-adjusted all p-values>0.87. These results suggest that drift data was independent of other oculomotor events.

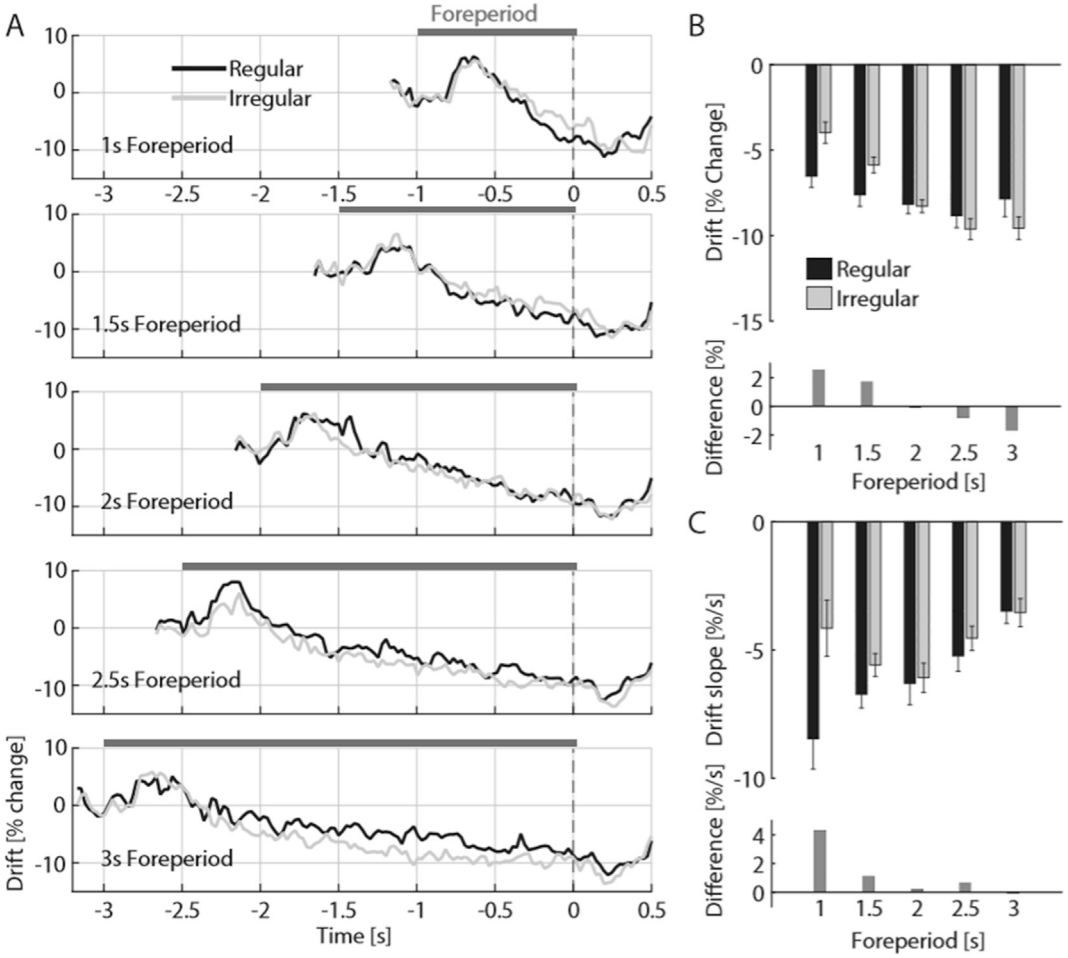

Fig. 5. *Drift rate by predictability and foreperiod* A) Grand average (N = 20) drift rate traces in the regular (black) and irregular (gray) conditions in each foreperiod duration measured in percentage of box count change from baseline. B) Top: Grand average pre-target drift rate in regular condition (black bars) and irregular (gray bars) at -300-0 ms relative to target onset; Bottom: difference between irregular and regular condition drift rate. C) Top: Drift rate slope along time in regular condition (black bars) and irregular (gray bars); Bottom: difference between irregular and regular drift rate slopes.

3.4. Behavioral consequences of oculomotor events

In the previous analyses we established that saccades and blinks are inhibited prior to a predictable target. However, it is an open question why this inhibition takes place. Blinks are relatively long and naturally impair perception for extended durations of time. Saccades are shorter, but due to saccadic suppression and motion blur, when they occur near the onset of a target they result in suppressed visual responses and impaired detection (Hafed and Krauzlis, 2010; Herrington et al., 2009). Indeed, consistently with previous studies (Herrington et al., 2009; Martinez-conde et al., 2013; Zuber and Stark, 1966) we find that in trials where no saccade onsets occurred during target presentation (0–33 ms relative to stimulus onset), mean accuracy was higher (Mean ± SD) and RTs were faster than in trials with saccades (Accuracy: 76.6 ± 8.9% vs. 66.0 ± 15.3%; $t(19) = 4.04$, $p < 0.001$; RTs: 646 ± 93 ms vs. 791 ± 256 ms; $t(19) = 3.33$, $p = 0.0037$; Fig. 6A–D).

Perception of targets that occurred during saccade execution is poor. To eliminate these trivial effects, we conducted the same analysis for the time-range of −100 to −20 ms relative to target onset. The last 20 ms of the interval (-20-0 ms) were not included in this analysis to avoid the influence of late saccades, which could overlap with the stimulus. The cutoff at −20 was chosen because ~90% of the microsaccades lasted less than 20 ms and this cutoff left no microsaccades overlapping with the stimulus. There was no evidence for differences in accuracy-rates or RTs between trials with and without saccades in this time window (Accuracy: 76.3 ± 10.4% vs. 76.1 ± 8.9%; $t(19) = 0.19$, $p = 0.84$; RTs: 648 ± 93 ms vs. 675 ± 112 ms, $t(19) = 1.39$, $p = 0.17$; Fig. 6E–F). This is important as it suggests that the long pre-target inhibition of saccades has no clear perceptual advantages.

3.5. Contingent negative variation (CNV)

3.5.1. Pre-target CNV amplitudes

The CNV is a centro-parietal ERP negativity that is evident during intervals of anticipation and resolves after target presentation (Praamstra et al., 2006; Trillenberg et al., 2000; Verleger et al., 2000; Walter et al., 1964). We examined how the regularity of interval and the foreperiod modulated the CNV. A repeated measures ANOVA with factors Predictability and Foreperiod revealed marginally significant main effects (Predictability: $F(1,18) = 3.83$, $p = 0.066$; Foreperiod: $F(4,72) = 2.85$, $p = 0.063$, $\varepsilon = 0.65$) and no significant interaction between these two factors ($F(4,72) = 1.55$, $p = 0.19$; Fig. 7A–B). As in the oculomotor data analysis we compared the regular and irregular conditions separately for the different foreperiods. These conditions only differed in the shortest foreperiod (1s: $t(18) = 3.70$, $p = 0.0081$; 1.5s: $t(18) = 0.69$, $p = 0.82$; 2s: $t(18) = 1.19$, $p = 0.62$; 2.5s: $t(18) = 0.12$, $p = 0.90$; 3s: $t(18) = 0.31$, $p = 0.90$; p's FDR-adjusted). The difference between the CNV amplitudes of the irregular and the regular conditions yielded a marginally significant negative linear trend ($F(1,18) = 3.74$, $p = 0.069$), suggesting that the effect of predictability decreased for longer foreperiods (Fig. 7B).

Further analysis was performed separately on the regular and the irregular conditions. In the regular condition, there was no evidence for

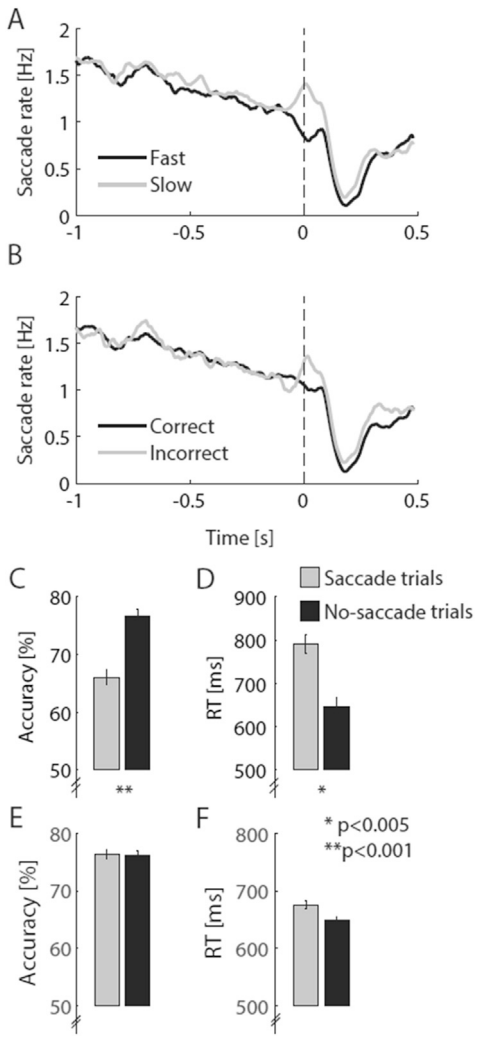

Fig. 6. *Behavioral consequences of saccades and blinks*. A) Trials were divided in slow and fast responses according to median split on their RTs. The figure depicts saccade rate in fast (gray) vs. slow (black) trials. B) Saccade rate in correct (black) vs. incorrect (gray) response trials. C) Accuracy rates and D) RTs in trials in which a saccade occurred (gray) vs. not occurred (black) during target presentation. E) Accuracy rates and F) RTs in trials in which a saccade occurred (gray) vs. not occurred (black) during target presentation in the pre-target window −100 to −20 ms relative to the target.

difference in the magnitude of CNV among the different foreperiods ($F(4,18) = 0.57$, $p = 0.68$), consistently with previous findings (Pfeuty et al., 2005; Praamstra et al., 2006). In contrast, in the irregular condition, there was a significant negative linear trend ($F(1,18) = 9.21$, $p = 0.007$) with more negative amplitudes for longer foreperiods.

The pattern of correlations analysis was similar to that of the oculomotor measures. In the irregular condition, the mean correlations of CNV amplitudes with the linear weights and with hazard weights were both high (Mean r across participants = -0.50, $t(18) = 3.27$, $p = 0.0043$ and Mean r across participants = -0.33, $t(18) = 2.39$, $p = 0.027$, respectively), with a significant difference between them: $t(18) = 2.93$, $p = 0.0089$). The mean partial correlation between the pre-target CNV and the linear trend weights, while controlling for the hazard-rate was significant (Mean r across participants = −0.57, $t(18) = 3.61$, $p = 0.0020$), and the complementary partial correlation of the CNV and the hazard-rate, while controlling for the linear trend was also significant (Mean r across participants = 0.33, $t(18) = 2.20$, $p = 0.04$). The difference between the two was also significant ($t(18) = 3.06$,$p = 0.0067$).

A repeated measures ANOVA performed on the slopes of the regular condition CNV amplitudes in the different foreperiods revealed a significant effect ($F(4,72) = 4.79$,$p = 0.002$; Fig. 7C) with a significant negative linear trend ($F(1,18) = 7.80$,$p = 0.012$). This result indicates that CNV, similar to saccade rate, was modulated by expectations: CNV slope was adjusted according to the expected foreperiod duration. There was no such effect in the irregular condition ($F(4,72) = 0.045$,$p = 0.83$).

As with the findings with oculomotor measurements, these findings provide no evidence that the hazard-rate explains the CNV modulation better than a linear trend.

3.5.2. CNV slopes

In the regular condition there was a significant positive trend of the CNV slopes across the foreperiods (more negative slopes for shorter intervals; $F(1,18) = 7.18$, $p = 0.012$). This finding is similar to that of saccade rate and consistent with previous studies (Pfeuty et al., 2005; Praamstra et al., 2006). This effect has been interpreted to reflect adjustment of the slope according to the foreperiod duration, to achieve a similar voltage at the presentation of the target. In the irregular condition, there was no evidence for slope differences among the foreperiods ($F(4,72) = 0.33$,$p = 0.76$, $\varepsilon = 0.62$), supporting a linear rather than non-linear (e.g. hazard-rate) modulation of the CNV. This result is consistent with results described above, showing no evidence for the involvement of conditional probabilities in the modulation of the CNV by foreperiod.

3.6. Alpha-band suppression

In this study we focused on alpha amplitudes given that previous studies indicated that temporal expectations modulate the amplitude and not the phase of alpha oscillations (Rohenkohl and Nobre, 2011; van Diepen et al., 2015). Consistently, in supplementary analysis we found no effects of alpha phase (see Supplementary Material S3).

3.6.1. Pre-target alpha suppression

Previous studies have found a suppression of occipital alpha power when targets are anticipated. Consistently with other studies using central stimuli (Breska and Deouell, 2017; Praamstra et al., 2006), we found alpha amplitude to be more negative than baseline in central-occipital sites (Fig. 8C). Alpha power was averaged across a parieto-occipital group of electrodes and across the time window of -300-0 ms relative to the target (following Breska and Deouell, 2017). As in the CNV analysis, alpha amplitudes were measured relative to the baseline of -200-0 (see Supplementary Material S2 for the same analysis with a longer baseline, which yielded a similar pattern of results). A repeated measures ANOVA with factors Predictability and Foreperiod revealed no main effect of Predictability ($F(1,18)<1$) a main effect of Foreperiod ($F(4, 72) = 3.09$,$p = 0.04$, $\varepsilon = 0.63$), and a marginally significant interaction ($F(4,72) = 2.66$,$p = 0.07$ $\varepsilon = 0.60$; Fig. 8A). We performed 5 separate t-tests for each foreperiod and revealed no significant predictability effects (1s: $t(18) = 1.99$, $p = 0.06$; 1.5s: $t(18) = 1.69$, $p = 0.10$; 2s: $t(18) = 0.57$, $p = 0.57$; 2.5s: $t(18) = 0.04$, $p = 0.96$; 3s: $t(18) = 1.4$, $p = 0.17$ p's uncorrected). The difference between the alpha amplitudes of the irregular and the regular conditions yielded a negative linear trend ($F(1,18) = 9.46$, $p = 0.0065$), indicating that the effect of predictability decreased as the foreperiod increased (Fig. 8A).

We analyzed pre-target alpha suppression index separately for the regular and the irregular conditions across the foreperiods. In the regular condition, there was no significant difference among the different foreperiods ($F(4,18) = 0.2$, $p = 0.89$; Fig. 8A, black bars). In the irregular condition, there was a significant negative linear trend ($F(1,18) = 11.14$, $p = 0.0033$, Fig. 8A, gray bars).

We correlated the pre-stimulus alpha-band power of each participant for the 5 different foreperiods with the weights of the linear function and the weights of the hazard function. The mean correlations with both functions were high, but slightly higher for the hazard ($r = 0.76$, different than zero: $t(18) = 4.48$, $p < 0.001$) than the linear function ($r = 0.70$,

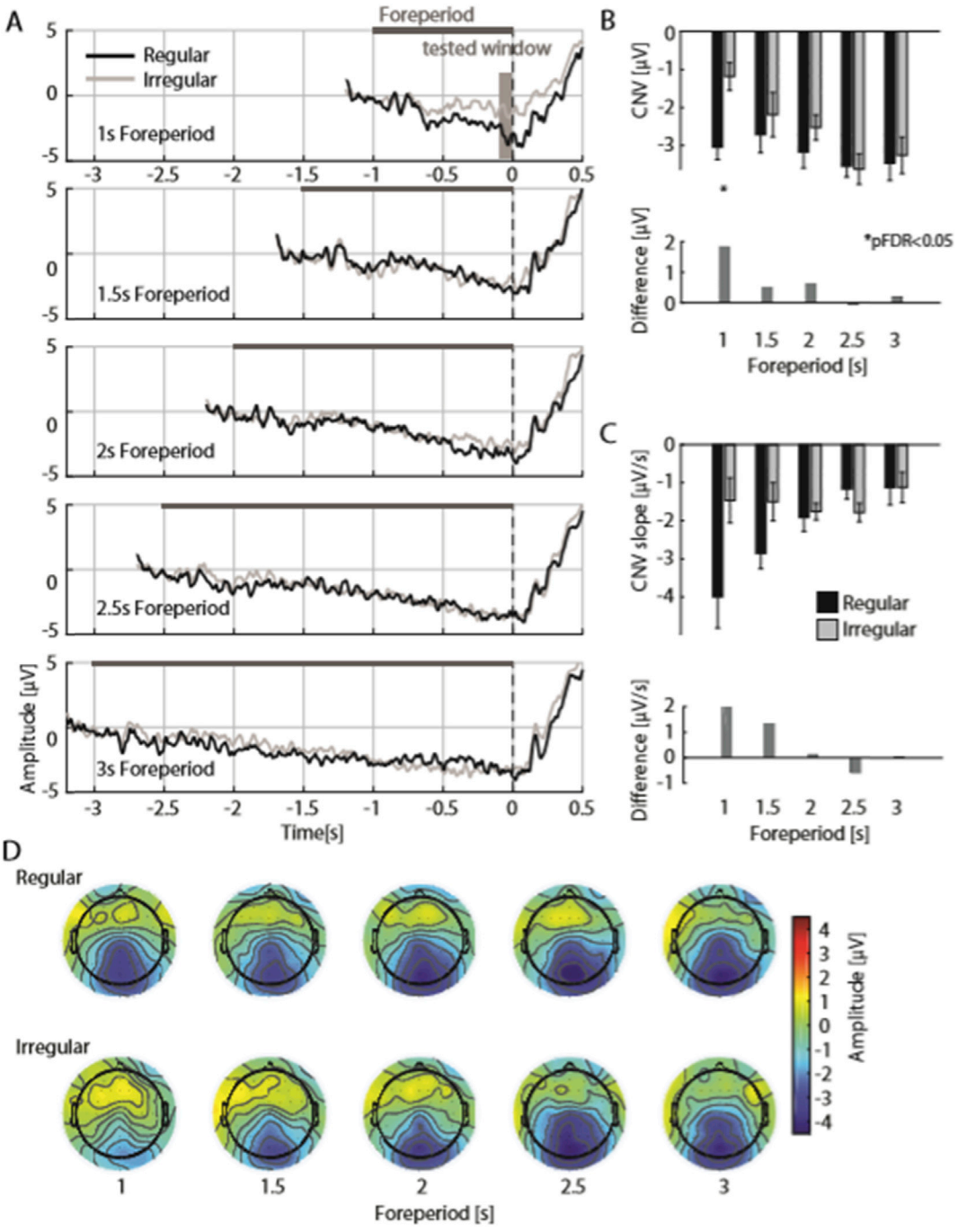

Fig. 7. *CNV as a function of foreperiod and predictability*. A) Mean voltage averaged across a parietal electrode cluster in the regular (black) and irregular (gray) conditions at each foreperiod. Grand average across participants (N = 19). B) Top: pre-target CNV at -100-0 ms relative to target onset, in the regular (black bars) and irregular (gray bars) conditions; Bottom: The difference between the regular and irregular conditions. C) Top: CNV slope along time in the regular (black bars) and irregular (gray bars) conditions; Bottom: The difference between the regular and irregular conditions. D) Scalp-topography of the CNV.

different than zero: $t(18) = 6.32$, $p < 10^{-5}$) but the difference between them was not significant ($t(18) = 1.05$, $p = 0.30$). Unlike the previous measurements, there was no better fit for the linear trend relative to the hazard.

We further analyzed the partial correlations to examine the fit of the data with the linear and the hazard rate functions. The mean partial correlation between the pre-target alpha and the linear trend weights, while controlling for the hazard-rate was low and insignificant (Mean r across participants = 0.006; $t(18) = 0.02$, $p = 0.98$). In contrast, the partial correlation between the pre-target alpha and the hazard-rate, while controlling for the linear trend was high and significant (mean r across participants = 0.57; $t(18) = 3.49$, $p = 0.0026$). This indicates that, unlike the oculomotor measures and CNV, alpha band suppression is more correlated with the hazard function than with the linear function. This effect is likely generated by the conditional probabilities across time.

3.6.2. Alpha slopes

In the regular condition, there was no difference in the alpha slope among foreperiod durations ($F(4,72) = 0.19$, $p = 0.93$). In contrast, in the irregular condition, there was a significant difference between the alpha slopes of the foreperiods ($F(4,72) = 4.39$ $p = 0.020$, $\varepsilon = 0.48$), with a negative linear trend ($F(1,18) = 7.13$, $p = 0.016$; Fig. 8B, gray bars). This

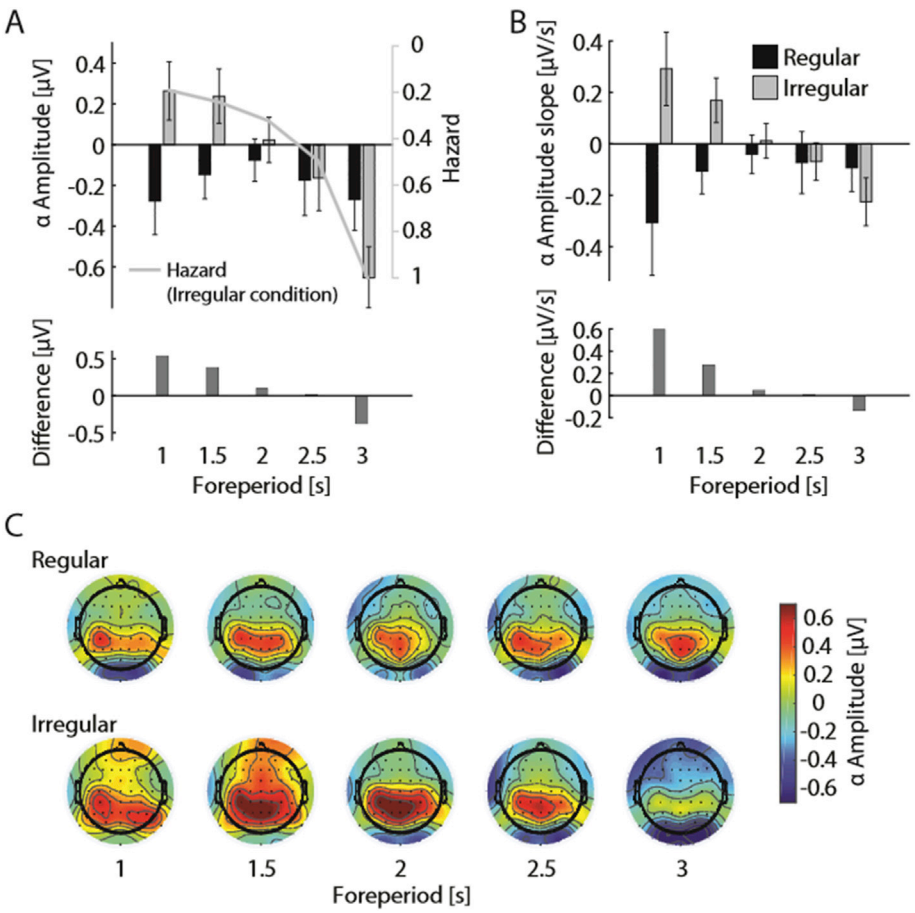

Fig. 8. *Alpha suppression modulated by predictability and foreperiod.* A) Top: Grand average (N = 19) alpha amplitude averaged across an occipital electrode cluster (-300-0 ms pre-target) in the regular (black) and irregular condition (gray) at each foreperiod. Gray line - Theoretical hazard-rate for the irregular condition closely matches alpha suppression; Bottom: The difference between regular and irregular. B) Top: Alpha amplitude slope along time in the regular (black bars) and irregular (gray bars) condition; Bottom: The difference between regular and irregular by foreperiod duration. C) Pre-target alpha amplitude topography at the regular (top) and irregular condition (bottom), at each foreperiod (horizontal axis).

indicates that as time passed within a trial, not only did the alpha amplitude become more suppressed, but also the slope of this suppression became steeper. This is another indication for a non-linear effect on alpha amplitude in the irregular condition. Taking the slopes and the partial correlations analysis together, these results support the involvement of non-linear conditional probabilities in determining the pre-target alpha suppression.

4. Discussion

Temporal predictability was manipulated in a non-rhythmic procedure, by having the duration of the cue-target interval (foreperiod) be either fixed (regular) or varied (irregular). An oculomotor predictability effect was evident by (a) an inhibition of saccades and blinks (oculomotor markers) prior to the onset of regular relative to irregular targets; and (b) a steeper negative slope of saccades and drift for shorter than for longer foreperiods in the regular condition, suggesting that they were adjusted according to the anticipated interval. The oculomotor inhibition effect was so consistent that it enabled a reliable single-trial classification of predictability according to pre-target saccades and blinks.

Furthermore, the pre-target oculomotor inhibition effect (irregular minus regular) of saccades, drifts and blinks was gradually diminished with prolongation of the foreperiod, due to both a decrease in inhibition in the regular condition and an increase in the irregular condition. The decrease in the regular condition is consistent with previous RT findings (Niemi and Näätänen, 1981) and probably reflects the diminished ability to estimate intervals when they become long. The opposite effect in the irregular condition is consistent with an increase in anticipation due to conditional probabilities, but we found no evidence supporting this possibility.

The oculomotor measurements were sensitive to interval-regularity, even in the longest foreperiod that showed no effect in the behavioral and electrophysiological measurements. However, the specific changes of conditional probabilities with the passage of time were reflected by alpha-suppression and not by the oculomotor measures.

4.1. The purpose of pre-target oculomotor inhibition

It is an open question why are saccades, drift and blinks inhibited prior to predictable task-relevant stimuli. In addition to their role in supporting vision, saccades and blinks trivially impair perception when they overlap with the presentation of the stimulus (Bristow et al., 2005; Diamond et al., 2000; Hafed, 2013; Martinez-conde et al., 2013; Ross et al., 2001; Uematsu et al., 2013; Zuber and Stark, 1966). Moreover, a previous study showed that when a saccade occurred up to 200 ms prior to target onset, it impaired perceptual performance (Herrington et al., 2009). It is, therefore, reasonable to hypothesize that inhibiting saccades and blinks shortly before stimulus onsets would be advantageous for perception and could be the source of the observed phenomenon. The timelines of the behavioral and the oculomotor effects were, however, inconsistent with this hypothesis: the perceptual cost in the present procedure was evident only for saccades that occurred during target presentation and not earlier as previously found. In contrast, the oculomotor predictability effect (regular vs. irregular) was evident earlier, from around 500 ms before target onset. This temporal incompatibility questions whether oculomotor inhibition can be explained by a simple motivation to avoid the perceptual costs of saccades. Alternatively, we speculate that oculomotor inhibition is the manifestation of a general non-specific expectation mechanism that interacts with the oculomotor system.

There are a few perceptual mechanisms that are known to interact with the oculomotor system (e.g. Drewes and VanRullen, 2011; Staudigl

et al., 2017). One possible candidate for a general mechanism is the striatal dopaminergic system, which has been related to temporal expectations (Merchant et al., 2013; Parker et al., 2013; Terhune et al., 2016), the prediction of future rewards (Cohen et al., 2012; Salimpoor et al., 2011; Schultz et al., 1997), and response readiness as manifested by the CNV component (Linssen et al., 2011). Specifically, gradual increase in dopamine signals was observed while rats moved toward distant goals (Howe et al., 2013), which could reflect a similar process to the one observed here, as dopamine signaling may gradually increase during the foreperiod until the target appears. Because the output of the Basal Ganglia to the Superior Colliculus is inhibitory (Hikosaka et al., 2000), increase in striatal dopamine is associated with oculomotor inhibition (Hood et al., 2007). Such gradual increase could lead to the sustained oculomotor inhibition we observed. This speculation is supported by our recent finding (Dankner et al., 2017) of reduced anticipatory oculomotor inhibition for individuals with attention deficit hyperactivity disorder (ADHD), a deficit associated with sub-performance of dopamine circuits (Sergeant et al., 2003); and also by the finding of reduced pre-target saccades when methylphenidate, a dopamine agonist, is administered to ADHD individuals (Fried et al., 2014).

4.2. Other markers of temporal expectations

In addition to the oculomotor markers, we measured three other common markers of temporal expectations: RTs, CNV and alpha-suppression. Oculomotor markers have some methodological advantages over the other measuremens. Compared to RTs, oculomotion is an ongoing behavior, which can be measured during the formation of expectations and not just after they have ended. Additionally, oculomotor behavior is involuntary and often unconscious (Spering and Carrasco, 2015) and can therefore be measured without an explicit instruction, unlike RTs. Compared to electrophysiological measures, oculomotor markers have the advantages of being simpler to measure, and not requiring extensive preprocessing.

We compared the modulation by regularity of the different markers. The purpose of this was: (a) to establish, using traditional methods, that our procedure manipulated predictability; (b) to compare the oculomotor markers to other markers in their sensitivity to expectations and their modulation by foreperiods.

All the examined markers were modulated by temporal expectations, as established by the gradual decrease in the regularity effect with prolongation of the foreperiod. For CNV and the oculomotor markers we found a modulation of slope by foreperiod in the regular condition: the slope was shallower for longer than shorter foreperiods indicating its adjustement according to expecations (Praamstra et al., 2006).

Examining specific foreperiods revealed fine temporal differences in the sensitivity of these markers: RTs showed an effect only in the shortest foreperiod; CNV and alpha showed no effects in individual foreperiods; but the oculomotor markers were sensitive to regularity even in long forperiods of up to 2.5s (excluding 2s, possibly because it is the mean of the distribution and therefore more predictable).

With alpha acitivity there was no effect of regularity, which could be attributed to differences in experimental protocol relative to previous studies that used peripheral stimuli (e.g. Rohenkohl and Nobre, 2011) or shorter foreperiods (e.g. van Diepen et al., 2015). However, with this marker we found evidence for the effect of conditional probabilities across time in the irregular condition, which was not observed with the other markers.

4.3. Conditional probabilities (hazard-rate)

In the irregular condition, there were no cue-related regularities and therefore consistent effects may only be attributed to statistical regularities. Specifically, as time progresses and the target had not appeared, the probability of its appearance at a given moment is increased. In line with previous studies using different response-readiness measurements (e.g. Niemi and Näätänen, 1981; Trillenberg et al., 2000; Bherer and Belleville, 2004; Nobre et al., 2007), we observed a consistent increase in all indices of expectations when the foreperiod was extended. Such trends were interpreted as reflecting changes in conditional probabilities, and a few studies showed that different electrophysiological responses are modulated by manipulations of the hazard function (Schoffelen et al., 2005; Trillenberg et al., 2000). These studies did not demonstrate, however, that non-linear hazard-rate functions provide better fit to the data than linear trends. Monotonic decreasing trends, such as a linear trend, are ambiguous as the may reflect non-conditional effects of the passage of time rather than conditional probabilities. We took a conservative approach and considered linear trends as a baseline for comparison with the hazard-rate trend. With CNV and the oculomotor markers, we found the fit with the hazard-rate to be no better than the fit with the linear function and therefore the interpretation remains unclear. In contrast, alpha-suppression showed a better fit with the hazard-rate function than the linear function, suggesting that it is a correlate of conditional probabilities. It is important to note, however, that with the current experimental protocol of only five foreperiods occurring at equal probabilities, other mechanisms such as estimation of the mean expected time (2s in our experiment) could have also caused some effects on blinks and saccades in the irregular condition (e.g. a U-shape function centered at 2s). Future experiments would be required to test this hypothesis.

5. Conclusion

Inhibition of oculomotor behavior can serve as a sensitive index of temporal expectations. This effect is due to predictability and not to neural entrainment as it is evident for non-rhythmic associative regularities. These oculomotor markers estimate temporal expectations directly and implicitly throughout each trial and are easier to measure than electrophysiological markers. As with the CNV, we found no evidence that the oculomotor markers reflect conditional probabilities, but, we show for the first time that conditional probabilities are reflected in alpha amplitudes.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.09.026.

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