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Visual cortex combines a stimulus and an error-like signal with a proportion that is dependent on time, space, and stimulus contrast

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The study was designed and conceived by David Eriksson. The data analysis and computer simulations were done by David Eriksson. The experiments were performed by David Eriksson, Thomas Wunderle, and Kerstin Schmidt. The paper was written by David Eriksson and Kerstin Schmidt.

Even though the visual cortex is one of the most studied brain areas, the neuronal code in this area is still not fully understood. In the literature, two codes are commonly hypothesized, namely stimulus and predictive (error) codes. Here, we examined whether and how these two codes can coexist in a neuron. To this end, we assumed that neurons could predict a constant stimulus across time or space, since this is the most fundamental type of prediction. Prediction was examined in *time* using electrophysiology and voltage-sensitive dye imaging in the supragranular layers in area 18 of the anesthetized cat, and in *space* using a computer model. The distinction into stimulus and error code was made by means of the orientation tuning of the recorded unit. The stimulus was constructed as such that a maximum response to the non-preferred orientation indicated an error signal, and the maximum response to the preferred orientation indicated a stimulus signal. We demonstrate that a single neuron combines stimulus and error-like coding. In addition, we observed that the duration of the error coding varies as a function of stimulus contrast. For low contrast the error-like coding was prolonged by around 60–100%. Finally, the combination of stimulus and error leads to a suboptimal free energy in a recent predictive coding model. We therefore suggest a straightforward modification that can be applied to the free energy model and other predictive coding models. Combining stimulus and error might be advantageous because the stimulus code enables a direct stimulus recognition that is free of assumptions whereas the error code enables an experience dependent inference of ambiguous and non-salient stimuli.

Keywords: error coding, predictive coding, temporal contextual modulation, spatial contextual modulation, adaptation, spatial suppression, voltage sensitive dye, VSD

INTRODUCTION

Since the early days of electrophysiology one goal in neuroscience has been to find a correspondence between action potentials and stimulus. Experimental studies show that correspondence is not perfect. For example repeated presentations of the same stimulus do not result in the same response amplitude (Schiller et al., 1976; Heggelund and Albus, 1978; Scobey and Gabor, 1989; Vogels et al., 1989; Snowden et al., 1992; Softky and Koch, 1993). This motivates the question why and how action potentials differ from the mere coding of the stimulus. The discrepancy between stimulus coding and action potentials may be ascribed to spontaneous fluctuations of ongoing activity (Arieli et al., 1995, 1996; Kenet et al., 2003). Spontaneous fluctuations could be the result of predictions (Ringach, 2009).

The most fundamental form of prediction is that a stimulus will repeat in space or in time. If the stimulus is repeating, the local stimulus can be used to predict a nearby or future stimulus, respectively. Thus, the error will be small. If neurons perform error coding the firing rate should drop (Koch and Poggio, 1999). The opposite is also true, i.e., when the brain is "surprised" by a stimulus, the activity should be high. For space, it has been observed that the firing rate drops when a grating stimulus becomes larger than a certain optimal radius, i.e., the stimulus repeats across space (Maffei and Fiorentini, 1976; Nelson and Frost, 1978; Angelucci et al., 2002). This effect is normally termed contextual suppression. For time, a firing rate decrease usually occurs when the visual stimulus remains constant for more than an optimal time span, i.e., the stimulus repeats across time (Kuffler, 1953). This effect is normally termed adaptation (Barlow, 1953; Muller et al., 1999; Kohn, 2007). In addition to those basic response properties, the error coding principle has explained responses to a range of stimuli such as overlapping gratings, textured surrounds, and apparent motion (Rao and Ballard, 1999; Alink et al., 2010; Spratling, 2010).

Although there is growing evidence for error coding there is also recent evidence for a true stimulus coding (Benucci et al., 2009). True stimulus coding means that the luminance pattern of the currently shown stimulus is represented by the neuronal activity. This is in contrast to error coding where not only the current luminance pattern is represented but also a prediction that was generated from a combination of previously shown stimuli and the knowledge about the environment. Interestingly, both stimulus and error coding were observed in one and the same visual area (V1). Models of predictive coding generally assume separate

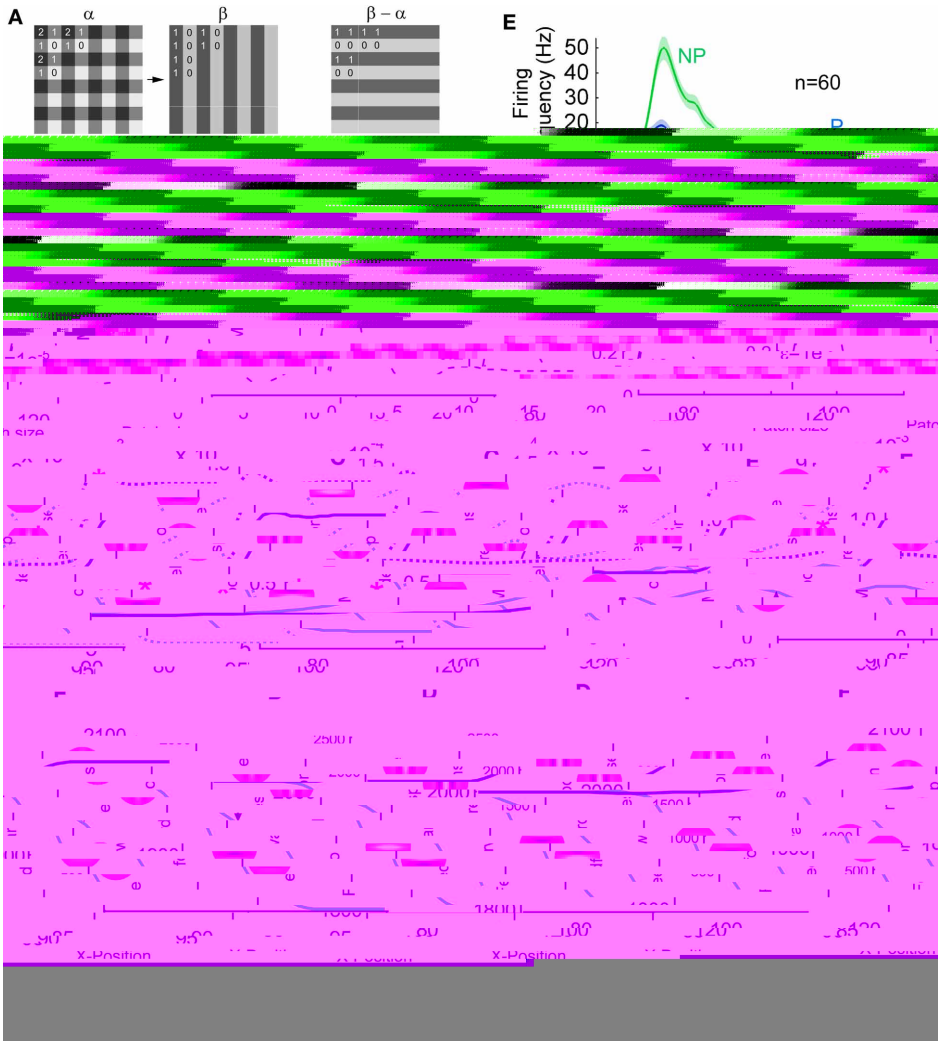

FIGURE 1 | Combination of a stimulus and an error-like signal across time. (A) Transition from priming to grating pattern (left). The difference (error) pattern between priming and grating pattern has a horizontal orientation (right). **(B)** The instantaneous firing rate for a horizontally preferring complex cell when the stimulus is rotated and displayed at eight different orientations separated by 22 1/2° (*y*-axis). Grating onset at 200 ms and offset at 450 ms (*x*-axis). **(C)** The response of the same unit as in **B**, but for the priming to pattern transition (see **A**). The blue (green) rectangle outline indicates when the test grating matches the preferred (non-preferred) horizontal orientation of the cell. Note that the non-preferred grating orientation now generates the largest response at around 550 ms. **(D)** Peri-stimulus time histogram (PSTH) of the instantaneous firing rate for stimulation with, in this example, horizontal (P: preferred, blue line, stimulus) and vertical (NP: non-preferred, green line, error) gratings after the stimulus transition (at 0 ms). The transparent field around each curve denote the standard deviation of the mean. **(E)** Same as **(D)** but the average of all 60 units. **(F)** Scatter plot of all units. The *x*-coordinate is the average firing rate during 40–90 ms after transition onset for the non-preferred orientation minus the average firing rate during 40–90 ms after transition onset for the preferred orientation. The *y*-coordinate is like the *x*-coordinate but for 90–250 ms instead of 40–90 ms. **(G)** Spike raster plot for the preferred and non-preferred orientations for the unit shown in **B–D**. **(H)** Extracellularly recorded spike waveform from unit in **G** for stimulus (blue) and error (green) spikes.

extent of the lateral spread we have used extensive averaging (see methods) and false discovery rate statistics (see methods). Even the most peripheral pixels exhibited an activation pattern anti-correlated to that evoked by the grating stimulus presented alone ($p < 0.05$ for both animals) (**Figure 2G**). Pixels outside this region were not significantly modulated by stimulus orientation.

To summarize, the voltage-sensitive dye signal combines a stimulus and an error-like code. It seems unlikely that the conversion from error to stimulus can be done within V1 because the ambiguous and non-linear transformation from simple to complex neurons renders the above hypothesized linear de-convolution difficult (Benucci et al., 2007). A de-convolution could be implemented in a presumably more linear feed forward pathway from layer three (complex cells) to layer four (simple cells) of a higher area.

Another way to eliminate the error from the stimulus signal could be to detect spikes that code exclusively for the

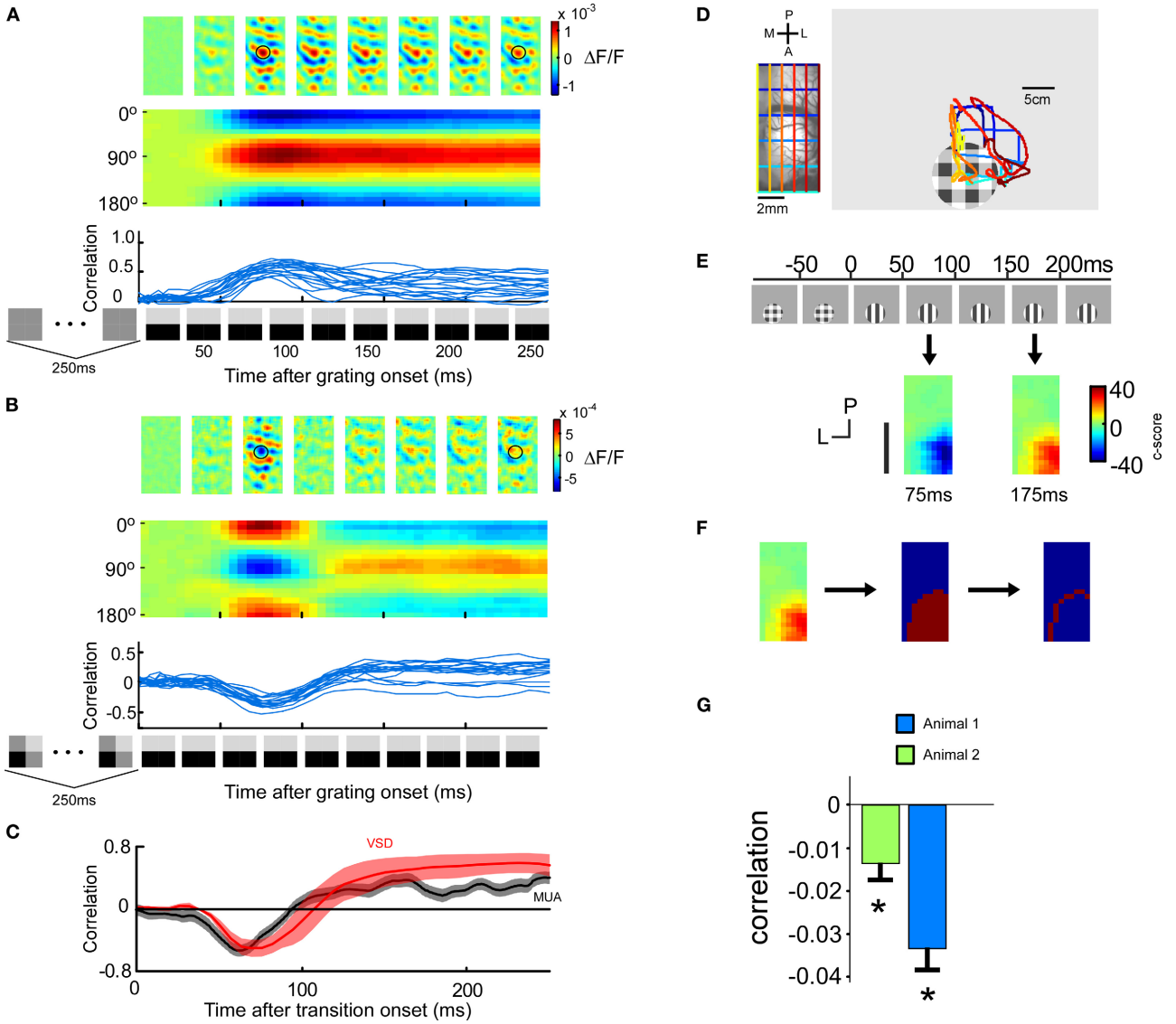

FIGURE 2 | Voltage-sensitive dye signal after a stimulus transition. (four animals) **(A)** Cortical activation pattern as a function of time (upper row). VSD signal evoked by the transition from a 250 ms blank screen to a 250 ms horizontal grating. Population responses after 81 ms and 143 ms are similar. Icons on the *x*-axis denote stimulus sequence. Encoded orientation as a function of time (middle row). Trial by trial correlation of the population response at a certain time after grating onset with the average (across time) population response evoked by that grating when preceded by a blank screen (lower row). The correlation raises around 40 ms and stays high. **(B)** Same as in **A**, but with a 250 ms priming pattern preceding the 250 ms horizontal grating. Interestingly, the population response after 81 ms is orthogonal to that at 143 ms. **(C–F)** The stimulus image cannot be retrieved by the post-synaptic membrane potential. **(C)** Comparison of spiking and VSD response. The spiking was quantified by subtracting the non-preferred correlation from the preferred correlation. The preferred correlation was calculated as follows: for a given time point after the transition the instantaneous firing profile across the eight orientations were correlated with the instantaneous firing profile across the eight orientations for the grating preceded by a blank screen. The non-preferred correlation was calculated similarly but instead shifting the orientations by 90°. The encoding of the voltage-sensitive dye signal is represented by the correlation curve computed in **B** averaged across four animals (red). **(D)** Positioning of a patch stimulus for VSD recording using Fourier imaging retinotopy of visual cortex. Left: Imaged cortical region with superimposed retinotopic iso-lines. Blue (posterior) and green (anterior) lines indicate iso-lines for which the anterior posterior position is constant, and yellow (medial) and red (lateral) lines indicate iso-lines for which the lateral medial position is constant. Right: We have superimposed the cortical retinotopy on the stimulus monitor (left). **(E)** Lateral spread of the errorsignal. Upper panel: a localized stimulus (10° diameter) positioned to evoke responses in the anterior part of the imaged cortical area (guided by retinotopic imaging). Lower panel: spatial orientation coding at 75 ms and at 175 ms. Population activity evoked by the grating was pixel wise correlated with the average population activity within a 800 × 800 μm window centered around each pixel. Negative values indicate negative correlations, and thus error encoding (blue color). Positive values indicate positive correlations, and thus stimulus encoding (red color). **(F)** Extraction of the most peripheral pixels at time point 175 ms, i.e., when the stimulus is encoded. The peripheral pixels are those which mark the outer margin of the area containing significant information about stimulus orientation.
The *c*-score is calculated by dividing the mean (across trials) correlation with the standard deviation (across trials) of the correlation. **(G)** Correlation of the peripheral pixel response at the time of error encoding (75 ms) with the averaged population response. For both animals the correlation is significantly ($p < 0.05$, $n = 12$) negative indicating that the error is encoded.

stimulus. Error coding generates spikes that are not representing the currently shown stimulus. This is because it takes time to form a prediction, i.e., the prediction builds-up over time and can therefore outlast the stimulus. It is well-known that for example OFF-responses, per definition, outlast the stimulus. Consequently, the orthogonal response can be interpreted as an OFF response since the transition consists of the disappearance of the orthogonal grating. To investigate if a population of neurons can distinguish between ON and OFF responses we defined each time point of a stimulus as containing an orientation or not (**Figure 3A**). We tested if this "stimulus existence code" was correlated with the population firing rate. If this would be the case the population firing rate could be used to distinguish stimulus coding spikes from spikes that codes for a disappeared stimulus. The population code was defined as the ratio between the instantaneous firing rate of one unit and the instantaneous firing rate of another unit. All possible combinations between 34 neurons and all orientations were used, i.e., $34 \times 34 \times 16$ combinations (See red points in **Figure 3B**). The best combination (see encircled point in **Figure 3B**) is located far away from ratio 1 (origo in log-log-plot) along the diagonal meaning that the ratio for "ON" is much smaller than the ratio for "OFF" on average. Hence, the combination should be well suited to discriminate between "ON" and "OFF." However, when inspecting individual stimulus constellations of that combination the ratios behave rather unsystematic (see **Figure 3C**). Whereas the firing rate is normally larger for unit 1 than for unit 2 in case of "ON"-coding, and larger for unit 2 than for unit 1 in case of "OFF" coding, there are a few time-points for the grating condition (first column in **Figure 3C**) where the opposite is true. Therefore, this combination does not speak in favor of a very reliable code. To be able to generalize the potential of "ON" and "OFF" coding it was compared to orientation population decoding. Instead of using three different transitions we only used the second transition, grating preceded by a screen. Instead of dividing pair-wise ratios into "ON" and "OFF" we divided them into "orientation 1" and "orientation 2". Orientation 2 was orthogonal to orientation 1. All possible combinations between

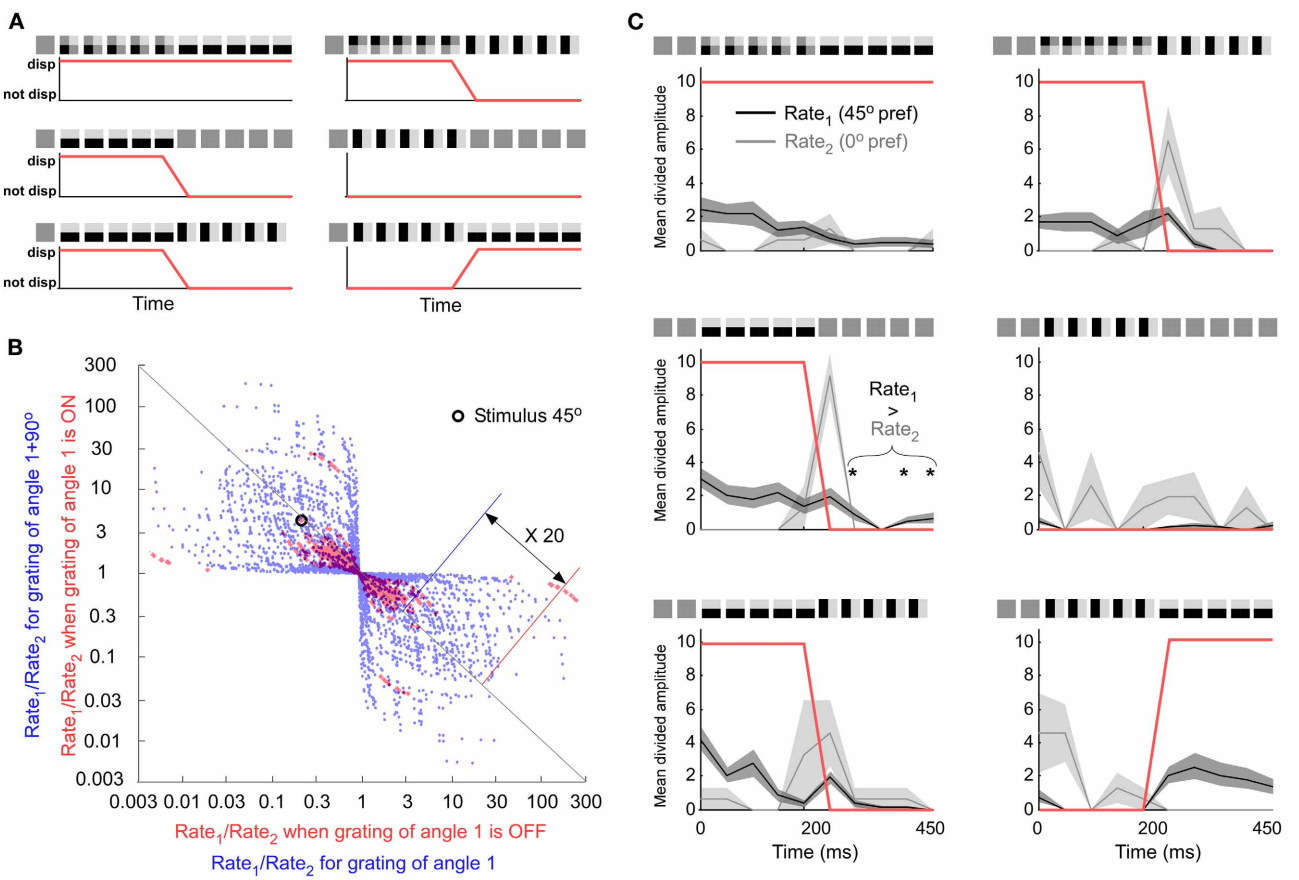

FIGURE 3 | Comparing an orientation population code with an "ON" or "OFF" population code. (A) The three different stimulus transitions (rows). All stimulus transitions were also presented after 90° rotation (second column). Under each transition is the group assignment into ON ("up state") and OFF ("down state") groups (red curve). **(B)** All neuronal pairs and all orientations. The combination discriminating best is encircled. Best neuron combination for the "ON" and "OFF" code. **(C)** The preference of the first and second unit is 45° and 0°, respectively. The horizontal orientation is shown at 45° on the screen. If $Rate_1$ is larger than $Rate_2$ the orientation is on (displayed). This rule works for most cases except second row and first column when the stimulus is off (not displayed).

34 neurons and all 16 orientations were used, i.e., 34 × 34 × 16 combinations (See blue points in **Figure 3B**). The ratios in orientation coding were around 20 times larger than those for "ON" and "OFF" coding, thus leaving the latter coding relatively unreliable.

Rather than having to eliminate the OFF response, downstream neurons might need ON as well as OFF responses. The ON response is needed to detect increased stimulus contrast and the OFF response to detect decreased stimulus contrast. Both are necessary for a complete coverage of the subtractive error calculation (**Figure 4**). That also the ON response is related to error coding, in addition to the OFF response, is further motivated by the significant correlation between the transciency index of the ON response and the strength of error coding (**Figure 5**). To summarize, eliminating the error-like signal from the stimulus code might not be feasible. It is more likely that the brain makes use of the combined code. In the next section we examined if a combined code can be read out by a neuronal model.

CONSEQUENCE OF MIXING STIMULUS AND ERROR CODING

Both the extracellular spiking signal and the voltage-sensitive dye signal showed a combination of error and stimulus coding. Since both code types are used in predictive coding models we studied how such models handle a combination of the codes. We used the dynamic expectation maximization (DEM) model because it is very general (Friston et al., 2008, see Methods). The particular version of the model applied here consists of a feed-forward network with fixed connections that forms simple edge detectors (**Figure 6A**). Its default response to a simple stimulus is depicted in **Figure 6B**. As expected from a prediction model the activity in the prediction unit follows the stimulus. The error is the difference between the stimulus and the activity in the prediction unit. Since the activity of the error units goes to zero between time steps 12 and 20, i.e., the activity for the stimulus (unit 2 with a vertical RF) is not larger than that of the error (unit 1 with a horizontal RF), it means that the stimulus is not represented during this time period. Whereas only the error signal is represented in the model, both error and stimulus signal are represented in the experimental data. Therefore, we forced the error unit to also encode a stimulus signal. This resulted in a suboptimal behavior of the model since the prediction units diverged from the stimulus (**Figure 6C**) and since the free energy deviated from the optimal value (low free energy is optimal) (**Figure 6D**).

Next, we modified the model in a straightforward way such that it could handle the combined stimulus and error coding. To this end, the error unit was replaced with a new type of error unit in which stimulus in the multiplied by a constant was added to the error signal. The constant defines the percentage of stimulus coding in the error unit. As a consequence, the new error unit could combine stimulus and error at the same time as the prediction unit followed the stimulus (**Figure 6E**). The error is extracted by subtracting the stimulus prediction from the new error unit. The modification proposed here is simple and can thus most likely be applied to other predictive coding models.

TIME: WHEN THE ERROR SIGNAL LOOKS LIKE A STIMULUS SIGNAL

In the remaining three sections we investigated how the proportion between stimulus and error depends on stimulus history, stimulus contrast, and stimulus structure in space. To study the influence of stimulus history we ran the stimulus described above either with different durations of the priming image, or with

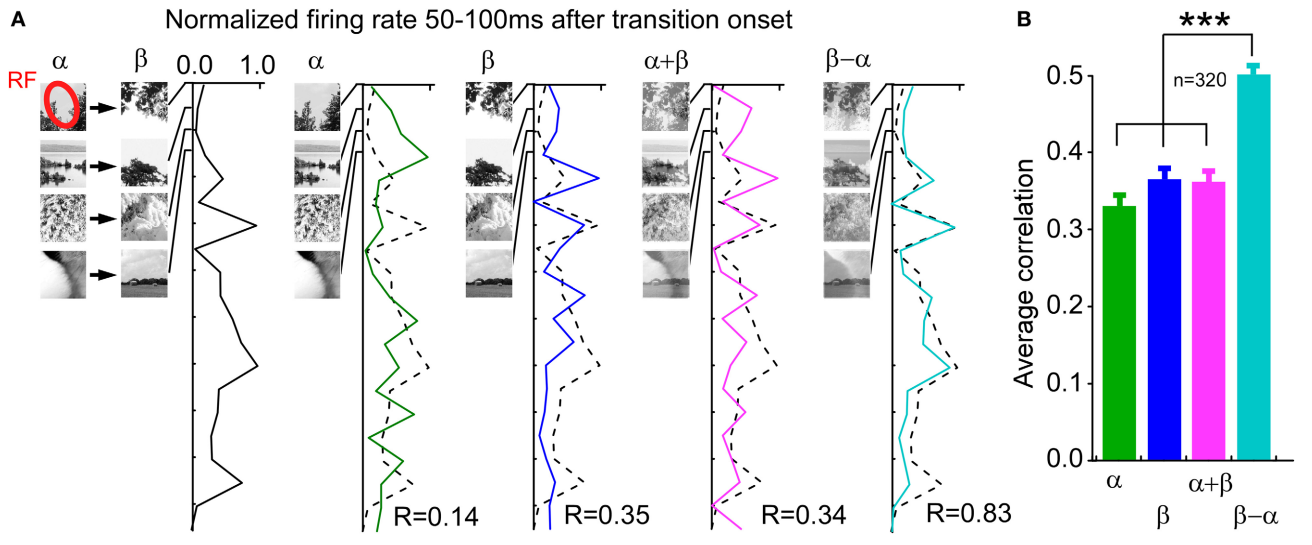

FIGURE 4 | Operator between previous and current image, encoded by the instantaneous firing rate during the time of the ON and OFF response, is best described by a subtraction. (A) Example neuron. Different pairs of natural images where used irrespective of whether the image transition elicited ON or OFF responses. The first column shows the average firing rate between 50 and 100 ms after the transition onset. The remaining columns show the average firing rate between 50 and 100 ms after the test image onset (Observe that each test image was preceded by a blank screen). Note the high correlation in the last column. **(B)** Average correlations across all neurons ($n = 320$).