Aversive Conditioning of Spatial Position Sharpens Neural Population-Level Tuning in Visual Cortex and Selectively Alters Alpha-Band Activity

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Processing capabilities for many low-level visual features are experientially malleable, aiding sighted organisms in adapting to dynamic environments. Explicit instructions to attend a specific visual field location influence retinotopic visuocortical activity, amplifying responses to stimuli appearing at cued spatial positions. It remains undetermined both how such prioritization affects surrounding nonprioritized locations, and if a given retinotopic spatial position can attain enhanced cortical representation through experience rather than instruction. The current report examined visuocortical response changes as human observers ($N = 51$, 19 male) learned, through differential classical conditioning, to associate specific screen locations with aversive outcomes. Using dense-array EEG and pupillometry, we tested the preregistered hypotheses of either sharpening or generalization around an aversively associated location following a single conditioning session. Competing hypotheses tested whether mean response changes would take the form of a Gaussian (generalization) or difference-of-Gaussian (sharpening) distribution over spatial positions, peaking at the viewing location paired with a noxious noise. Occipital 15 Hz steady-state visual evoked potential responses were selectively heightened when viewing aversively paired locations and displayed a non-linear, difference-of-Gaussian profile across neighboring locations, consistent with suppressive surround modulation of non-prioritized positions. Measures of alpha-band (8–12 Hz) activity were differentially altered in anterior versus posterior locations, while pupil diameter exhibited selectively heightened responses to noise-paired locations but did not evince differences across the nonpaired locations. These results indicate that visuocortical spatial representations are sharpened in response to location-specific aversive conditioning, while top-down influences indexed by alpha-power reduction exhibit posterior generalization and anterior sharpening.

Key words: alpha; associative learning; conditioning; EEG; generalization; steady-state visual evoked potential

Significance Statement

It is increasingly recognized that early visual cortex is not a static processor of physical features, but is instead constantly shaped by perceptual experience. It remains unclear, however, to what extent the cortical representation of many fundamental features, including visual field location, is malleable by experience. Using EEG and an aversive classical conditioning paradigm, we observed sharpening of visuocortical responses to stimuli appearing at aversively associated locations along with location-selective facilitation of response systems indexed by pupil diameter and EEG alpha power. These findings highlight the experience-dependent flexibility of retinotopic spatial representations in visual cortex, opening avenues toward novel treatment targets in disorders of attention and spatial cognition.

Introduction

Humans excel at distilling the statistical regularities of experienced events into general rules of behavior. While accurately associating harmful events with valid warning cues is important for survival, incorrectly linking benign situational cues to noxious events can be maladaptive, and may contribute to various psychopathologies (Lissek et al., 2014; Dunsmoor and Paz, 2015). Characterizing the neurophysiological processes of associating sensory cues with aversive outcomes is necessary to advance understanding of this fundamental learning mechanism.

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Mounting evidence (Weinberger, 2004; Chen et al., 2011; Aizenberg and Geffen, 2013; Kass et al., 2013) indicates that neural representations within primary sensory cortices respond to learned contingencies as well as to basic physical features. How the representation of visual field position is affected by such learning, however, remains unknown. Classical (Pavlovian) differential aversive conditioning paradigms, which pair an initially neutral stimulus with an intrinsically aversive outcome, offer a well established method for investigating learning-induced neural response changes. Aversive conditioning studies have, for example, demonstrated that oriented gratings predicting aversive outcomes (associated conditioned stimuli; CS⁺) come to prompt selectively potentiated visuoocortical responses in nonhuman primates (Li et al., 2019) and human observers (Moratti and Keil, 2009; Song and Keil, 2014; McTeague et al., 2015). Moreover, responses to stimuli varying in physical similarity to the CS⁺ along an ordered continuum of a manipulated feature can be used both to characterize the extent of acquired changes in sensory sensitivity (Schechtman et al., 2010; Holt et al., 2014) and to inform as to underlying neural mechanisms (Ringach et al., 2003; Dunsmoor and Paz, 2015; Onat and Büchel, 2015).

Two response distributions widely used to describe neuronal selectivity along a continuum of features are the Gaussian (Onat and Büchel, 2015; Tuominen et al., 2019) and the difference-of-Gaussian (DOG; Ringach et al., 2003; Yeonan-Kim and Bertalmio, 2016). Applied to aversive conditioning, a monotonic Gaussian pattern peaking at the CS⁺ could suggest that responses to test stimuli are actively graded according to their similarity to the CS⁺ (Struyf et al., 2015; Tuominen et al., 2019). Meanwhile, a nonmonotonic DOG gradient, as seen when stimuli most physically similar to the CS⁺ elicit weaker responses than do those that are more distinct, likely implies that a mechanism of suppression is involved (Shapley, 2004; Isaacson and Scanziani, 2011; Angelucci et al., 2017).

In addition to processing biases stemming from the objective characteristics of an observed stimulus, humans invoke numerous higher-order cognitive processes to facilitate stimulus–response association (Rescorla, 1988; Dunsmoor and Murphy, 2015). Changes in neuronal population-level oscillatory activity in the alpha band (~8–14 Hz) have been linked to activation of the attention network (Capotosto et al., 2009; Romei et al., 2010), which exerts strong, top-down effects on sensory processing (for review, see Fiebelkorn and Kastner, 2020). For instance, increased alpha-band activity within sensory cortices is inversely associated with neuronal firing rate (Haegens et al., 2011; Johnston et al., 2019) and overall sensory processing (Foxe and Snyder, 2011).

The present study examined the hypothesis that the representation of spatial position within early visual cortex is malleable via aversive conditioning. Spatial location tuning profiles were obtained with steady-state visual evoked potentials (ssVEPs), which emerge primarily from V1 and higher-order visual cortices (Di Russo et al., 2007). Alpha-band amplitude served as an index of extrastriate, higher-order cortical processes during the associative learning process.

Gaze fixation was monitored with eye tracking to ensure consistent retinotopic mapping. Our preregistered hypothesis was that within retinotopic visual cortex, neuronal population-level tuning to a threat location would prompt the suppression of location representations proximal to the CS⁺, resulting in a difference-of-Gaussian response gradient. Meanwhile, decreases in alpha-band amplitude were

Figure 1. Gaussian and difference-of-Gaussian gradients. Gray dotted lines depict each pattern plotted on a continuous horizontal axis. Black lines and black filled circles illustrate the competing hypotheses as tested in the present study with five ordered categorical levels of spatial position. Note that this example fits the hypothesized signal change trend for ssVEP power, these gradients were predicted to be inverted for alpha-power change (i.e., maximum alpha decrease at the CS⁺).

expected to show a Gaussian profile peaking at the threat-associated location, consistent with less stimulus-specific attentive processing of the threat cue. While not part of our preregistered hypotheses, pupillary responses are presented as an additional measure of learning-induced physiological change.

Materials and Methods

Testing the primary signals of interest (alpha-power and ssVEP amplitude) against our hypotheses generally proceeded as follows: (1) transform signals from time domain to frequency domain in sensor space; (2) source estimation; (3) test the fit-of-Gaussian and DOG patterns (Fig. 1) of experience-dependent signal change across the entire estimated source volume; and (4) test the effect of conditioning as a function of spatial distance from the CS⁺ for source locations exhibiting Gaussian or DOG trends.

Participants

Fifty-three students at the University of Florida with normal or corrected-to-normal vision participated in the study for course credit. All participants reported no personal or family history of epilepsy or photic seizures. One participant chose to discontinue testing because of discomfort with the auditory unconditioned stimulus (US), and data from one participant were excluded because of a defective EEG sensor net, leaving a final sample of 51 participants (19 males; mean age = 19.49 years; SD for age = 1.22). All participants provided informed consent in accordance with the Declaration of Helsinki and the institutional review board of the University of Florida.

Figure 2. Experimental paradigm. A sequence of two stimulus presentations is shown for habituation (no US noise) and acquisition (90 dB white noise blast at one location) trial blocks.

Stimuli

Visual stimuli consisted of high contrast Gabor patches (1.18 cycles/°) presented against a black background (0.01 cd/m²). Gabor patches subtended 7.07° of visual angle and had a maximum luminance of 96 cd/m². Gabors were presented individually at one of five equally spaced locations, having their inner border at 2.12° of eccentricity from a central fixation dot (Fig. 2). The Gabor appearing at screen location one (right side of the screen, vertically centered) was centered at the horizontal meridian, with each of the five presentation locations appearing along the circumference of a circle with an inner angle of 72° (360/5), resulting in an arc length of $8.86 \pi/5$ (~278.3 mm) or 13.23° of visual angle separating the centers of adjacent stimulus locations. Compared with centrally presented stimuli, these stimulus locations are expected to engage deeper regions within the calcarine fissure (Aine et al., 1996). The scalp voltage projection out of these calcarine regions to the scalp tends to vary greatly across stimulus locations and across individual observers. Signal source-space estimation (detailed below) was used as a means of reducing this substantial individual variability in scalp voltage topography by representing the more narrowly defined sources in the occipital lobe. A small white fixation dot remained on screen at all times, except during the assessment of participants' awareness of the US/CS⁺ pairing contingency during acquisition trials (see below). Visual stimuli were presented on a calibrated LCD display (Display ++, Cambridge Research Systems) running at 120 Hz connected to a PC running Linux Ubuntu 18.04. Stimuli were created in MATLAB (MathWorks) with the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007). Gabor patches were flickered at a rate of 15 times/s (hertz) to drive cortical oscillatory responses at the desired steady-state temporal frequency. The US was a 90 dB SPL white noise delivered binaurally through two small computer speakers located behind participants' seated location.

Procedure

Participants were seated in a comfortable chair with their heads placed on a chin rest in a dimly lit (~60 cd/m²) room. Viewing distance to the display monitor was adjusted to 120 cm, and distance to the eye-tracker lens was adjusted to 60 cm. Participants were instructed to limit blinking to the intertrial interval and to maintain gaze at the central fixation dot throughout testing. The spatial position at which Gabor patches appeared in each trial was quasi-random, such that within every grouping of 15 trials a Gabor would be shown at each of the five spatial positions exactly three times.

To assess awareness of the US/CS⁺ association, after every 15 trials (three US/CS⁺ pairings) in the acquisition block participants indicated the screen location where they expected the Gabor to be located when the US noise was played. Participants identified this spatial location by moving (using the mouse) a Gabor-patch indicator into one of five

predetermined screen locations corresponding to the screen coordinates at which Gabors appeared during trials. Spatial position error thus ranged from a minimum of 0 (correctly identified CS⁺ location) to a maximum of 2 (two locations clockwise or counterclockwise from the actual CS⁺ location).

Data recording and analysis

Eye tracker

Pupil and gaze were recorded continuously at 500 Hz with an EyeLink 1000 Plus (SR Research) eye tracker using a 16 mm lens. Pupil diameter was approximated via ellipse mode, and the illumination level of the infrared signal was set to 100%. To calibrate and validate the eye tracker, participants fixated on a nine-point grid, which showed a white circle (5° visual angle) at nine locations against a black background. Pupil segments were discarded if the diameter was not between 0.01 and 5 mm (~400–16 000 in default manufacturer arbitrary units). Offline, pupil trials were rejected if artifacts such as blinks obscured

>200 sample points in an epoch, or if they contained any eye movements. Brief (<200 sample points) disruptions in the data were interpolated using piecewise cubic interpolation (for information on the algorithm used, see <http://dx.doi.org/10.6084/m9.figshare.688002>). To evaluate compliance with fixation instructions, we calculated the proportion of time during which the eye gaze was outside a 2° area centered around the fixation cross. This was done separately by experimental condition, only for the time period where experimental stimuli were on the screen. A simple ratio of time outside fixation divided by the presentation time was used.

EEG recording

EEG was recorded continuously from a 128-channel Electrical Geodesics (EGI) system at a sampling rate of 500 Hz, with the vertex electrode (Cz) as recording reference. Data recording was constrained by Butterworth filters both online (low-pass filter, 3 dB point at 170 Hz; high-pass filter, 3 dB point at 0.05 Hz) and offline (low-pass filter, 40 Hz, 18th order, 3 dB point at 45 Hz; high-pass filter, 4 Hz, second order, 3 dB point at 18 Hz). After arithmetically transforming the data to the average reference, artifact rejection was performed according to the SCADS (statistical correction of artifacts in dense array studies) procedure described in the study by Junghöfer et al. (2000). Electrode impedances were kept at <50 kΩ, as recommended for EGI high-impedance amplifiers.

The total number of retained trials was similar for habituation (mean = 22.65) and acquisition (mean = 22.82) trial blocks, as was the number of retained trials as a function of distance from the CS⁺: a Bayesian repeated-measures ANOVA performed in JASP (JASP Team, 2020) revealed that effects of conditioning block, position, and block-by-position interaction all had Bayes factor favoring the alternative hypothesis (BF₁₀) values <0.15. In tangible terms, the largest mean difference in retained trials was between the CS⁺ position in acquisition (mean = 23.67) and the farthest-from-CS-position in habituation (mean = 22.44), which was judged unlikely to impact statistical comparisons of the dependent variables.

Spectral analysis of EEG signals. Following data preprocessing, EEG data were transformed from the time to the frequency domain using functions provided in the FieldTrip toolbox (Oostenveld et al., 2011) for MATLAB, generally following steps detailed in the study by Popov et al. (2018). Time ranges (see below) were determined based on a body of previous work (Wieser et al., 2016; Friedl and Keil, 2020) showing that alpha-power changes in response to conditioned stimuli occur early and extend over 1–2 s, whereas ssVEP differences occur predominantly in the second before US onset.

Steady-state visual-evoked potentials. A time-locked, full-trial post-stimulus onset (1800 ms) average of 15 Hz activity for each participant, across all artifact-free trials in each condition, was first obtained with the

Figure 3. Pre-source estimation ssVEP and alpha frequency spectra. The grand mean of sensor space of 15 Hz ssVEP (top) and 8–12 Hz alpha (bottom) amplitude is shown for one representative central occipital sensor location (Oz). Steady-state responses were tightly confined to the driven frequency.

function *ft_timelockanalysis*. Trial averaging was only performed before spectral decomposition for ssVEPs, as the phase consistency of driven oscillations across trials prevents potentially offsetting effects when averaging (Popov et al., 2018). Next, for each participant and at each of the five screen locations in habituation and acquisition trial blocks, power spectra were extracted from the trial-averaged data by means of a fast Fourier transformation (FFT) with the function *ft_freqanalysis*. Using default options, *ft_freqanalysis* applies a multitaper (Mittra and Pesaran, 1999) window based on discrete prolate spheroidal sequences (DPSSs) before Fourier analysis over the entire length of data. The spectral smoothing value for the multitaper was set to 0.55 Hz, equal to the frequency resolution in the present application such that no additional frequency smoothing was performed. Frequencies between 7.2 and 22.8 Hz were extracted, and the grand average (over all participants, spatial locations, and trial blocks) power spectrum at one representative sensor (Oz) is shown in Figure 3.

Alpha band. Power spectra were extracted from a 500 ms segment (500–1000 ms, post-stimulus onset) of individual trials for each participant at each of the five spatial locations of stimulus presentation in habituation and acquisition trial blocks (number of retained trials $\times$ 51 $\times$ 10) by means of an FFT with the function *ft_freqanalysis*. The multitaper window based on DPSSs applied before Fourier analysis over the entire length of data used a spectral smoothing value of 2 Hz, equal to the alpha-band frequency resolution in the present analysis. Frequencies between 4 and 26 Hz were extracted, and the grand average (over all participants, spatial locations, and trial blocks) power spectrum at one representative sensor (Oz) is shown in Figure 3.

Source localization of EEG signals. Source estimation of the ssVEP and alpha-band signals was performed using a boundary element model (BEM) in conjunction with the eLORETA (exact low resolution brain electromagnetic tomography) algorithm proposed by Pascual-Marqui (2007) and Pascual-Marqui et al. (2011) using functions from the FieldTrip toolbox (Oostenveld et al., 2011), as follows: first, a BEM

Figure 4. Grand mean source-localized topographies. Top, Steady-state 15 Hz topographical activity of position mean, source-localized responses to Gabor stimuli appearing at each depicted location. Bottom, Alpha-band (8–12 Hz) topographical activity of source-localized responses to Gabor stimuli averaged over all viewing locations.

model was constructed from an existing standard structural MR image representative of the current population, made up of an average of 12 matched brains of University of Florida undergraduate students. The model was computed with the *dipoli* option in FieldTrip (using the function *ft_prepare_headmodel*) and included brain, skull, and scalp boundaries, assuming standard conductivity values of 0.33, 0.0041, and 0.33 for these respective tissue types, represented by 3000, 2000, and 1000 vertices, respectively. A source model with 3528 sources was then constructed based on the structural MR image and the sources confined to the gray matter. A lead field was then computed linking the source model and head model to the 129 electrode locations. The inverse solution was then computed for each spectrum using the eLORETA algorithm with a lambda of 3, estimated based on the signal-to-noise ratios of both alpha and ssVEP signals. Source estimation was performed on spectral representations of alpha-band power and ssVEP amplitude, as described above. Results from eLORETA estimation are returned in unitless values, not current density (Pascual-Marqui et al., 2011), standardized such that the expected variance is unity (i.e., 1; Jatoi et al., 2014) and typically labeled “Z.”

Grand-mean source-estimated 15 Hz ssVEP activity for each spatial position of stimulus presentation is shown at the top of Figure 4, while the nonretinotopic alpha-power response is shown averaged over all spatial positions at the bottom of Figure 4. Note that the average activity values depicted in Figure 4 are for illustrative purposes only, as all numerical operations and statistical comparisons herein use each individual’s source-estimated signal activity for each stimulus position in habituation and acquisition trial blocks.

Statistical analysis

All statistical inference was performed with BFs (Jeffreys, 1961; Wetzels et al., 2011) using JZS (Jeffreys–Zellner–Siow) priors (Rouder et al., 2009) and scale factors of 0.707 for two-group comparisons. We used Bayesian hypothesis testing given the problems of using *p* values specifically (Edwards et al., 1963; Wagenmakers, 2007) and dichotomous decision criteria generally (McShane et al., 2019) to summarize research results.

Questions of when, whether, and how to adjust Bayesian statistical results for multiple comparisons are currently unsettled (Berry and Hochberg, 1999; Gelman and Tuerlinckx, 2000; Dienes, 2008, 2014; Gelman et al., 2012; Johnson, 2013). In addition to Bayesian hypothesis testing, however, several aspects of the present study guard against results owing simply to having performed many comparisons. First and most importantly, specific hypotheses as to the direction and trend of

the signal change for alpha-band and ssVEP activity were preregistered (https://osf.io/h7tqa/?view_only=eee3c81e66854d1bb1723ea25cd07f5d), eliminating concern that many additional hypotheses were tested but not reported. Second, the contrast analyses performed to test for the hypothesized trends in the data (detailed below) are focused, single-degree of freedom tests free from the multiple comparisons inherent in, for instance, factorial ANOVA (Luck and Gaspelin, 2017). Third, to quantify the danger that strong evidence in favor of our alternative hypotheses could arise by chance from testing 3528 estimated cortical sources, permutation tests for each hypothesis were performed (10,000 iterations, randomly shuffling the order of conditions 3528 times within participants). Permutation tests have been used extensively to control type 1 errors when analyzing neuroimaging data from a frequentist statistical perspective (Maris and Oostenveld, 2007; Winkler et al., 2014) and conceptually tie directly to the Bayesian assumption of exchangeability (O'Neill, 2009). The 95th percentiles of the empirical distributions of Bayes factor values arising from these permutation tests were far below (ssVEP, 0.54; alpha, 1.079) the minimum Bayes factor of 3:1 in favor of the alternative hypothesis that we adopt in displaying or discussing statistical comparisons. Finally, the reported results section distinguishes between our main preregistered comparisons and those that were more exploratory or were not spelled out explicitly before data analysis: the latter should, as always, be regarded as potentially interesting but pending corroborating evidence via replication.

As the hypotheses of interest concerned the effect of relative distance from an aversively paired spatial location, not of differential responses at these locations themselves (due, for instance, to differences in the volume of cortical tissue sensitive to different regions of the visual field), all EEG analyses rotated the signal data from viewing each spatial position such that the five spatial positions were transformed into five bins representing relative distance from the conditioned spatial location.

For the pupil data time series, the two spatial distance bins either one or two position steps away from the CS⁺ location were merged, with all subsequent analyses performed on the resulting three bins of data (CS⁺, near, far). A JZS Bayes factor (Rouder et al., 2009) was computed for each location condition at each time point to quantify the likelihood that these signals differed in acquisition compared with habituation trials.

Model comparison

As habituation trials in differential conditioning paradigms provide a subject-specific nonassociative control condition (Schneiderman, 1972), we first computed change scores (acquisition minus habituation) for each signal, following the method of meaningful differences (Rosenthal, 1987). Data submitted to contrast analysis for each signal had dimensions of 1 (change score) by 5 (spatial position). Signed *F* contrasts (Rosenthal et al., 2000; Rosnow et al., 2000), weighting each spatial position to account for the hypothesized trend (Gaussian or difference-of-Gaussian) of the change in each signal following aversive conditioning, were then calculated for each source. At each source location, *F* contrast values quantified how closely the signal change across spatial positions followed each of the hypothesized trends at that location. Change scores for each spatial position were multiplied by their corresponding contrast weights, then summed over positions to arrive at an overall contrast score. The contrast weights chosen sum to zero, ensuring that an overall contrast score of zero corresponds to an absence of the tested trend (Wiens and Nilsson, 2017) and large positive values indicate that the change scores are well described by the tested contrast. The square roots of these *F* values (Rosenthal et al., 2000, p. 41) were then converted to JZS Bayes factors, as detailed by Rouder et al. (2009).

Our hypotheses regarding the specific order of mean change scores across spatial positions would not have been well addressed by traditional factorial ANOVA (Rosnow and Rosenthal, 1995; Abelson and Prentice, 1997) as ANOVA captures any difference, regardless of order, among mean values when there are multiple degrees of freedom in the numerator (Wiens and Nilsson, 2017). In comparison, contrasts always have a single degree of freedom in the numerator, providing a specific test of the hypothesis (Rosenthal et al., 2000; Wiens and Nilsson, 2017) and allowing for a direct assessment of the specific numerical ordering of mean values across experimental conditions (Rosnow and Rosenthal,

Figure 5. Grand mean source-estimated activity change. Overall ssVEP (top) and alpha (bottom) acquisition minus habituation block differences are shown as a function of distance from the CS⁺. Shaded error bars indicate the across-subject SEM.

1989). A traditional two-group *t* test, for instance, is implicitly a contrast with the two compared groups receiving contrast weights of positive and negative one. In the present context, mean signal change values for each participant at each spatial location were separately multiplied by the contrast weights corresponding to Gaussian and difference-of-Gaussian mean patterns and summed (i.e., the dot or inner product was computed), quantifying how closely each signal in each participant resembled response generalization (Gaussian) and/or response sharpening (DOG). For direct model comparisons, the transitive property of Bayes factors allows the ratio of BFs in support of Gaussian and DOG profiles to quantify the evidential support favoring one trend over the other.

Individual-level changes in ssVEP and alpha-band activity were tested for correspondence with Gaussian and DOG trends by taking, for each source value, the dot (inner) product of signal change and the weight values for each contrast.

Data availability

Code and preprocessed BEM-localized (whole-trial averaged for alpha-band activity) data for performing the main model comparisons can be freely obtained at this project's OSF page (DOI: [10.17605/OSF.IO/7BMN6](https://doi.org/10.17605/OSF.IO/7BMN6)). The custom MATLAB script for performing contrast analysis at each source location is also available on the OSF page, and Burkhardt and Titz (2019) provide similar functionality in the *cofad* package for R. Code for performing permutation tests in both MATLAB and R is given in the study by Smith and Batchelder (2008).

Results

Confirmatory results

Overall change as a function of distance from the CS⁺ viewing location, averaged over all source locations, is shown for ssVEP and alpha-band signals in Figure 5. Averaging the two locations adjacent to the CS⁺ and the two locations most distant from the CS⁺, and considering only sources showing at least moderate

Figure 6. Source-space comparison of competing models. Difference-of-Gaussian (left) and Gaussian (right) models of source-localized signal change following conditioning are shown for steady-state (top) and alpha-band (bottom) signals.

correspondence (contrast BF_{10} , >3 ; Fig. 6) with the trends evident by visual inspection of these overall averages (DOG for ssVEPs, Gaussian for alpha, respectively), Cohen's d was calculated as a standardized measure of effect size. Effect sizes here quantify the change in each signal from habituation to acquisition at each of the three stimulus distances (far, near, CS^+) tested. Cohen's d for ssVEP power change was 0.20 for far stimuli, -0.09 for near stimuli, and 0.32 for the CS^+ location. Cohen's d for alpha-band power change was 0.38 for far stimuli, 0.25 for near stimuli, and -0.18 for the CS^+ location.

ssVEP power

There were 114 source locations (Fig. 6, top) where the ssVEP power change DOG contrast yielded BF_{10} values >3 . The average BF_{10} value supporting a DOG trend across these 114 locations was 6.57 ($SD = 3.87$; minimum/maximum, 3.01–27.69). These same 114 source locations had 0 sources at which the Gaussian contrast reached a BF_{10} value of 3 (mean = 0.16, $SD = 0.01$; minimum/maximum, 0.10–0.20). At these source locations, the DOG contrast is favored over the Gaussian by an average (mean) factor of 41.19 ($SD = 25.34$; minimum/

maximum, 15.08–181.93). Thus, there is strong evidence (Jeffreys, 1961) both that activity within regions consistent with retinotopic stimulus processing is altered in a manner well described by the DOG model, and that the response-sharpening (DOG) model describes the change in ssVEP response following conditioning better than does a generalization (Gaussian) pattern.

Alpha power

There were 708 source locations (Fig. 6, bottom) where the alpha-band power change Gaussian contrast yielded BF_{10} values >3 . The average BF_{10} value in support of a Gaussian trend across these 708 parietal-occipital locations was 17.77 ($SD = 18.23$; minimum/maximum, 3.01–151.98). These source locations had 0 sources at which the DOG contrast reached a BF_{10} value of 3 (mean = 0.26, $SD = 0.17$; minimum/maximum, 0.15–2.22). At these source locations, the Gaussian contrast is favored over the DOG by an average (mean) factor of 85.99 ($SD = 104.9$; minimum/maximum, 1.36–919.67).

There were 183 anterior source locations (Fig. 6, bottom) where the alpha-band power change DOG contrast produced BF_{10} values >3 . The average BF_{10} value across these locations was 9.51 ($SD = 10.21$; minimum/maximum, 3.01–64.34). These source locations had 0 sources at which the Gaussian contrast reached a BF_{10} value of 3 (mean = 0.35, $SD = 0.31$; minimum/maximum, 0.31–2.3). At these more anterior locations, the DOG contrast is favored over the Gaussian by a mean factor of 37.15 ($SD = 41.18$; minimum/maximum, 1.39–268.54).

Both contrast patterns of alpha-power change were strongly supported at different, nonoverlapping cortical source locations.

Exploratory results

Awareness of CS^+ /US association

Over the second half of acquisition trials, 43 participants made no errors in identifying the spatial location serving as a cue for the US, while an additional 3 participants erred only on a single reporting trial (each by only one spatial position). Overall, $\sim 90\%$ of participants (46 of 51) consistently identified the spatial relationship between the US and the CS^+ correctly throughout the second half of the acquisition trial block, indicating that results reported here are unlikely to have been impacted by ambiguity regarding the associative contingency. The time course of mean and individual participant expectancy reports across acquisition trials is shown in Figure 7 (top). The five participants who made more than one spatial position error over the second half of acquisition trials were considered “unaware” and are depicted as blue triangles in Figure 7. As has been previously observed (Moratti and Keil, 2005, 2009), awareness of the contingency between the CS^+ and the US does not appear to systematically influence the response patterns of either EEG signal.

Individual subject EEG signal trends

Individual dot product values, indicating the degree of correspondence between observed signal change and the hypothesized trends at sources showing strong correspondence in the overall average comparison, is shown in the middle and bottom portions of Figure 7. Strong correspondence was defined as sources with BF_{10} contrast values equal to or greater than the average of all values for each contrast shown in the overall source model comparison (Fig. 6; i.e., all sources with BF_{10} values >3). The proportions of individual participants exhibiting each signal change trend to some degree (dot product > 0) were as follows: 34 of 51 for the ssVEP DOG trend; 32 of 51 for the alpha-band Gaussian

Figure 7. Conditioning contingency awareness and individual contrast fits. Top, Awareness of the association between the CS⁺ location and the US noise is shown for 46 aware individuals (black dots) and 5 unaware individuals (blue triangle) and for the average over participants (orange line) during the acquisition trial block. The first assessment ($x=0$) was performance at the beginning of the acquisition trial block before any US presentations (i.e., participants were randomly guessing the position at which they would hear the US). Random jitter was added to individual responses for purposes of illustration. Middle, bottom, Individual subject correspondence with contrast patterns as quantified by the signal change-by-contrast weight dot product. Dotted lines indicate the permutation estimated 95% dot product cutoff values for randomly shuffled condition weights over source locations. Blue triangles depict participants who remained unaware of the location of the US throughout the acquisition block. Inset source model images show the regions used for calculating the dot product values.

trend; and 35 of 51 for the alpha-band DOG trend. There was little correlation between the rank ordering of individual dot products for any pairwise combination of trends revealed in the averaged data reported above (Spearman's ρ values: ssVEP DOG–alpha Gaussian = 0.24; ssVEP DOG–alpha DOG = 0.25; alpha Gaussian–alpha DOG = −0.11).

Early versus late acquisition

Overall change as a function of distance from the CS⁺ viewing location, averaged over all source locations with DOG (ssVEP)

or Gaussian (alpha) contrast BF₁₀ values >3, is shown Figure 8. While the alpha-power Gaussian contrast values at these source locations consistently exhibited a generalization trend that was more pronounced in the early phase (mean BF₁₀ = 440.19 over the 642 source locations where the overall Gaussian contrast exceeded a BF₁₀ value of 3) compared with the late phase (mean BF₁₀ = 13.25, 471 source locations) of the acquisition block, the ssVEP sharpening response was evident only for the first half (mean BF₁₀ = 7.62 over all 114 source locations where the overall Gaussian contrast exceeded a BF₁₀ value of 3) of acquisition trials (second half had 0 sources where the DOG contrast exceeded a BF₁₀ value of 3, with a maximum value of 0.71). Steady-state signal change values for the second half of acquisition did not show DOG, Gaussian, or inverted-Gaussian patterns (all BF₁₀, <3). The anterior alpha sharpening trend (data not shown) seen in the overall average comparison was also evident in early acquisition (mean BF₁₀ = 5.18 over the 79 of the 183 sources where the overall DOG contrast exceeded a BF₁₀ value of 3), and nearly nonexistent in late acquisition (mean BF₁₀ = 3.19, three sources).

Pupil and gaze

The proportion of deviations from fixation did not vary by spatial position during habituation trials (Bayes factor in favor of the null hypothesis; BF₀₁ = 96.48), implying that no stimulus presentation position differentially impacted participants' ability to maintain fixation. More importantly, the change in proportion of fixation deviations from habituation to acquisition did not vary by aligned location condition (i.e., it did not differ for the CS⁺ compared with other locations; BF₀₁ = 91.9), ruling out the possibility that heightened neural responses to CS⁺ locations were caused by preferentially foveating them. As the time course of pupil activity indicates a model of binary CS selectivity (CS⁺ > all non-CS), we tested the change in pupil for far, near, and CS⁺ locations with contrast weights of −0.5, −0.5, and 1, respectively, to quantify the strength and temporal evolution this pattern. Results of this *post hoc* contrast analysis are shown at the bottom of Figure 9.

Discussion

The present study examined experience-dependent changes in visuospatial representation wrought by a brief (~30 min) aversive conditioning regimen in which one on-screen location was

paired with an aversive noise stimulus while leaving four equidistant locations unassociated.

Comparing pupil diameter, alpha-power reduction, and visuocortical ssVEP enhancement between acquisition and habituation, we found evidence for experience-related changes in all measures.

Consistent with sharpened tuning of visuospatial representations in visual cortex, ssVEPs followed a difference-of-Gaussian pattern at occipital source locations, with reduced cortical responsiveness to proximal unpaired screen locations and enhanced responses to the CS⁺ location. This pattern of experience-driven response change supports the hypothesis that retinotopic visual cortex possesses mechanisms for enhancing the spatial contrast between representations of threat-associated versus non-threat-associated locations. Furthermore, sharpened visuocortical responses to aversively paired screen locations developed within minutes of exposure to the noxious noise stimulus, transitioning to generally elevated ssVEP responses undifferentiated by proximity to the CS⁺ in the second half of acquisition trials. The DOG pattern of visuocortical response change across the range of tested spatial positions observed here closely mirrors responses to oriented gratings (McTeague et al., 2015) and faces (Stegmann et al., 2020) parametrically varied in similarity to conditioned threat cues. The finding that altered tuning of the ssVEP emerges whether the low-level visual feature predicting an upcoming aversive event is a particular orientation or a specific visual field location points to response sharpening as a common mechanism operating at this early stage of the associative learning process. As in the present report, potentiated steady-state responses to threat cues have been observed following few associations with the US (Moratti and Keil, 2005; Moratti et al., 2006; McTeague et al., 2015). Together, these results suggest that suppressive interactions as a means of sharpening macroscopic representations of threat locations represent a rapidly implemented and quickly habituating response.

Narrowly tuned response profiles, as observed in ssVEPs here, diverge from what would be expected under generalization models based purely on perceptual discrimination (Lissek, 2012; Lissek et al., 2014). Following a perceptual discrimination model, response strength should decrease monotonically as stimuli become more distinct from the CS⁺ (Onat and Büchel, 2015). Onat and Büchel (2015) instead cite the active integration of “hypersharp” responses within several brain regions including the hippocampus and anterior insula with more broadly tuned responses from other regions as responsible for producing the stereotypical Gaussian-shaped generalization gradient. While Onat and Büchel (2015) assert that generalization is not solely driven by perceptual ability, Tuominen et al. (2019) found that measures of skin conductance, expectancy ratings, and fMRI

Figure 8. Early and late acquisition activity change. First half (blue, solid line) and second half (orange, dotted line) signal change from habituation for ssVEP (top) and alpha (bottom) as a function of distance from the CS⁺. Shaded error bars indicate the across-subject SEM. The right-hand side of the figure shows the source-estimated fits of depicted competing models of signal change for each half of acquisition.

BOLD responses in anterior insula and superior frontal gyrus only showed signs of generalization when discrimination performance was low (i.e., near individual perceptual thresholds). Notably, studies of stimulus discrimination and generalization, including those cited above, generally neglect primary sensory regions, focusing exclusively on regions higher in the cortical processing hierarchy. The present work suggests early visual cortex as an additional region capable of hypersharply responding, which may contribute to behaviorally assessed perceptual discrimination performance.

Within the visual system, suppression mechanisms are thought to contribute to transforming broadly tuned excitatory outputs from lateral geniculate nucleus relay cells into the more narrowly feature-selective responses observed in visual cortex (Shapley et al., 2007; Isaacson and Scanziani, 2011; Angelucci et al., 2017; but see Priebe and Ferster, 2008). Compared with visual perception, the spatial resolution of focused visual attention is relatively poor (He et al., 1996; Intriligator and Cavanagh, 2001), implying that cortical responses indexing visual attention are likely to be broader than those originating from early visual cortex. Previous conditioning studies manipulating features other than visual field location (McTeague et al., 2015; Friedl and Keil, 2020), along with the present results, provide evidence that threat-associated cortical response changes do manifest differently for alpha-band and ssVEP signals.

Figure 9. Pupil response time course. Pupil response as a function of spatial distance from an aversively paired location is shown as a percentage of mean manufacturer (SR Research)-reported arbitrary units (1000–100 ms pre-stimulus onset) in habituation (top, left) and acquisition (top, right) trial blocks. Bottom, left, Percentage change (acquisition minus habituation) and across-subject SEM in pupil activity across trial blocks. Bottom, right, Time course of support for a binary model (depicted in the inset) of CS selectivity in relative pupil dilation.

Aversively conditioning one visual location resulted in cortical source-dependent alpha-power reduction, linearly generalizing across viewing locations at occipital-parietal locations and sharpening at more anterior regions. Generalization in the alpha band was expected, given that behavioral response gradients in both humans and animals (for review, see Ghirlanda and Enquist, 2003) as well as attention-linked parietal EEG response gradients (McTeague et al., 2015) are well described by a Gaussian function. The right hemisphere bias in alpha reduction evident in Figure 6 is consistent with increased activity in visuospatial attention networks for left relative to right visual field stimulation (Siman-Tov et al., 2007), which is thought to reflect the primary role of right hemisphere posterior parietal cortex in deploying spatial attention (Posner and Petersen, 1990; for review, see Bartolomeo and Malkinson, 2019). While the anterior sharpening of alpha-band responses was unexpected, frontoparietal regions generally corresponding to those displaying a DOG pattern in the present report are preferentially activated by (Fullana et al., 2016) and have specifically been implicated in the modulation of visuocortical responses to (Petro et al., 2017) aversively conditioned stimuli.

Phasic reduction in alpha-band power following presentation of a visual stimulus has been linked to numerous cognitive functions, most notably arousal (Lang et al., 1997; Mather and Sutherland, 2011) in addition to attention. While an overall elevation of general arousal levels is expected during conditioning trials (Lissek et al., 2008), the selectively graded alpha-band decrease, peaking at the CS⁺ viewing location, indicates that this

effect is more consistent with focused enhancement brought about through attentive processing (Posner and Petersen, 1990). The seminal work of Posner (1980) established that covert, spatially directed attention enhances processing at attended locations. Such shifts are typically prompted by explicit attention cues, conveyed through verbal or on-screen instructions (Sprague and Serences, 2013; Buschman and Kastner, 2015). Here, we show that an experientially acquired spatial association with an unpleasant stimulus prompts a similar facilitation of neural mass activity for stimuli presented at a conditioned location. Comparing parietal alpha-band generalization gradients from the first half to the second half of acquisition trials, the magnitude of decrement in alpha power was more pronounced in early trials but retained a Gaussian distribution across stimulus locations throughout the experimental session. Tenets of several formal models of classical conditioning can readily account for the reduced magnitude of alpha responding over trials, as in the model by Rescorla and Wagner (1972), by positing that as the CS⁺ becomes a better predictor of the US (i.e., there is less “surprise”), there is correspondingly less error correction evident in response to the CS⁺, and in the model by Pearce and Hall (1980), by ascribing less attention to a CS⁺ as it comes to more accurately predict a US. In contrast, the model of Mackintosh (1975), in which attention to a CS⁺ increases along with its

ability to predict a US, is contraindicated by the present results.

One caveat regarding the pattern of alpha-band responses reported here is that the activity of a cortically diffuse signal such as alpha is likely to vary according to either (1) the assumptions made by the source-localization method used or (2) the electrodes considered if analyzing voltage recorded at the scalp. For instance, a nongraded, all-or-none pattern of alpha-power modulation following aversive conditioning emerged in a previous study where Gabor patches varied along a continuum of spatial frequencies (Friedl and Keil, 2020). There, using sensor clusters defined by activity at the group level may have resulted in decreased sensitivity to individual differences compared with the present approach of using each participant’s individual source-estimated activity.

Like reduced alpha-band responses, pupil dilation has long been associated with arousal level (Loewenfeld, 1958), but has also been linked to the employment of covert attention (Naber et al., 2013; Olmos-Solis et al., 2018; for review, see Mathôt, 2018). Pupil activity change, an index of autonomic engagement with the stimulus, was tightly confined to the CS⁺ condition, with nearby and more spatially distant, nonpaired viewing locations displaying undifferentiated activity. Unlike the graded responses of ssVEPs and alpha, pupil diameter here appears to index a binary discrimination between threat and nonthreat cues.

The significance of sharply tuned neural response profiles for perceptual discrimination, as well as the relationship between response gradients measured at the behavioral and neural level,

have strong translational and clinical implications (Dunsmoor and Paz, 2015) and remain pressing questions for future study. An additional open question is whether neural sharpening results exclusively from altered sensitivity in feature-specific neuronal populations (Summerfield and Egner, 2016; Liu, 2019), or whether a learned categorical distinction (threat vs safety) also contributes (Dunsmoor et al., 2014).

The generally well defined structural and functional properties of the visual cortex make it an appealing model system for investigating fundamental brain processes (Creutzfeldt, 1977; Priebe and Ferster, 2008) such as associative learning. The present work evaluated neural population-level response gradients to determine the extent to which conditioning an on-screen stimulus location influences visuocortical responses to objects appearing at surrounding visual field locations. Illustrating the dissociable signatures of early visuocortical (ssVEP) and alpha-band responses to spatially contingent aversive events highlights two mechanisms used by the visual system in adapting to dynamic environments.

References

- Abelson RP, Prentice DA (1997) Contrast tests of interaction hypothesis. *Psychol Methods* 2:315–328.
- Aine CJ, Supek S, George JS, Ranken D, Lewine J, Sanders J, Best E, Tiee W, Flynn ER, Wood CC (1996) Retinotopic organization of human visual cortex: departures from the classical model. *Cereb Cortex* 6:354–361.
- Aizenberg M, Geffen MN (2013) Bidirectional effects of aversive learning on perceptual acuity are mediated by the sensory cortex. *Nat Neurosci* 16:994–996.
- Angelucci A, Bijanzadeh M, Nurminen L, Federer F, Merlin S, Bressloff PC (2017) Circuits and mechanisms for surround modulation in visual cortex. *Annu Rev Neurosci* 40:425–451.
- Bartolomeo P, Malkinson TS (2019) Hemispheric lateralization of attention processes in the human brain. *Curr Opin Psychol* 29:90–96.
- Berry DA, Hochberg Y (1999) Bayesian perspectives on multiple comparisons. *J Stat Plan Inference* 82:215–227.
- Brainard DH (1997) The psychophysics toolbox. *Spat Vis* 10:433–436.
- Burkhardt M, Titz J (2019) cofad: contrast analysis for factorial designs. R package version 0.1.0. Vienna, Austria: R Foundation for Statistical Computing.
- Buschman TJ, Kastner S (2015) From behavior to neural dynamics: an integrated theory of attention. *Neuron* 88:127–144.
- Capotosto P, Babiloni C, Romani GL, Corbetta M (2009) Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *J Neurosci* 29:5863–5872.
- Chen CFF, Barnes DC, Wilson DA (2011) Generalized vs. stimulus-specific learned fear differentially modifies stimulus encoding in primary sensory cortex of awake rats. *J Neurophysiol* 106:3136–3144.
- Creutzfeldt OD (1977) Generality of the functional structure of the neocortex. *Naturwissenschaften* 64:507–517.
- Di Russo F, Pitzalis S, Aprile T, Spironi G, Patria F, Stella A, Spinelli D, Hillyard SA (2007) Spatiotemporal analysis of the cortical sources of the steady-state visual evoked potential. *Hum Brain Mapp* 28:323–334.
- Dienes Z (2008) Understanding psychology as a science: an introduction to scientific and statistical inference. New York: Macmillan International Higher Education.
- Dienes Z (2014) Using Bayes to get the most out of non-significant results. *Front Psychol* 5:781.
- Dunsmoor JE, Murphy GL (2015) Categories, concepts, and conditioning: how humans generalize fear. *Trends Cogn Sci* 19:73–77.
- Dunsmoor JE, Paz R (2015) Fear generalization and anxiety: behavioral and neural mechanisms. *Biol Psychiatry* 78:336–343.
- Dunsmoor JE, Kragel PA, Martin A, LaBar KS (2014) Aversive learning modulates cortical representations of object categories. *Cereb Cortex* 24:2859–2872.
- Edwards W, Lindman H, Savage LJ (1963) Bayesian statistical inference for psychological research. *Psychol Rev* 70:193–242.
- Fiebelkorn IC, Kastner S (2020) Functional specialization in the attention network. *Annu Rev Psychol* 71:221–249.
- Foxe JJ, Snyder AC (2011) The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Front Psychol* 2:154.
- Friedl WM, Keil A (2020) Effects of experience on spatial frequency tuning in the visual system: behavioral, visuocortical, and alpha-band responses. *J Cogn Neurosci* 32:1153–1169.
- Fullana MA, Harrison BJ, Soriano-Mas C, Vervliet B, Cardoner N, Avila-Parcet A, Radua J (2016) Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. *Mol Psychiatry* 21:500–508.
- Gelman A, Tuerlinckx F (2000) Type S error rates for classical and Bayesian single and multiple comparison procedures. *Comput Stat* 15:373–390.
- Gelman A, Hill J, Yajima M (2012) Why we (usually) don't have to worry about multiple comparisons. *J Res Educ Eff* 5:189–211.
- Ghirlanda S, Enquist M (2003) A century of generalization. *Anim Behav* 66:15–36.
- Haegens S, Nacher V, Luna R, Romo R, Jensen O (2011) α -Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmic inhibition of neuronal spiking. *Proc Natl Acad Sci U S A* 108:19377–19382.
- He S, Cavanagh P, Intriligator J (1996) Attentional resolution and the locus of visual awareness. *Nature* 383:334–337.
- Holt DJ, Boeke EA, Wolthuisen RP, Nasr S, Milad MR, Tootell RB (2014) A parametric study of fear generalization to faces and non-face objects: relationship to discrimination thresholds. *Front Hum Neurosci* 8:624.
- Intriligator J, Cavanagh P (2001) The spatial resolution of visual attention. *Cogn Psychol* 43:171–216.
- Isaacson JS, Scanziani M (2011) How inhibition shapes cortical activity. *Neuron* 72:231–243.
- JASP Team (2020) JASP, version 0.14. 1. Amsterdam, The Netherlands: Department of Psychological Methods, University of Amsterdam.
- Jatoui MA, Kamel N, Malik AS, Faye I (2014) EEG based brain source localization comparison of sLORETA and eLORETA. *Australas Phys Eng Sci Med* 37:713–721.
- Jeffreys H (1961) Theory of probability. Oxford, UK: Oxford UP.
- Johnson VE (2013) Revised standards for statistical evidence. *Proc Natl Acad Sci U S A* 110:19313–19317.
- Johnston K, Ma L, Schaeffer L, Everling S (2019) Alpha oscillations modulate preparatory activity in marmoset area 8Ad. *J Neurosci* 39:1855–1866.
- Junghöfer M, Elbert T, Tucker DM, Rockstroh B (2000) Statistical control of artifacts in dense array EEG/MEG studies. *Psychophysiology* 37:523–532.
- Kass MD, Rosenthal MC, Pottackal J, McGann JP (2013) Fear learning enhances neural responses to threat-predictive sensory stimuli. *Science* 342:1389–1392.
- Kleiner M, Brainard D, Pelli D (2007) What's new in Psychtoolbox-3? Natick, MA: MathWorks.
- Lang PJ, Bradley MM, Cuthbert BN (1997) Motivated attention: affect, activation, and action. Attention and orienting: sensory and motivational processes (Lang PJ, Simons RF, Balaban MT, eds), pp 97–135. New York: Psychology Press.
- Li Z, Yan A, Guo K, Li W (2019) Fear-related signals in the primary visual cortex. *Curr Biol* 29:4078–4083.
- Lissek S (2012) Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. *Depress Anxiety* 29:257–263.
- Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, Grillon C (2008) Generalization of conditioned fear-potentiated startle in humans: experimental validation and clinical relevance. *Behav Res Ther* 46:678–687.
- Lissek S, Bradford DE, Alvarez RP, Burton P, Espensen-Sturges T, Reynolds RC, Grillon C (2014) Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. *Soc Cogn Affect Neurosci* 9:1134–1142.
- Liu T (2019) Feature-based attention: effects and control. *Curr Opin Psychol* 29:187–192.
- Loewenfeld IE (1958) Mechanisms of reflex dilatation of the pupil. *Doc Ophthalmol* 12:185–448.
- Luck SJ, Gaspelin N (2017) How to get statistically significant effects in any ERP experiment (and why you shouldn't). *Psychophysiology* 54:146–157.
- Mackintosh NJ (1975) A theory of attention: variations in the associability of stimuli with reinforcement. *Psychol Rev* 82:276–298.
- Maris E, Oostenveld R (2007) Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods* 164:177–190.
- Mather M, Sutherland MR (2011) Arousal-biased competition in perception and memory. *Perspect Psychol Sci* 6:114–133.

- Mathôt S (2018) Pupillometry: psychology, physiology, and function. *J Cogn* 1:16.
- McShane BB, Gal D, Gelman A, Robert C, Tackett JL (2019) Abandon statistical significance. *Am Stat* 73:235–245.
- McTeague LM, Gruss LF, Keil A (2015) Aversive learning shapes neuronal orientation tuning in human visual cortex. *Nat Commun* 6:1–8.
- Mitra PP, Pesaran B (1999) Analysis of dynamic brain imaging data. *Biophys J* 76:691–708.
- Moratti S, Keil A (2005) Cortical activation during Pavlovian fear conditioning depends on heart rate response patterns: an MEG study. *Brain Res Cogn Brain Res* 25:459–471.
- Moratti S, Keil A (2009) Not what you expect: experience but not expectancy predicts conditioned responses in human visual and supplementary cortex. *Cereb Cortex* 19:2803–2809.
- Moratti S, Keil A, Miller GA (2006) Fear but not awareness predicts enhanced sensory processing in fear conditioning. *Psychophysiology* 43:216–226.
- Naber M, Alvarez GA, Nakayama K (2013) Tracking the allocation of attention using human pupillary oscillations. *Front Psychol* 4:919.
- Olmos-Solis K, van Loon AM, Olivers CN (2018) Pupil dilation reflects task relevance prior to search. *J Cogn* 1:11.
- Onat S, Büchel C (2015) The neuronal basis of fear generalization in humans. *Nat Neurosci* 18:1811–1818.
- O'Neill B (2009) Exchangeability, correlation, and Bayes' effect. *Int Stat Rev* 77:241–250.
- Oostenveld R, Fries P, Maris E, Schoffelen JM (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011:156869.
- Pascual-Marqui RD (2007) Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. *arXiv*: 0710.3341.
- Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, Tanaka H, Hirata K, John ER, Prichep L, Biscay-Lirio R, Kinoshita T (2011) Assessing interactions in the brain with exact low-resolution electromagnetic tomography. *Philos Trans A Math Phys Eng Sci* 369:3768–3784.
- Pearce JM, Hall G (1980) A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychol Rev* 87:532–552.
- Petro NM, Gruss LF, Yin S, Huang H, Miskovic V, Ding M, Keil A (2017) Multimodal imaging evidence for a frontoparietal modulation of visual cortex during the selective processing of conditioned threat. *J Cogn Neurosci* 29:953–967.
- Popov T, Oostenveld R, Schoffelen JM (2018) FieldTrip made easy: an analysis protocol for group analysis of the auditory steady state brain response in time, frequency, and space. *Front Neurosci* 12:711.
- Posner MI (1980) Orienting of attention. *Q J Exp Psychol* 32:3–25.
- Posner MI, Petersen SE (1990) The attention system of the human brain. *Annu Rev Neurosci* 13:25–42.
- Priebe NJ, Ferster D (2008) Inhibition, spike threshold, and stimulus selectivity in primary visual cortex. *Neuron* 57:482–497.
- Rescorla RA (1988) Pavlovian conditioning: it's not what you think it is. *Am Psychol* 43:151–160.
- Rescorla RH, Wagner AF (1972) A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: *Classical conditioning II: Current research and theory* (Black AH, Prokasy WF, eds), pp 64–99. New York: Appleton-Century-Crofts.
- Ringach DL, Hawken MJ, Shapley R (2003) Dynamics of orientation tuning in macaque V1: the role of global and tuned suppression. *J Neurophysiol* 90:342–352.
- Romei V, Gross J, Thut G (2010) On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? *J Neurosci* 30:8692–8697.
- Rosenthal R (1987) *Judgment studies: design, analysis, and meta-analysis*. Cambridge, UK: Cambridge UP.
- Rosenthal R, Rosnow RL, Rubin DB (2000) *Contrasts and effect sizes in behavioral research: a correlational approach*. Cambridge, UK: Cambridge UP.
- Rosnow RL, Rosenthal R (1989) Definition and interpretation of interaction effects. *Psychol Bull* 105:143–146.
- Rosnow RL, Rosenthal R (1995) Some things you learn aren't so": Cohen's paradox, Asch's paradigm, and the interpretation of interaction. *Psychol Sci* 6:3–9.
- Rosnow RL, Rosenthal R, Rubin DB (2000) Contrasts and correlations in effect-size estimation. *Psychol Sci* 11:446–453.
- Rouder JN, Speckman PL, Sun D, Morey RD, Iverson G (2009) Bayesian tests for accepting and rejecting the null hypothesis. *Psychon Bull Rev* 16:225–237.
- Schechtman E, Laufer O, Paz R (2010) Negative valence widens generalization of learning. *J Neurosci* 30:10460–10464.
- Schneiderman N (1972) Response system divergencies in aversive classical conditioning. In: *Classical conditioning II: current research and theory* (Black AH, Prokasy WF, eds), pp 341–376. New York: Appleton-Century-Crofts.
- Shapley R (2004) A new view of the primary visual cortex. *Neural Netw* 17:615–623.
- Shapley R, Hawken M, Xing D (2007) The dynamics of visual responses in the primary visual cortex. *Prog Brain Res* 165:21–32.
- Siman-Tov T, Mendelsohn A, Schonberg T, Avidan G, Podlipsky I, Pessoa L, Gadoth N, Ungerleider LG, Hendler T (2007) Bihemispheric leftward bias in a visuospatial attention-related network. *J Neurosci* 27:11271–11278.
- Smith JB, Batchelder WH (2008) Assessing individual differences in categorical data. *Psychon Bull Rev* 15:713–731.
- Song I, Keil A (2014) Differential classical conditioning selectively heightens response gain of neural population activity in human visual cortex. *Psychophysiology* 51:1185–1194.
- Sprague TC, Serences JT (2013) Attention modulates spatial priority maps in the human occipital, parietal and frontal cortices. *Nat Neurosci* 16:1879–1887.
- Stegmann Y, Ahrens L, Pauli P, Keil A, Wieser MJ (2020) Social aversive generalization learning sharpens the tuning of visuocortical neurons to facial identity cues. *Elife* 9:e55204.
- Struyf D, Zaman J, Vervliet B, Van Diest I (2015) Perceptual discrimination in fear generalization: mechanistic and clinical implications. *Neurosci Biobehav Rev* 59:201–207.
- Summerfield C, Egner T (2016) Feature-based attention and feature-based expectation. *Trends Cogn Sci* 20:401–404.
- Tuominen L, Boeke E, DeCross S, Wolthuisen RP, Nasr S, Milad M, Vangel M, Tootell R, Holt D (2019) The relationship of perceptual discrimination to neural mechanisms of fear generalization. *Neuroimage* 188:445–455.
- Wagenmakers EJ (2007) A practical solution to the pervasive problems of p values. *Psychon Bull Rev* 14:779–804.
- Weinberger NM (2004) Specific long-term memory traces in primary auditory cortex. *Nat Rev Neurosci* 5:279–290.
- Wetzels R, Matzke D, Lee MD, Rouder JN, Iverson GJ, Wagenmakers EJ (2011) Statistical evidence in experimental psychology: an empirical comparison using 855 *t* tests. *Perspect Psychol Sci* 6:291–298.
- Wiens S, Nilsson ME (2017) Performing contrast analysis in factorial designs: from NHST to confidence intervals and beyond. *Educ Psychol Meas* 77:690–715.
- Wieser MJ, Miskovic V, Keil A (2016) Steady-state visual evoked potentials as a research tool in social affective neuroscience. *Psychophysiology* 53:1763–1775.
- Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014) Permutation inference for the general linear model. *Neuroimage* 92:381–397.
- Yeonan-Kim J, Bertalmio M (2016) Retinal lateral inhibition provides the biological basis of long-range spatial induction. *PLoS One* 11:e0168963.