JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles: Behavioral/Cognitive

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

https://doi.org/10.1523/JNEUROSCI.2889-20.2021

Cite as: J. Neurosci 2021; 10.1523/JNEUROSCI.2889-20.2021

Received: 14 November 2020
Revised: 22 April 2021
Accepted: 12 May 2021

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

Abbreviated title: Aversive Conditioning of Spatial Position

Wendel M. Friedl and Andreas Keil

Center for the Study of Emotion and Attention,

University of Florida,

Gainesville, Florida 32610

Correspondence should be addressed to Wendel M. Friedl, Department of Psychology,

University of Florida. wfriedl@ufl.edu

Number of pages: 39
Number of figures: 9
Number of tables: 0
Number of words in abstract: 250
Number of words in significance statement: 108
Number of words in introduction: 648
Number of words in discussion: 1494

The authors declare no conflicts of interest

Acknowledgments: This research was supported by grants from the National Institutes of Health (R01MH112558 and R01MH097320) and Grant N00014-18-1-2306 from the Office of Naval Research to A. K.

We thank Pierce Imperialbobis and Varna Venkatachalam for help with data collection

Abstract

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 non-prioritized 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 pre-registered hypotheses of either sharpening or generalization around an aversively associated location following a single conditioning session. Competing hypotheses tested if 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 (ssVEP) 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 non-paired 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.

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 towards novel treatment targets in disorders of attention and spatial cognition.

68 Aversive Conditioning of Spatial Position Sharpens Population-level Visuocortical Responses
69 and Selectively Alters Alpha-band Activity

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

77 Mounting evidence (e.g. Weinberger, 2004; Chen, Barnes, & Wilson, 2011; Aizenberg &
78 Geffen, 2013; Kass, Rosenthal, Pottackal, & McGann, 2013) indicates that neural representations
79 within primary sensory cortices respond to learned contingencies as well as to basic physical
80 features. How the representation of visual field position is affected by such learning, however,
81 remains unknown. Classical (Pavlovian) differential aversive conditioning paradigms, which pair
82 an initially neutral stimulus with an intrinsically aversive outcome, offer a well-established
83 method for investigating learning-induced neural response changes. Aversive conditioning
84 studies have, for example, demonstrated that oriented gratings predicting aversive outcomes
85 (CS+ stimuli) come to prompt selectively potentiated visuocortical responses in non-human
86 primates (Li,Yan, Guo, & Li, 2019) and human observers (Moratti & Keil, 2009; Song & Keil,
87 2014; McTeague, Gruss, & Keil, 2015). Moreover, responses to stimuli varying in physical
88 similarity to the CS+ along an ordered continuum of a manipulated feature can be used to both
89 characterize the extent of acquired changes in sensory sensitivity (Schechtman, Laufer, & Paz,

2010; Holt et al., 2014) and inform as to underlying neural mechanisms (Ringach, Hawken, & Shapley, 2003; Dunsmoor & Paz, 2015; Onat & Büchel, 2015).

Two response distributions widely used to describe neuronal selectivity along a continuum of features are the gaussian (Onat & Büchel, 2015; Tuominen et al., 2019) and the difference-of-gaussian (DOG; Ringach, Hawken, & Shapley, 2003; Yeonan-Kim & Bertalmío, 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, Zaman, Vervliet, & Van Diest, 2015; Tuominen et al., 2019). Meanwhile, a non-monotonic 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 & 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 & 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 (e.g. Capotosto, Babiloni, Romani, & Corbetta, 2009; Romei, Gross, & Thut, 2010), which exerts strong, top-down effects on sensory processing (reviewed in Fiebelkorn & Kastner, 2020). For instance, increased alpha-band activity within sensory cortices is inversely associated with neuronal firing rate (Haegens et al., 2011; Johnston, Ma, Schaeffer, & Everling, 2019) and overall sensory processing (Foxe & 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 extra-striate, higher-order cortical processes during the associative learning process. Gaze fixation was monitored with eye-tracking to ensure consistent retinotopic mapping. Our pre-registered hypothesis was that within retinotopic visual cortex, neuronal population-level tuning to a threat location would prompt suppression of location representations proximal to the CS+, resulting in a difference-of-gaussian response gradient. Meanwhile, decreases in alpha-band amplitude were 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 pre-registered 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: (a) transform signals from time domain to frequency domain in sensor space, (b) source estimation, (c) test the fit of gaussian and DOG patterns (figure 1) of experience-dependent signal change across the entire estimated source volume, and (d) 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 due to discomfort with the auditory US, and data from one participant was excluded due to a defective EEG sensor net, leaving a final sample of 51 (19 male; M_{age}=19.49, SD_{age}=1.22) participants. All participants

provided informed consent in accordance with the Declaration of Helsinki and the institutional review board of the University of Florida.

Stimuli

Visual stimuli consisted of high contrast Gabor patches (1.18 cycles/degree) presented against a black background (0.01 cd/m^2). Gabor patches subtended 7.07 degrees of visual angle and had a maximum luminance of 96 cd/m^2. Gabors were presented individually at one of five equally spaced locations, having their inner border at 2.12 degrees of eccentricity from a central fixation dot (figure 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 degrees (360/5), resulting in an arc length of 8.86π / 5 (~278.3 mm) or 13.23 degrees of visual angle separating the centers of adjacent stimulus locations. Compared to 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 employed 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 assessment of participants' awareness of the US / CS+ pairing contingency during acquisition trials (see below). Visual stimuli were presented on a calibrated LCD display (Cambridge Research Systems Display ++) running at 120 Hz connected to a PC running Linux Ubuntu 18.04. Stimuli were created in MATLAB (MathWorks, Natick, MA) with the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007). Gabor patches were flickered at a rate of 15 times per second (Hz) to drive cortical oscillatory responses at the desired steady-state temporal frequency. The unconditioned stimulus (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/m^2) room. Viewing distance to the display monitor was adjusted to 120 cm and distance to the eye-tracker lens adjusted to 60 cm. Participants were instructed to limit blinking to the ITI 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.

Awareness of CS+ spatial position. To assess awareness of the US/CS+ association, after every 15 trials (3 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 pre-determined 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 (2 locations clockwise or counter-clockwise 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 degrees visual angle) at nine locations against a black background. Pupil segments were discarded if the diameter was not between 0.01 and 5 mm (approximately 400–16,000 in default manufacturer arbitrary

units). Offline, pupil trials were rejected if artifacts such as blinks obscured more than 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 (Mathôt, 2013). To evaluate compliance with fixation instructions, we calculated the proportion of time during which the eye gaze was outside a 2-degree 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 3-dB point at 170 Hz, high-pass 3-dB point at 0.05 Hz) and off-line (low-pass 40 Hz, 18th order, 3-dB point at 45 Hz, high-pass 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 Junghöfer, Elbert, Tucker, and Rockstroh (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 (M = 22.65) and acquisition (M = 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 BF_{10}'s < 0.15. In tangible terms, the largest mean difference in retained trials was between the CS+ position in acquisition (M = 23.67) and the farthest-from-CS-position in habituation (M = 22.44), which was judged unlikely to impact statistical comparisons of the dependent variables.

Spectral analysis of EEG signals. Following data pre-processing, EEG data was

transformed from the time to the frequency domain using functions provided in the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) for MATLAB, generally following steps detailed in Popov, Oostenveld, and Schoffelen (2018). Time ranges (see below) were determined based on a body of previous work (e.g. Friedl & Keil, 2020; Wieser, Miskovic, & Keil, 2016) showing that alpha-power changes in response to conditioned stimuli occur early and extend over 1-2 seconds, whereas ssVEP differences occur predominantly in the second prior to 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 trial in each condition, was first obtained with the function *ft_timelockanalysis*. Trial averaging was only performed prior to spectral decomposition for ssVEPs, as the phase consistency of driven oscillations across trials prevents potentially offsetting effects when averaging (Popov, Oostenveld, & Schoffelen, 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 (Mitra & Pesaran, 1999) window based on discrete prolate spheroidal sequences (DPSS) prior to 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 (# of retained trials x 51 x 10)

by means of a fast Fourier transformation (FFT) with the function *ft_freqanalysis*. The multitaper window based on discrete prolate spheroidal sequences (DPSS) applied prior to 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 (BEM) model in conjunction with the eLORETA (exact low resolution brain electromagnetic tomography) algorithm proposed by Pascual-Marqui and colleagues (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011), using functions from the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011): First, a BEM 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 leadfield 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 signal to noise 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. one; Jatoi, Kamel, Malik, & Faye, 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 non-retinotopic alpha power response is shown averaged over all spatial positions at the bottom of figure 4. Note that 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 Bayes factors (BFs; Jeffreys, 1998; 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 utilized Bayesian hypothesis testing given the problems of using *p*-values specifically (e.g. Edwards, Lindman, & Savage, 1963; Wagenmakers, 2007) and dichotomous decision criteria generally (McShane, Gal, Gelman, Robert, & Tackett, 2019) to summarize research results.

Questions of when, whether, and how to adjust Bayesian statistical results for multiple comparisons are currently unsettled (Berry, & Hochberg, 1999; Dienes, 2008, 2014; Gelman and Tuerlinckx, 2000; Gelman, Hill, & Yajima., 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 signal change for alpha-band and ssVEP activity were pre-registered (https://osf.io/h7tqa/?view_only=eee3c81e66854d1bb1723ea25cd07f5d), eliminating concern that many additional hypotheses were tested but not reported. Secondly, 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 & Gaspelin, 2017). Thirdly, to quantify the danger that strong evidence

291 in favor of our alternative hypotheses could arise by chance from testing 3528 estimated cortical
292 sources, permutation tests for each hypothesis were performed (10000 iterations, randomly
293 shuffling the order of conditions 3528 times within participants). Permutation tests have been
294 employed extensively to control type-1 errors when analyzing neuroimaging data from a
295 frequentist statistical perspective (e.g. Maris & Oostenveld, 2007; Winkler, Ridgway, Webster,
296 Smith, & Nichols, 2014), and conceptually tie directly to the Bayesian assumption of
297 exchangeability (O'Neill, 1999). The 95th percentiles of the empirical distributions of Bayes
298 factor values arising from these permutation tests were far below (0.54 for ssVEP, 1.079 for
299 alpha, respectively) the minimum Bayes factor of 3:1 in favor of the alternative hypothesis that
300 we adopt in displaying or discussing statistical comparisons. Finally, the reported results section
301 distinguishes between our main, pre-registered comparisons and those that were more
302 exploratory or were not spelled out explicitly prior to data analysis: the latter should, as always,
303 be regarded as potentially interesting but pending corroborating evidence via replication.
304 As the hypotheses of interest concerned the effect of relative distance from an aversively-
305 paired spatial location, not differential responses at these locations themselves (due, for instance,
306 to differences in the volume of cortical tissue sensitive to different regions of the visual field), all
307 EEG analyses rotated the signal data from viewing each spatial position such that the five spatial
308 positions were transformed into five bins representing relative distance from the conditioned
309 spatial location.
310 For the pupil data time series the two spatial distance bins either one or two position
311 steps away from the CS+ location were merged, with all subsequent analyses performed on the
312 resulting three bins of data (CS+, near, far). A JZS Bayes factor (Rouder et al., 2009) was
313 computed for each location condition at each time point to quantify the likelihood that these
314 signals differed in acquisition as compared to habituation trials.
315 **Model comparison.** As habituation trials in differential conditioning paradigms provide

316 a subject-specific non-associative control condition (Schneiderman, 1972), we first computed
317 change scores (acquisition minus habituation) for each signal, following the *method of*
318 *meaningful differences* (Rosenthal, 1987). Data submitted to contrast analysis for each signal had
319 dimensions of 1 (change score) by 5 (spatial position). Signed *F*-contrasts (Rosenthal, Rosnow,
320 & Rubin, 2000; Rosnow, Rosenthal, & Rubin, 2000), weighting each spatial position to account
321 for the hypothesized trend (gaussian or difference-of-gaussian) of the change in each signal
322 following aversive conditioning, were then calculated for each source. At each source location,
323 *F*-contrast values quantified how closely the signal change across spatial positions followed each
324 of the hypothesized trends at that location. Change scores for each spatial position were
325 multiplied by their corresponding contrast weights, then summed over positions to arrive at an
326 overall contrast score. The contrast weights chosen sum to zero, ensuring that an overall contrast
327 score of zero corresponds to an absence of the tested trend (Wiens & Nilsson, 2017) and large
328 positive values indicate that the change scores are well described by the tested contrast. The
329 square roots of these *F*-values (Rosenthal, Rosnow, & Rubin, 2000, p. 41) were then converted
330 to JZS Bayes factors as detailed by Rouder and colleagues (2009).

331 Our hypotheses regarding the specific order of mean change scores across spatial
332 positions would not have been well addressed by traditional factorial ANOVA (Abelson &
333 Prentice, 1997; Rosnow & Rosenthal, 1995), as ANOVA captures any difference, regardless of
334 order, among mean values when there are multiple *df*s in the numerator (Wiens & Nilsson,
335 2017). In comparison, contrasts always have a single *df* in the numerator, providing a specific
336 test of the hypothesis (Rosenthal, Rosnow, & Rubin, 2000; Wiens & Nilsson, 2017), and
337 allowing for a direct assessment of the specific numerical ordering of mean values across
338 experimental conditions (Rosnow & Rosenthal, 1989). A traditional two-group *t*-test, for
339 instance, is implicitly a contrast with the two compared groups receiving contrast weights of
340 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.

Code Accessibility

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/H7TQA). The custom MATLAB script for performing contrast analysis at each source location is also available at 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 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 correspondence (contrast $BF_{10} > 3$, figure 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 3 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 (figure 6, top) where the ssVEP power change DOG contrast yielded BF_{10} values greater than 3. The average BF_{10} value supporting a DOG trend across these 114 locations was 6.57 (SD=3.87, min/max 3.01-27.69). These same 114 source locations had 0 sources at which the gaussian contrast reached a BF_{10} value of 3 (M=0.16, SD=0.01, min/max 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, min/max 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 (figure 6, bottom) where the alpha-band power change gaussian contrast yielded BF_{10} values greater than 3. The average BF_{10} value in support of a gaussian trend across these 708 parietal-occipital locations was 17.77 (SD=18.23, min/max 3.01-151.98). These source locations had 0 sources at which the DOG contrast reached a BF_{10} value of 3 (M=0.26, SD=0.17, min/max 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, min/max 1.36-919.67).

There were 183 anterior source locations (figure 6, bottom) where the alpha-band power change DOG contrast produced BF10 values greater than 3. The average BF_{10} value across these locations was 9.51 (SD=10.21, min/max 3.01-64.34). These source locations had 0 sources at which the gaussian contrast reached a BF_{10} value of 3 (M=0.35, SD=0.31, min/max 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, min/max 1.39-268.54).

Both contrast patterns of alpha power change were strongly supported at different, non-overlapping 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 only erred on a single reporting trial (each by only 1 spatial position). Overall, approximately 90% (46/51) of participants 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 5 participants who made > 1 spatial position errors 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 & Keil, 2005; 2009), awareness of the contingency between the CS+ and the US does not appear to systematically influence the response patters 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 or greater than the average of all values for each contrast shown in the overall source model comparison (figure 6; i.e. all sources with BF_{10} values > 3). The proportion of individual participants exhibiting each signal change trend to some degree (dot product > 0) was: 34/51 for the ssVEP DOG trend, 32/51 for the alpha-band gaussian trend, and 35/51 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 rho 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 BF_{10} values >3, is shown figure 8. While the alpha power gaussian contrast values at these source locations consistently exhibited a generalization trend which was more pronounced in the early (mean BF_{10} = 440.19 over the 642 source locations where the overall gaussian contrast exceeded a BF_{10} value of 3) compared to the late (mean BF_{10} = 13.25, 471 source locations) phase of the acquisition block, the ssVEP sharpening response was evident only for the first half (mean BF_{10} = 7.62 over all 114 source locations where the overall gaussian contrast exceeded a BF_{10} value of 3) of acquisition trials (second half had 0 sources where the DOG contrast exceeded a BF_{10} 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 $BF_{10} < 3$). The anterior alpha sharpening trend (not shown) seen in the overall average comparison was also evident in early acquisition (mean BF_{10} = 5.18 over the 79 of the 183 sources where the overall DOG contrast exceeded a BF_{10} value of 3), and nearly non-existent in late acquisition (mean BF_{10} = 3.19, 3 sources).

Pupil and gaze. Proportion of deviations from fixation did not vary by spatial position during habituation trials (BF_{01} = 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 habitation to acquisition did not vary by aligned location condition (i.e. it did not differ for the CS+ compared to other locations; BF_{01} = 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+

442 locations with contrast weights of -.5, -.5, and 1, respectively, to quantify the strength and
443 temporal evolution this pattern. Results of this *post hoc* contrast analysis are shown at the
444 bottom of figure 9.

445 **Discussion**

446 The present study examined experience-dependent changes in visuospatial representation
447 wrought by a brief (~30 min) aversive conditioning regimen in which one on-screen location was
448 paired with an aversive noise stimulus while leaving four equidistant locations unassociated.
449 Comparing pupil diameter, alpha-power reduction, and visuocortical ssVEP enhancement
450 between acquisition and habituation, we found evidence for experience-related changes in all
451 measures.

452 Consistent with sharpened tuning of visuospatial representations in visual cortex, ssVEPs
453 followed a difference-of-gaussian pattern at occipital source locations, with reduced cortical
454 responsiveness to proximal unpaired screen locations and enhanced responses to the CS+
455 location. This pattern of experience-driven response change supports the hypothesis that
456 retinotopic visual cortex possesses mechanisms for enhancing the spatial contrast between
457 representations of threat-associated versus non-threat-associated locations. Furthermore,
458 sharpened visuocortical responses to aversively paired screen locations developed within
459 minutes of exposure to the noxious noise stimulus, transitioning to generally elevated ssVEP
460 responses undifferentiated by proximity to the CS+ in the second half of acquisition trials. The
461 DOG pattern of visuocortical response change across the range of tested spatial positions
462 observed here closely mirrors responses to orientated gratings (McTeague, Gruss, & Keil, 2015)
463 and faces (Stegmann, Ahrens, Pauli, Keil, & Wieser, 2020) parametrically varied in similarity to
464 conditioned threat cues. The finding that altered tuning of the ssVEP emerges whether the low-
465 level visual feature predicting an upcoming aversive event is a particular orientation or a specific
466 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 (McTeague et al., 2015; Moratti & Keil, 2005; Moratti, Keil, & Miller, 2006). 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 upon perceptual discrimination (e.g. 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 & Buchel, 2015). Onat and Buchel (2015) instead cite the active integration of "hyper-sharp" 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 Buchel (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 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 "hyper-sharp" 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 (LGN) relay cells into the more narrowly feature selective responses observed in visual cortex (Shapley, Hawken,

& Xing, 2007; Isaacson & Scanziani, 2011; Angelucci et al., 2017; but see Priebe & Ferster, 2008). Compared to visual perception, the spatial resolution of focused visual attention is relatively poor (He, Cavanagh, & Intriligator, 1996; Intriligator & 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 (e.g., McTeague et al., 2015; Friedl & Keil, 2020), along with the present results, provide evidence that threat-associated cortical response changes do manifest differently for alpha band and ssVEP signals.

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 (reviewed in Ghirlanda & 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), thought to reflect the primary role of right-hemisphere posterior parietal cortex in deploying spatial attention (e.g. Posner & Peterson, 1990; reviewed in Bartolomeo & 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 (e.g. Lang, Bradley, & Cuthbert, 1997; Mather & Sutherland, 2011), in addition to attention. While an overall elevation

517 of general arousal levels is expected during conditioning trials (Lissek et al., 2008), the
518 selectively graded alpha-band decrease, peaking at the CS+ viewing location**,** indicates that this
519 effect is more consistent with focused enhancement brought about through attentive processing
520 (Posner & Petersen, 1990). Posner's (1980) seminal work established that covert, spatially
521 directed attention enhances processing at attended locations. Such shifts are typically prompted
522 by explicit attention cues, conveyed through verbal or on-screen instructions (Sprague &
523 Serences, 2013; Buschman & Kastner, 2015). Here, we show that an experientially acquired
524 spatial association with an unpleasant stimulus prompts a similar facilitation of neural mass
525 activity for stimuli presented at a conditioned location. Comparing parietal alpha band
526 generalization gradients from the first half to the second half of acquisition trials, the magnitude
527 of decrement in alpha power was more pronounced in early trials but retained a gaussian
528 distribution across stimulus locations throughout the experimental session. Tenets of several
529 formal models of classical conditioning can readily account for the reduced magnitude of alpha
530 responding over trials: the Rescorla-Wagner model (Rescorla & Wagner, 1972) by positing that
531 as the CS+ becomes a better predictor of the US (i.e. there is less "surprise") there is
532 correspondingly less error correction evident in response to the CS+, and the Pearce-Hall model
533 (Pearce & Hall, 1980) by ascribing less attention to a CS+ as it comes to more accurately predict
534 a US. In contrast, the Mackintosh model (Mackintosh, 1975), in which attention to a CS+
535 increases along with its ability to predict a US, is contra-indicated by the present results.

536 One caveat regarding the pattern of alpha-band responses reported here is that the activity
537 of a cortically diffuse signal such as alpha is likely to vary according to either (a) the
538 assumptions made by the source-localization method employed, or (b) the electrodes considered
539 if analyzing voltage recorded at the scalp. For instance, a non-graded**,** all-or-none pattern of
540 alpha-power modulation following aversive conditioning emerged in a previous study where
541 Gabor patches varied along a continuum of spatial frequencies (Friedl & Keil, 2020). There,

using sensor clusters defined by activity at the group level may have resulted in decreased sensitivity to individual differences compared to 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 (e.g. Loewenfeld, 1958), but has also been linked to the employment of covert attention (Naber, Alvarez, & Nakayama, 2013; Olmos-Solis, van Loon, & Olivers, 2018; reviewed in 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, non-paired 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 non-threat cues**.**

The significance of sharply tuned neural response profiles to perceptual discrimination, as well as the relationship between response gradients measured at the behavioral and neural level, have strong translational and clinical implications (Dunsmoor & Paz, 2015) and remain pressing questions for future study. An additional open question is if neural sharpening results exclusively from altered sensitivity in feature-specific neuronal populations (e.g., Summerfield & Egner, 2017; Liu, 2019), or if a learned categorical distinction (threat vs. safe) also contributes (Dunsmoor, Kragel, Martin, & LaBar, 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 & 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 employed by the visual system in adapting to dynamic environments.

References

Abelson, R. P., & Prentice, D. A. (1997). Contrast tests of interaction hypothesis. *Psychological Methods*, *2*(4), 315.

Aine, C. J., Supek, S., George, J. S., Ranken, D., Lewine, J., Sanders, J., ... & Wood, C. C. (1996). Retinotopic organization of human visual cortex: departures from the classical model. *Cerebral Cortex*, *6*(3), 354-361.

Aizenberg, M., & Geffen, M. N. (2013). Bidirectional effects of aversive learning on perceptual acuity are mediated by the sensory cortex. *Nature neuroscience, 16*(8), 994-996.

Angelucci, A., Bijanzadeh, M., Nurminen, L., Federer, F., Merlin, S., & Bressloff, P. C. (2017). Circuits and mechanisms for surround modulation in visual cortex. *Annual review of neuroscience*, *40*, 425-451.

Aizenberg, M., & Geffen, M. N. (2013). Bidirectional effects of aversive learning on perceptual acuity are mediated by the sensory cortex. *Nature neuroscience*, *16*(8), 994-996.

Bartolomeo, P., & Malkinson, T. S. (2019). Hemispheric lateralization of attention processes in the human brain. *Current opinion in psychology*, *29*, 90-96.

Berry, D. A., & Hochberg, Y. (1999). Bayesian perspectives on multiple comparisons. *Journal of Statistical Planning and Inference, 82*(1-2), 215-227.

Bosking, W. H., Crowley, J. C., & Fitzpatrick, D. (2002). Spatial coding of position and orientation in primary visual cortex. *Nature neuroscience*, *5*(9), 874-882.

Brainard, D. H. (1997). The psychophysics toolbox. *Spatial vision*, *10*(4), 433-436.

Burkhardt, M., & Titz, J. (2019). cofad: Contrast analysis for factorial designs. R package version 0.1.0. https://CRAN.R-project.org/package=cofad

Buschman, T. J., & Kastner, S. (2015). From behavior to neural dynamics: an integrated theory of attention. *Neuron*, *88*(1), 127-144.

Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2009). Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *Journal of Neuroscience*, *29*(18), 5863-5872.

Chen, C. F. F., Barnes, D. C., & Wilson, D. A. (2011). Generalized vs. stimulus-specific learned fear differentially modifies stimulus encoding in primary sensory cortex of awake rats. *Journal of neurophysiology*, *106*(6), 3136-3144.

Chklovskii, D. B., & Koulakov, A. A. (2004). Maps in the brain: what can we learn from them?. *Annu. Rev. Neurosci.*, *27*, 369-392.

Creutzfeldt, O. D. (1977). Generality of the functional structure of the neocortex. *Naturwissenschaften*, *64*(10), 507-517.

Dienes, Z. (2008). *Understanding psychology as a science: An introduction to scientific and statistical inference*. Macmillan International Higher Education.

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in psychology*, *5*, 781.

Di Russo, F., Pitzalis, S., Aprile, T., Spitoni, G., Patria, F., Stella, A., ... Hillyard, S. A. (2007). Spatiotemporal analysis of the cortical sources of the steady-state visual evoked potential. *Human Brain Mapping, 28*, 323–334. doi:10.1002/hbm.20276

Dunsmoor, J. E., Kragel, P. A., Martin, A., & LaBar, K. S. (2014). Aversive learning modulates cortical representations of object categories. *Cerebral Cortex*, *24*(11), 2859-2872.

Dunsmoor, J. E., & Murphy, G. L. (2015). Categories, concepts, and conditioning: how humans generalize fear. *Trends in cognitive sciences, 19*(2), 73-77.

Dunsmoor, J. E., & Paz, R. (2015). Fear generalization and anxiety: behavioral and neural mechanisms. *Biological psychiatry*, *78*(5), 336-343.

Edwards, W., Lindman, H., & Savage, L. J. (1963). Bayesian statistical inference for psychological research. *Psychological review*, *70*(3), 193.

625 Fiebelkorn, I. C., & Kastner, S. (2020). Functional specialization in the attention network.
626
627 *Annual review of psychology*, *71*, 221-249.
628
629 Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory
630 suppression mechanism during selective attention. *Frontiers in psychology*, *2*, 154.
631 Friedl, W. M., & Keil, A. (2020). Effects of Experience on Spatial Frequency Tuning in the
632 Visual System: Behavioral, Visuocortical, and Alpha-band Responses. *Journal of*
633 *Cognitive Neuroscience*, *32*(6), 1153-1169.
634 Fullana, M. A., Harrison, B. J., Soriano-Mas, C., Vervliet, B., Cardoner, N., Àvila-Parcet,
635 A., & Radua, J. (2016). Neural signatures of human fear conditioning: an updated
636 and extended meta-analysis of fMRI studies. *Molecular psychiatry*, *21*(4), 500-508.
637 Gelman, A., Hill, J., & Yajima, M. (2012). Why we (usually) don't have to worry about multiple
638 comparisons. *Journal of Research on Educational Effectiveness*, *5*(2), 189-211.
639 Gelman, A., & Tuerlinckx, F. (2000). Type S error rates for classical and Bayesian single and
640 multiple comparison procedures. *Computational Statistics*, *15*(3), 373-390.
641 Ghirlanda, S., & Enquist, M. (2003). A century of generalization. *Animal Behaviour*, *66*(1), 15-
642 36.
643 Haegens, S., Nácher, V., Luna, R., Romo, R., & Jensen, O. (2011). α-Oscillations in the monkey
644 sensorimotor network influence discrimination performance by rhythmical inhibition of
645 neuronal spiking. *Proceedings of the National Academy of Sciences*, *108*(48), 19377-
646 19382.
647 He, S., Cavanagh, P., & Intriligator, J. (1996). Attentional resolution and the locus of visual
648 awareness. *Nature*, *383*(6598), 334-337.
649 Holt, D. J., Boeke, E. A., Wolthusen, R. P., Nasr, S., Milad, M. R., & Tootell, R. B. (2014). A
650 parametric study of fear generalization to faces and non-face objects: relationship to
651 discrimination thresholds. *Frontiers in human neuroscience*, *8*, 624.

652 Hubel, D. H., & Wiesel, T. N. (1977). Ferrier lecture-Functional architecture of macaque
653 monkey visual cortex. *Proceedings of the Royal Society of London. Series B. Biological*
654 *Sciences*, *198*(1130), 1-59.
655 Intriligator, J., & Cavanagh, P. (2001). The spatial resolution of visual attention. *Cognitive*
656 *psychology*, *43*(3), 171-216.
657 Isaacson, J. S., & Scanziani, M. (2011). How inhibition shapes cortical activity. *Neuron*, *72*(2),
658 231-243.
659 JASP Team, J. A. S. P. (2020). JASP (version 0.14. 1)[computer software].
660 Jatoi, M. A., Kamel, N., Malik, A. S., & Faye, I. (2014). EEG based brain source localization
661 comparison of sLORETA and eLORETA. *Australasian physical & engineering*
662 *sciences in medicine*, *37*(4), 713-721.
663 Jeffreys, H. (1961). *Theory of Probability*. Oxford: UK Oxford University Press.
664
665 Johnson, V. E. (2013). Revised standards for statistical evidence. *Proceedings of the National*
666 *Academy of Sciences*, *110*(48), 19313-19317.
667 Johnston, K., Ma, L., Schaeffer, L., & Everling, S. (2019). Alpha oscillations modulate
668 preparatory activity in marmoset area 8Ad. *Journal of Neuroscience*, *39*(10), 1855-
669 1866.
670 Junghöfer, M., Elbert, T., Tucker, D. M., & Rockstroh, B. (2000). Statistical control of
671 artifacts in dense array EEG/MEG studies. *Psychophysiology, 37*(4), 523-532.
672 Kass, M. D., Rosenthal, M. C., Pottackal, J., & McGann, J. P. (2013). Fear learning enhances
673 neural responses to threat-predictive sensory stimuli. *Science*, *342*(6164), 1389-1392.
674 Kleiner, M., Brainard, D., & Pelli, D. (2007). What's new in Psychtoolbox-3?.
675
676 Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation,
677 and action. *Attention and orienting: Sensory and motivational processes*, *97*, 135.

678
679

Li, Z., Yan, A., Guo, K., & Li, W. (2019). Fear-related signals in the primary visual cortex. *Current Biology*, *29*(23), 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. *Depression and anxiety*, *29*(4), 257-263.

Lissek, S., Biggs, A. L., Rabin, S. J., Cornwell, B. R., Alvarez, R. P., Pine, D. S., & Grillon, C. (2008). Generalization of conditioned fear-potentiated startle in humans: experimental validation and clinical relevance. *Behaviour research and therapy*, *46*(5), 678-687.

Lissek, S., Bradford, D. E., Alvarez, R. P., Burton, P., Espensen-Sturges, T., Reynolds, R. C., & Grillon, C. (2014). Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. *Social cognitive and affective neuroscience*, *9*(8), 1134-1142.

Liu T (2019) Feature-based attention: effects and control. Current Opinion in Psychology 29:187–192.

Loewenfeld, I. E. (1958). Mechanisms of reflex dilatation of the pupil. *Documenta Ophthalmologica*, *12*(1), 185-448.

Luck, S.J., & Gaspelin, N. (2017). How to get statistically significant effects in any ERP experiment (and why you shouldn't). Psychophysiology 54:146–157.

Mackintosh, N. J. (1975). A theory of attention: Variations in the associability of stimuli with reinforcement. *Psychological review, 82*(4), 276.

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG-and MEG-data. *Journal of neuroscience methods, 164*(1), 177-190.

Mather, M., & Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspectives on psychological science*, *6*(2), 114-133.

709 Mathôt, S. (2013). A simple way to reconstruct pupil size during eye blinks. *figshare*.
710 http://dx.doi.org/10.6084/m9.figshare.688002
711 Mathôt, S. (2018). Pupillometry: Psychology, physiology, and function. *Journal of Cognition*,
712 *1*(1).
713 McShane, B. B., Gal, D., Gelman, A., Robert, C., & Tackett, J. L. (2019). Abandon statistical
714 significance. *The American Statistician*, *73*(sup1), 235-245.
715 Mitra, P. P., & Pesaran, B. (1999). Analysis of dynamic brain imaging data. *Biophysical*
716 *journal, 76*(2), 691-708.
717 McTeague, L. M., Gruss, L. F., & Keil, A. (2015). Aversive learning shapes neuronal orientation
718 tuning in human visual cortex. *Nature communications*, *6*(1), 1-8.
719 Moratti, S., & Keil, A. (2005). Cortical activation during Pavlovian fear conditioning depends on
720 heart rate response patterns: An MEG study. *Cognitive Brain Research, 25*, 459–471.
721 Moratti, S., & Keil, A. (2009). Not what you expect: experience but not expectancy predicts
722 conditioned responses in human visual and supplementary cortex. *Cerebral Cortex,*
723 *19*(12), 2803-2809.
724 Moratti, S., Keil, A., & Miller, G. A. (2006). Fear but not awareness predicts enhanced sensory
725 processing in fear conditioning. *Psychophysiology, 43*, 216–226.
726 Naber, M., Alvarez, G. A., & Nakayama, K. (2013). Tracking the allocation of attention using
727 human pupillary oscillations. *Frontiers in psychology*, *4*, 919.
728 Nurminen, L., Merlin, S., Bijanzadeh, M., Federer, F., & Angelucci, A. (2018). Top-down
729 feedback controls spatial summation and response amplitude in primate visual cortex.
730 *Nature communications*, *9*(1), 1-13.
731 Olmos-Solis, K., van Loon, A. M., & Olivers, C. N. (2018). Pupil dilation reflects task relevance
732 prior to search. *Journal of cognition*, *1*(1).
733

734 Onat, S., & Büchel, C. (2015). The neuronal basis of fear generalization in humans. *Nature*
735 *neuroscience*, *18*(12), 1811-1818.
736 O'Neill, B. (2009). Exchangeability, correlation, and Bayes' effect. *International statistical*
737 *review, 77*(2), 241-250.
738 Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source
739 software for advanced analysis of MEG, EEG, and invasive electrophysiological
740 data. *Computational intelligence and neuroscience, 2011*.
741 Pascual-Marqui, R. D. (2007). Discrete, 3D distributed, linear imaging methods of electric
742 neuronal activity. Part 1: exact, zero error localization. *arXiv preprint*
743 *arXiv*:0710.3341.
744 Pascual-Marqui, R. D., Lehmann, D., Koukkou, M., Kochi, K., Anderer, P., Saletu, B., ...
745 & Kinoshita, T. (2011). Assessing interactions in the brain with exact low-
746 resolution electromagnetic tomography. *Philosophical Transactions of the Royal*
747 *Society A: Mathematical, Physical and Engineering Sciences, 369*(1952), 3768-
748 3784.
749 Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: variations in the
750 effectiveness of conditioned but not of unconditioned stimuli. *Psychological*
751 *review*, *87*(6), 532.
752 Petro, N. M., Gruss, L. F., Yin, S., Huang, H., Miskovic, V., Ding, M., & Keil, A. (2017).
753 Multimodal imaging evidence for a frontoparietal modulation of visual cortex
754 during the selective processing of conditioned threat. *Journal of cognitive*
755 *neuroscience*, *29*(6), 953-967.
756 Popov, T., Oostenveld, R., & Schoffelen, J. M. (2018). FieldTrip made easy: an analysis
757 protocol for group analysis of the auditory steady state brain response in time,
758 frequency, and space. *Frontiers in neuroscience*, *12*, 711.

759 Posner, M. I. (1980). Orienting of attention. *Quarterly journal of experimental psychology*,
760 *32*(1), 3-25.
761 Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual review*
762 *of neuroscience*, *13*(1), 25-42.
763 Priebe, N. J., & Ferster, D. (2008). Inhibition, spike threshold, and stimulus selectivity in
764 primary visual cortex. *Neuron*, *57*(4), 482-497.
765 R Core Team (2018). R: A language and environment for statistical computing. R Foundation for
766 Statistical Computing, Vienna, Austria.
767 URL https://www.R-project.org/.
768
769 Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *American*
770 *psychologist*, *43*(3), 151.
771 Rescorla, R. H., & Wagner, A. F. (1972). Classical conditioning ii: Current research and
772 theory. In *Classical conditioning II: Current research and theory* (pp. 64-99).
773 New York: Appleton-Century-Crofts.
774 Ringach, D. L., Hawken, M. J., & Shapley, R. (2003). Dynamics of orientation tuning in
775 macaque V1: the role of global and tuned suppression. *Journal of*
776 *Neurophysiology*, *90*(1), 342-352.
777 Romei, V., Gross, J., & Thut, G. (2010). On the role of prestimulus alpha rhythms over occipito-
778 parietal areas in visual input regulation: correlation or causation?. *Journal of*
779 *Neuroscience*, *30*(25), 8692-8697.
780 Rosenthal, R. (1987). *Judgment studies: Design, analysis, and meta-analysis.* Cambridge
781 University Press.
782 Rosenthal, R., Rosnow, R. L., & Rubin, D. B. (2000). *Contrasts and effect sizes in behavioral*
783 *research: A correlational approach*. Cambridge University Press.
784

785 Rosnow, R. L., & Rosenthal, R. (1989). Definition and interpretation of interaction effects.
786 *Psychological Bulletin, 105*(1), 143.
787 Rosnow, R. L., & Rosenthal, R. (1995). “Some things you learn aren't so”: Cohen's paradox,
788 Asch's paradigm, and the interpretation of interaction. *Psychological Science, 6*(1), 3-
789 9.
790 Rosnow, R. L., Rosenthal, R., & Rubin, D. B. (2000). Contrasts and correlations in effect-size
791 estimation. *Psychological Science, 11*, 446–453.
792 Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for
793 accepting and rejecting the null hypothesis. *Psychonomic bulletin & review*, *16*(2), 225-
794 237.
795 Schechtman, E., Laufer, O., & Paz, R. (2010). Negative valence widens generalization of
796 learning. *Journal of Neuroscience*, *30*(31), 10460-10464.
797 Schneiderman, N. (1972). Response system divergencies in aversive classical
798 conditioning. *Classical conditioning II: Current research and theory*, 341-376.
799 Shapley, R. (2004). A new view of the primary visual cortex. *Neural Networks*, *17*(5-6), 615-
800 623.
801 Shapley, R., Hawken, M., & Xing, D. (2007). The dynamics of visual responses in the primary
802 visual cortex. *Progress in brain research*, *165*, 21-32.
803 Siman-Tov, T., Mendelsohn, A., Schonberg, T., Avidan, G., Podlipsky, I., Pessoa, L., ... &
804 Hendler, T. (2007). Bihemispheric leftward bias in a visuospatial attention-related
805 network. *Journal of Neuroscience*, *27*(42), 11271-11278.
806 Smith, J. B., & Batchelder, W. H. (2008). Assessing individual differences in categorical data.
807 *Psychonomic Bulletin & Review, 15*(4), 713-731.
808
809

Song, I., & Keil, A. (2014). Differential classical conditioning selectively heightens response gain of neural population activity in human visual cortex. *Psychophysiology*, *51*(11), 1185-1194.

Sprague, T. C., & Serences, J. T. (2013). Attention modulates spatial priority maps in the human occipital, parietal and frontal cortices. *Nature neuroscience*, *16*(12), 1879-1887.

Stegmann, Y., Ahrens, L., Pauli, P., Keil, A., & Wieser, M. J. (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. *Neuroscience & Biobehavioral Reviews*, *59*, 201-207.

Summerfield C, Egner T (2016) Feature-Based Attention and Feature-Based Expectation. *Trends in Cognitive Sciences, 20*, 401–404.

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, *2*(2), 1-11.

Tuominen, L., Boeke, E., DeCross, S., Wolthusen, R. P., Nasr, S., Milad, M., ... & Holt, D. (2019). The relationship of perceptual discrimination to neural mechanisms of fear generalization. *NeuroImage*, *188*, 445-455.

Yeonan-Kim, J., & Bertalmío, M. (2016). Retinal lateral inhibition provides the biological basis of long-range spatial induction. *PloS one*, *11*(12), e0168963.

Wagenmakers, E. J. (2007). A practical solution to the pervasive problems of p values. *Psychonomic bulletin & review*, *14*(5), 779-804.

Weinberger, N. M. (2004). Specific long-term memory traces in primary auditory cortex. *Nature Reviews Neuroscience*, *5*(4), 279-290.

838 Wetzels, R., Matzke, D., Lee, M. D., Rouder, J. N., Iverson, G. J., & Wagenmakers, E. J. (2011).
839
840 Statistical evidence in experimental psychology: An empirical comparison using 855 t
841 tests. *Perspectives on Psychological Science*, *6*(3), 291-298.
842 Wiens, S., & Nilsson, M. E. (2017). Performing contrast analysis in factorial designs: From
843 NHST to confidence intervals and beyond. *Educational and psychological*
844 *measurement, 77*(4), 690-715.
845 Wieser, M. J., Miskovic, V., & Keil, A. (2016). Steady-state visual evoked potentials as a
846 research tool in social affective neuroscience. *Psychophysiology*, *53*(12), 1763-1775.
847 Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014).
848 Permutation inference for the general linear model. *Neuroimage, 92*, 381-397.
849

Figure Captions

Figure 1 Gaussian and difference-of-gaussian gradients. Grey 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+).

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.

Figure 3 Pre-source estimation ssVEP and alpha frequency spectra. The grand mean of sensor-space 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.

Figure 4 Grand mean source-localized topographies. (top) Steady-state 15 Hz **t**opographical 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.

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.

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.

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 (black dots) and 5 unaware (blue triangle) individuals and for the average over participants (orange line) during the acquisition trial block. The first assessment (x=0) was done at the beginning of the acquisition trial block prior to 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 cut-off 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.

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.

Figure 9 Pupil response time course. Pupil response as a function of spatial distance from an aversively paired location is shown as a percent of mean manufacturer (SR Research) reported arbitrary units (1000 – 100 milliseconds pre-stimulus onset) in habituation (top, left) and acquisition (top, right) trial blocks. (bottom, left) Percent 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.