

EEG signals index a global signature of arousal embedded in neuronal population recordings

Richard Johnston^{1, 2, 3}, Adam C. Snyder^{4, 5, 6}, Rachel S. Schibler⁷, and Matthew A. Smith^{1, 2, 3}

¹Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, USA; ²Neuroscience Institute, Carnegie Mellon University, Pittsburgh, USA; ³Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, USA; ⁴Department of Brain and Cognitive Sciences, University of Rochester, Rochester, USA; ⁵Department of Neuroscience, University of Rochester, Rochester, USA; ⁶Center for Visual Science, University of Rochester, Rochester, USA; ⁷Harvey Mudd College, California, USA.

Corresponding author:

Matthew A. Smith, PhD

Carnegie Mellon University

Department of Biomedical Engineering and Neuroscience Institute

Mellon Institute, Room 115

Pittsburgh

Pa, 15213

Email: mattsmith@cmu.edu

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31 Abstract

32 Electroencephalography (EEG) has long been used to index brain states, from early studies
33 describing activity in the presence and absence of visual stimulation to modern work employing
34 complex perceptual tasks. These studies have shed light on brain-wide signals but often lack
35 explanatory power at the single neuron level. Similarly, single neuron recordings can suffer from an
36 inability to measure brain-wide signals accessible using EEG. Here, we combined these techniques
37 while monkeys performed a change detection task and discovered a novel link between spontaneous
38 EEG activity and a neural signal embedded in the spiking responses of neuronal populations. This
39 “slow drift” was associated with fluctuations in the subjects’ arousal levels over time: decreases in
40 pre-stimulus alpha power were accompanied by increases in pupil size and decreases in microsaccade
41 rate. These results show that brain-wide EEG signals can be used to index modes of activity present
42 in single neuron recordings, that in turn reflect global changes in brain state that influence perception
43 and behavior.

44 45 Significance Statement

46 Decades of research has used electroencephalography (EEG) to investigate how voltage fluctuations
47 on the scalp are related to cognition. These studies are useful for measuring brain-wide signals in a
48 non-invasive manner, but they lack the ability to detect small-scale changes at the level of single
49 neurons. In this study, we bridged this gap by recording EEG and spiking responses in the brain while
50 macaques performed a perceptual decision-making task. We found that a commonly used metric of
51 arousal in human EEG studies, pre-stimulus alpha power, is associated with slow drifts in the activity
52 of cortical neurons. Together, these recordings made non-invasively on the scalp and directly in the
53 brain were predictive of changes in arousal levels over time.

54

55 Introduction

56 For decades, researchers have investigated how the spiking responses of single cortical
57 neurons relate to performance on decision-making (Britten et al., 1996), attention (Moran and
58 Desimone, 1985) and working memory (Fuster and Alexander, 1971) tasks. Interactions between
59 pairs of neurons have also been studied extensively since technological advances in neural recording
60 systems (e.g. microelectrode arrays and two-photon imaging) made it possible to monitor the activity
61 of neural populations simultaneously (Zohary et al., 1994; Cohen and Maunsell, 2009; Leavitt et al.,
62 2017). At the same time, it is becoming increasingly apparent that major insight about the
63 neurobiological basis of cognition can be gained from the study of populations of neurons (Cohen
64 and Maunsell, 2011; Harvey et al., 2012; Mante et al., 2013; Driscoll et al., 2017; Murray et al., 2017;
65 Ni et al., 2018; Remington et al., 2018; Khanna et al., 2019; Oby et al., 2019; Valente et al., 2021).
66 Furthermore, it has been shown that low-dimensional neural activity patterns can be used to index
67 global brain states, which influence performance on cognitive tasks. For example, Stringer et al.
68 (2019) applied principal component analysis (PCA) to data recorded from more than 10,000 neurons
69 in the mouse and found that fluctuations in the first principal component were associated with a host
70 of arousal-related variables including whisking, pupil size, and running speed. Musall et al. (2019)
71 found that uninstructed movements, which themselves may occur at varying frequency based on
72 arousal, were related to brain-wide activity in the mouse. In our own work in rhesus macaques, we
73 have reported a pervasive “slow drift” of neural activity (Cowley et al., 2020), which is correlated
74 with a distinctive pattern of eye metrics that is strongly indicative of changes in arousal (Johnston et
75 al., 2021). However, it is unknown if slow drift is associated with other arousal-related variables that
76 can be measured in a rapid, accurate and non-invasive manner.

77 Spontaneous (i.e., pre-stimulus) oscillations in the alpha frequency band (~8-12Hz) are
78 associated with lateralized changes in spatial attention and global changes in arousal. For example,
79 studies investigating the effects of spatial attention on EEG activity have found that pre-stimulus
80 alpha power is decreased in the visual cortex contralateral to the attended location (Worden et al.,

2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006). In contrast, studies exploring the processes underlying perceptual decision-making have uncovered an association between task performance and brain-wide changes in pre-stimulus alpha power. To be more precise, the likelihood of detecting a near threshold visual stimulus increases when pre-stimulus oscillations in the alpha band decrease (Ergenoglu et al., 2004; Babiloni et al., 2006; Hanslmayr et al., 2007; van Dijk et al., 2008; Busch et al., 2009; Mathewson et al., 2009; Romei et al., 2010). Recent work suggests that these global effects (that occur across a range of frontal, midline, and occipital sites) arise due to changes in arousal. According to signal detection theory (Green and Swets, 1966), differences in performance on perceptual decision-making tasks can either reflect shifts in sensitivity or response criterion. Several studies have sought to dissociate these components in macaque monkeys (Luo and Maunsell, 2015, 2018; Crapse et al., 2018; Jun et al., 2021) and similar work has been conducted in human subjects using EEG. For example, it has been shown that brain-wide decreases in pre-stimulus alpha power are associated with increased hit rate and false alarm rate on perceptual decision-making tasks (Limbach and Corballis, 2016; Iemi et al., 2017). These results point to a link between pre-stimulus alpha power and response criterion, a variable that is modulated, at least in part, by subcortical regions that control arousal levels (de Gee et al., 2017).

One structure that has been implicated in the control of arousal is the locus coeruleus (LC) (Aston-Jones and Cohen, 2005; Sara, 2009; Chandler, 2016). This small region in the pons represents the primary source of norepinephrine to the central nervous system and drives fluctuations in raw and evoked (baseline-corrected) pupil size: non-invasive markers that have been used extensively in the neurosciences to index changes in arousal (Varazzani et al., 2015; Joshi et al., 2016; Reimer et al., 2016; Breton-Provencher and Sur, 2019). Given that the LC is involved in modulating response criterion (de Gee et al., 2017) and pupil size (Joshi and Gold, 2020), one might also expect it to exert an influence on pre-stimulus alpha power. To test this hypothesis non-invasively, one could determine if there is a significant association between pre-stimulus alpha power and pupil size. Several studies have used a combination of EEG and pupillometry to explore if this is the case in humans (Hong et

107 al., 2014; Van Kempen et al., 2019; Podvalny et al., 2021). For example, Compton et al. (2021) had
108 subjects perform a classic Stroop task and found that alpha power during inter-trial periods was
109 inversely related to raw pupil size. That is, trials with greater pupil size were associated with reduced
110 power in the alpha band and vice versa. These results suggest that spontaneous EEG signals can be
111 used to index global brain state and raise the possibility that they might be associated with other
112 arousal-related metrics such as microsaccade rate.

113 Microsaccades are small eye movements that occur at a rate of 1-2Hz through the activity of
114 neurons in the superior colliculus (SC) (Rolfs, 2009). As with larger saccades (Burr et al., 1994;
115 Diamond et al., 2000; Knöll et al., 2011), research has shown that visual perception is altered in the
116 hundreds of milliseconds following a microsaccade (Hafed and Krauzlis, 2010; Hafed, 2013; Chen
117 et al., 2015; Chen and Hafed, 2017; Scholes et al., 2018). Interestingly, Bellet et al. (2017) found that
118 these short timescale modulations occur in a rhythmic manner at a frequency of 8–20Hz. However, it
119 is unclear if a relationship exists between alpha oscillations and fixational eye movements at longer
120 timescales, which are more likely to be associated with changes in a subject’s internal state (Cowley
121 et al., 2020). Recent work in our laboratory found that slow fluctuations in raw pupil size over the
122 course of a recording session were negatively correlated with microsaccade rate (Johnston et al.,
123 2021). That is, microsaccade rate decreased under conditions of heightened arousal (as indexed by
124 greater pupil size) and vice versa. As described above, the relationship between pre-stimulus alpha
125 power and microsaccade rate has not yet been explored at long timescales. However, based on our
126 previous results, one might expect there to be a positive correlation between these two variables over
127 time.

128 The primary aim of this study was to determine if EEG signals recorded on the scalp can be
129 used to index a neural measure of brain state acquired directly from the spiking activity of neural
130 populations termed “slow drift”. In addition, we investigated if pre-stimulus oscillations in the alpha
131 band are associated with two non-invasive metrics that have previously been used to index global
132 shifts in arousal and that we have found to be related to “slow drift” (Johnston et al., 2021): raw pupil

size and microsaccade rate. EEG from the scalp and spiking activity from populations of neurons in V4 was simultaneously recorded from two monkeys while they performed an orientation-change detection task (Figure 1A). Results showed that fluctuations in pre-stimulus alpha power over the course of a recording session were accompanied by changes in raw pupil size and microsaccade rate. As expected, pre-stimulus power in the alpha band was negatively correlated with raw pupil size and positively correlated with microsaccade rate. Interestingly, we also found a significant correlation between pre-stimulus alpha power and neural slow drift. This finding is of particular importance as it suggests that spontaneous components of the EEG signal recorded non-invasively on the scalp index low-dimensional patterns of neural activity acquired from microelectrode array recordings in the brain. These results support previous research showing that slow drift is associated with changes in arousal over time (Cowley et al., 2020; Johnston et al., 2021), and provide a strong link between global measurements made across recording modalities and species.

Methods

Subjects

Two adult male rhesus macaque monkeys (*Macaca mulatta*) were used in this study. A previous report (Snyder et al., 2018b) presented analysis of different aspects of the same experiments described here. This study reports the results from a subset of the data from Snyder et al. (2018b) in which EEG was recorded. Surgical procedures to chronically implant a titanium head post (to immobilize the subjects' heads during experiments) and microelectrode arrays were conducted in aseptic conditions under isoflurane anesthesia, as described in detail by Smith and Sommer (2013). Opiate analgesics were used to minimize pain and discomfort during the perioperative period. Neural activity was recorded using 100-channel "Utah" arrays (Blackrock Microsystems) in V4 (Monkey Pe = right hemisphere; Monkey Wa = left hemisphere). The arrays comprised a 10x10 grid of silicon microelectrodes (1 mm in length) spaced 400 μ m apart. Experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh and were performed

158 in accordance with the United States National Research Council's Guide for the Care and Use of
159 Laboratory Animals.

160 Microelectrode array recordings

161 Signals from each microelectrode in the array were amplified and band-pass filtered (0.3–
162 7500Hz) by a Grapevine system (Ripple). Waveform segments crossing a threshold (set as a multiple
163 of the root mean square noise on each channel) were digitized (30KHz) and stored for offline analysis
164 and sorting. First, waveforms were automatically sorted using a competitive mixture decomposition
165 method (Shoham et al., 2003). They were then manually refined using custom time amplitude window
166 discrimination software (code available at <https://github.com/smithlabvision/spikesort>), which takes
167 into account metrics including (but not limited to) waveform shape and the distribution of interspike
168 intervals (Kelly et al., 2007). A mixture of single and multiunit activity was recorded, but we refer
169 here to all units as “neurons”. The mean number of V4 neurons across sessions was 41 (SD = 10) for
170 Monkey Pe and 21 (SD = 10) for Monkey Wa.

171 EEG recordings

172 We recorded EEG from 8 Ag/AgCl electrodes (Grass Technologies) adhered to the scalp with
173 electrically conductive paste. The electrodes were positioned roughly at the following locations: Fz,
174 Iz, CP3, CP4, F5, F6, PO7, and PO8 (see Fig. 1B). Signals for each electrode were referenced online
175 to a steel screw on the titanium head post, digitized at 1kHz and amplified by a Grapevine system
176 (Ripple) and low-pass filtered online at 250Hz. They were then rereferenced to the average activity
177 across all electrodes for the entire session. One of the challenges associated with simultaneously
178 recording EEG and the spiking responses of neural populations is the introduction of craniotomies
179 and microelectrode recording arrays. Importantly, previous work in our lab has shown that this does
180 not significantly alter the way current flows to the scalp (Snyder et al., 2018a). We found that FFTs
181 computed before and after craniotomies (performed to implant microelectrode arrays) are highly
182 correlated suggesting that our results are generalizable to EEG recorded from human subjects with
183 an intact skull. Segments of EEG data were recorded for each electrode during the first 300ms of pre-

184 stimulus periods on the change detection task (Figure 1A). A constant duration was needed in order
185 to remove aperiodic activity that has a 1/f-like distribution (Donoghue et al., 2020). We did not include
186 the first pre-stimulus period due to an increase in eye position variability resulting from fixation
187 having been established a short time earlier. Such variability was not present in the following pre-
188 stimulus periods (see Figure 1 in Johnston et al., 2021). Several outlier rejection steps were then
189 taken. First, segments of EEG data were considered excessively noisy and removed if any of the
190 electrodes had a standard deviation that was 10 times greater than the mean of the entire session, or
191 if any of the electrodes exhibited a flat signal defined as a standard deviation less than 300 nanovolts
192 (Snyder et al., 2018a). Segments of EEG data were also removed if there was evidence of excessive
193 variability in the eye trace. For each session, we computed 1D eye velocity during each pre-stimulus
194 period. EEG segments were removed if the standard deviation of the eye velocity was 2 times greater
195 than the mean eye velocity across all pre-stimulus periods. This final step was necessary to ensure
196 that changes in pre-stimulus alpha power did not arise due to eye movement artifacts.

197 Visual stimuli

198 Visual stimuli were generated using a combination of custom software written in MATLAB
199 (The MathWorks) and Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). They were
200 displayed on a CRT monitor (resolution = 1024 X 768 pixels; refresh rate = 100Hz), which was viewed
201 at a distance of 36cm and gamma-corrected to linearize the relationship between input voltage and
202 output luminance using a photometer and look-up-tables.

203 Behavioral task

204 Subjects fixated a central point (diameter = 0.6°) on the monitor to initiate a trial (Figure 1A).
205 Each trial comprised a sequence of stimulus periods (400ms) separated by brief pre-stimulus
206 (fixation) periods. The duration of each pre-stimulus period was drawn at random from a uniform
207 distribution spanning 300-500ms but EEG data were only analyzed during the first 300ms (see
208 above). The 400ms stimulus periods comprised pairs of drifting full-contrast Gabor stimuli. One
209 stimulus was presented in the aggregate receptive field (RF) of the recorded V4 neurons, whereas the

other stimulus was presented in the mirror-symmetric location in the opposite hemifield. Although the spatial (Monkey Pe = 0.85cycles/°; Monkey Wa = 0.85cycles/°) and temporal frequencies (Monkey Pe = 8cycles/s; Monkey Wa = 7cycles/s) of the stimuli were not optimized for each individual V4 neuron they did evoke a strong response from the population. The orientation of the stimulus in the aggregate RF was chosen at random to be 45 or 135°, and the stimulus in the opposite hemifield was assigned the other orientation. There was a fixed probability (Monkey Pe = 30%; Monkey Wa = 40%) that one of the Gabors would change orientation by ± 1 , ± 3 , ± 6 , or $\pm 15^\circ$ on each stimulus presentation. The sequence continued until the subject: 1) made a saccade to the changed stimulus within 400ms (“hit”); 2) made a saccade to an unchanged stimulus (“false alarm”); or 3) remained fixating for more than 400ms after a change occurred (“miss”). If the subject correctly detected an orientation change, they received a liquid reward. In contrast, a time-out occurred if the subject made a saccade to an unchanged stimulus delaying the beginning of the next trial by 1s. It is important to note that the effects of spatial attention were also investigated (although not analyzed in this study) by cueing blocks of trials such that the orientation change was 90% more likely to occur in one hemifield relative to the other hemifield.

Eye tracking

Eye position and pupil diameter were recorded monocularly at a rate of 1000Hz using an infrared eye tracker (EyeLink 1000, SR Research).

Microsaccade detection

Microsaccades were defined as eye movements that exceeded a velocity threshold of 6 times the standard deviation of the median velocity for at least 6ms (Engbert and Kliegl, 2003). They were required to be separated in time by at least 100ms. In addition, we removed microsaccades with an amplitude greater than 1° and a velocity greater than 100°/s. To assess the validity of our microsaccade detection method, the correlation (Pearson product-moment correlation coefficient) between the amplitude and peak velocity of detected microsaccades (i.e., the main sequence) was computed for each session. The mean correlation between these two metrics across sessions was 0.84

236 (SD = 0.06) indicating that our detection algorithm was robust as microsaccades fell on the main
237 sequence (Zuber et al., 1965).

238 Pre-stimulus power

239 For each electrode, FFTs were computed using Hanning-windowed segments of EEG data
240 spanning the first 300ms of the pre-stimulus period (Figure 1A). Note that we did not include the first
241 pre-stimulus period due to an increase in eye position variability resulting from fixation having been
242 established a short time earlier (see above). The data for each electrode was then binned using a 30-
243 minute sliding window (step size = 6 minutes), which yielded eight FFTs per time bin (one for each
244 electrode). We wanted to rule out the possibility that slow drift was associated with gradual changes
245 in 1/f noise (Donoghue et al., 2021). Therefore, the aperiodic component of the signal was estimated
246 by fitting an exponential to the binned FFTs for each electrode (Donoghue et al., 2020). Residual
247 power was then computed by subtracting off the aperiodic portion of the signal. Previous research
248 has shown that pre-stimulus alpha power is associated with performance on visual detection tasks
249 across a range of frontal, midline, and posterior electrodes (Ergenoglu et al., 2004; Busch et al., 2009;
250 Iemi et al., 2017). Hence, the aperiodic adjusted (residual) FFTs from all eight electrodes were
251 averaged together for each time bin. Finally, we computed the mean residual power in different
252 frequency bands. For each time bin, residual power was computed in the theta (4-8Hz), alpha (8-
253 12Hz), beta (12-30Hz) and gamma (30-50Hz) bands.

254 Eye metrics

255 Mean pupil diameter was measured during stimulus periods, whereas microsaccade rate was
256 measured during pre-stimulus periods (Johnston et al., 2021). We did not include the initial fixation
257 period when measuring microsaccade rate. As described above, there was an increase in eye position
258 variability during this period resulting from fixation having been established a short time earlier (300-
259 500ms). Such variability was not present in following pre-stimulus periods (see Figure 1 in Johnston
260 et al., 2021). Reaction time and saccade velocity were measured on trials in which the subjects were
261 rewarded for correctly detected an orientation change. Reaction time was defined as the time from

262 when the change occurred to the time at which the saccade exceeded a velocity threshold of 150°/s.
263 Saccade velocity was the peak velocity of the saccade to the changed stimulus. To isolate slow
264 changes in the eye metrics over time, the data for each session was binned using a 30-minute sliding
265 window stepped every 6 minutes. The width of the window, and the step size, were chosen to isolate
266 slow changes over time based on previous research. They were the same as those used by Cowley et
267 al. (2020) and Johnston et al. (2021), which meant direct comparisons could be made across studies.

268 Calculating slow drift

269 The spiking responses of populations of neurons in V4 were measured during a 400ms period
270 that began 50ms after stimulus presentation (Figure 1A). Research has shown that neurons in V4 are
271 tuned for stimulus orientation (Desimone and Schein, 1987). To prevent the PCA identifying
272 components related to stimulus tuning, residual spike counts were computed by subtracting the mean
273 response for a given orientation (45 or 135°) across the entire session from individual responses to
274 that orientation. To isolate slow changes in neural activity over time, residual spike counts for each
275 V4 neuron were binned using a 30-minute sliding window stepped every 6 minutes. PCA was then
276 performed to reduce the high-dimensional residual data to a smaller number of latent variables
277 (Cunningham and Yu, 2014). Slow drift in V4 was estimated by projecting the binned residual spike
278 counts for each neuron along the first principal component.

279 Aligning slow drift across sessions

280 As described above, slow drift was calculated by projecting binned residual spike counts along
281 the first principal component. The weights in a PCA can be positive or negative (Jolliffe and Cadima,
282 2016), which meant the sign of the correlation between slow drift and a given metric was arbitrary.
283 Preserving the sign of the correlations was particularly important in this study because we were
284 interested in whether slow drift was associated with a pattern that is indicative of changes in the
285 subjects' arousal levels over time i.e., decreased pre-stimulus alpha power, increased pupil size and
286 decreased microsaccade rate. For simplicity, we adopted an identical approach to that used in our
287 previous study (Johnston et al., 2021). That is, the sign of the slow drift was flipped if the majority of

neurons had negative weights. Forcing the majority of neurons to have positive weights established a common reference frame in which an increase in the value of slow drift was associated with higher firing rates among the majority of neurons.

Estimating the timescale of slow drift and pre-stimulus alpha power

To determine the timescale at which each variable fluctuated over the course of a session Gaussian smoothing was performed (Cowley et al., 2020). The first thing to note is that slow drift was computed in a slightly different manner. To improve temporal resolution, the thirty-minute sliding window (used to bin residual spike counts) was stepped every 1 minute instead of every 6 minutes. The same approach was taken when computing pre-stimulus alpha power. Gaussian smoothing was then performed in a cross-validated manner using standard deviations (i.e., timescales) ranging from 1 to 90 minutes (step size = 1 minute). To determine the timescale of the fluctuation, a R^2 was computed for each standard deviation by leaving out randomly chosen time points for each fold (10 in total) and then predicting the value of each held-out point by calculating a Gaussian weighted average of its neighbors. We found the standard deviation with the maximum R^2 and the standard deviation at which the R^2 dropped to 75% of the maximum R^2 . The latter was taken to be the timescale of the fluctuation.

Choice of analysis time windows

We chose to analyze spiking responses during stimulus periods for consistency across studies. This was the approach taken in our original paper that discovered a slow drift of neural activity in macaque visual and prefrontal cortex (Cowley et al., 2020) and in a follow-up study that included other eye-related metrics such as microsaccade rate and evoked pupil size (Johnston et al., 2021). The reason we chose to analyze microsaccade rate during pre-stimulus periods was to avoid bi-phasic changes that occur during visual stimulus presentation. More specifically, microsaccade rate decreases shortly after a visual stimulus has been presented and then increases later (Engbert and Kliegl, 2003; Rolfs et al., 2008; Hafed and Ignashchenkova, 2013). With regards to segments of EEG data, decades of research has shown that decreased alpha power during pre-stimulus periods is

314 associated with improved performance on change detection tasks (Ergenoglu et al., 2004; Babiloni et
315 al., 2006; Hanslmayr et al., 2007; van Dijk et al., 2008; Busch et al., 2009; Mathewson et al., 2009;
316 Romei et al., 2010). Therefore, we adopted the same approach and analyzed segments of EEG data
317 during pre-stimulus periods.

318 Data availability

319 All data and code for this manuscript are available at the following link:

320 <https://doi.org/10.1184/R1/19248827>

321

322 Results

323 To determine if spontaneous components of the EEG signal can provide insight into the
324 internal brain state associated with slow drift, we trained two macaque monkeys to perform an
325 orientation-change detection task in which pairs of stimuli were repeatedly presented (Figure 1A).
326 Spiking responses of populations of neurons in visual cortex (V4) were recorded using 100-channel
327 “Utah” arrays as well as EEG on the scalp (Figure 1B). For each electrode, FFTs were computed
328 using segments of EEG data recorded during pre-stimulus periods. The data were then binned using
329 a 30-minute sliding window stepped every 6 minutes (Figure 2A). Prior to averaging across
330 electrodes, aperiodic activity that was 1/f-like in nature was estimated and subtracted off (see
331 *Methods*). Finally, mean residual power was computed in distinct frequency bands. Our primary focus
332 was on pre-stimulus alpha oscillations, but we also computed pre-stimulus power in the theta, beta,
333 and gamma bands. In addition, raw pupil size and microsaccade rate were recorded during stimulus
334 and pre-stimulus periods, respectively.

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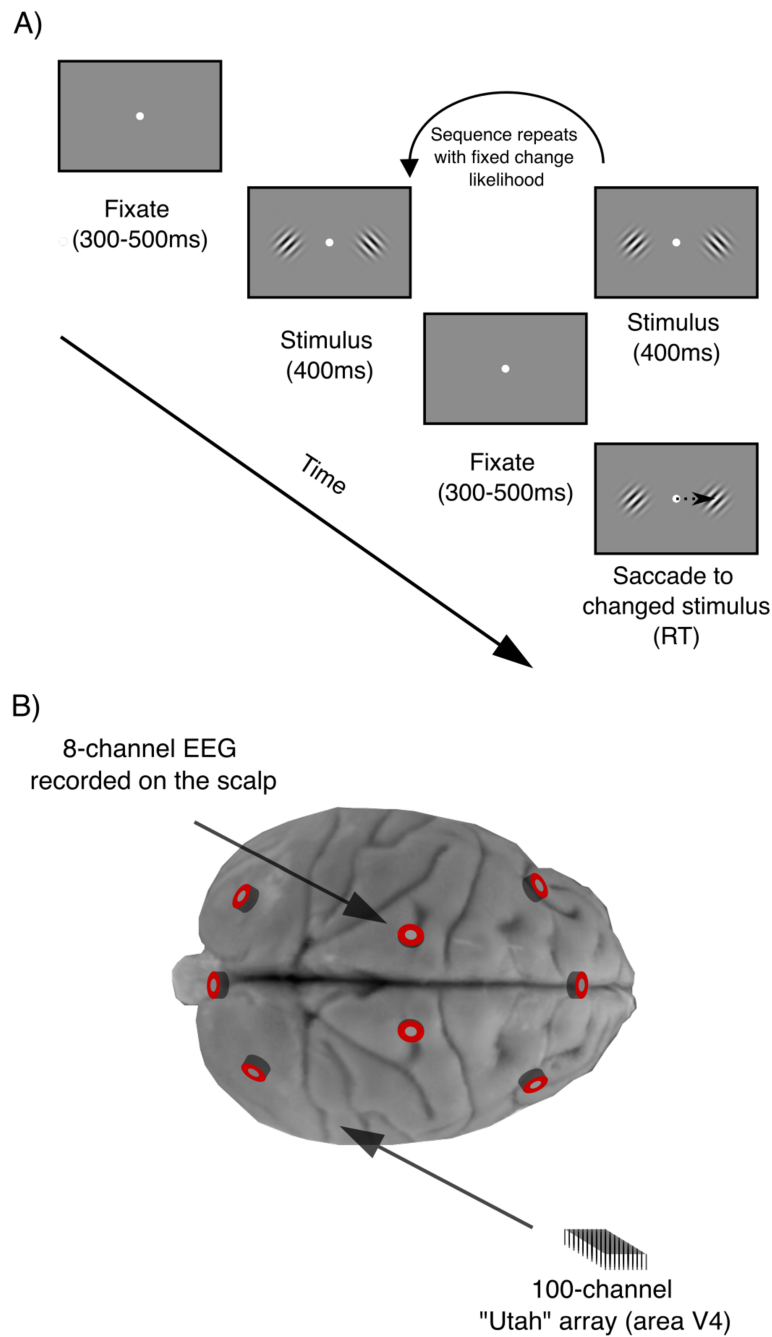


Figure 1. Experimental methods. (A) Orientation-change detection task. After an initial fixation period, a sequence of stimuli (orientated Gabor pairs separated by brief pre-stimulus periods spanning 300-500ms) was presented. The subject's task was to detect an orientation change in one of the stimuli and make a saccade to the changed stimulus. (B) Electrophysiological recordings. We simultaneously recorded: 1) spiking responses of populations of neurons in V4 using 100-channel microelectrode ("Utah") arrays; and 2) EEG from 8 electrodes positioned on the scalp. Spiking responses of populations of neurons in V4 were recorded during 400ms stimulus periods, whereas EEG was recorded during the first 300ms of pre-stimulus periods.

Correlation between pre-stimulus alpha power and raw pupil size

First, we explored the relationship between pre-stimulus alpha power and raw pupil size. As described above, several studies in humans have established a link between these two variables using a combination of EEG and pupillometry (Hong et al., 2014; Van Kempen et al., 2019; Podvalny et al., 2021). Most recently, Compton et al. (2021) found that alpha power during inter-trial periods on a Stroop task was inversely related to raw pupil size. That is, trials with greater pupil size were associated with reduced power in the alpha band and vice versa. To investigate if a similar relationship was found in our data, raw pupil size measurements were binned using the same 30-minute sliding window that was used to bin the EEG data. Note that the width of the window, and the step size, were chosen to isolate slow changes over time based on previous studies we performed (Cowley et al., 2020; Johnston et al., 2021). Example sessions for Monkey Pe and Monkey Wa are shown in Figure 2B (top and bottom rows, respectively). In support of previous research, pre-stimulus power in the alpha band was negatively associated with raw pupil size in each example session for both subjects.

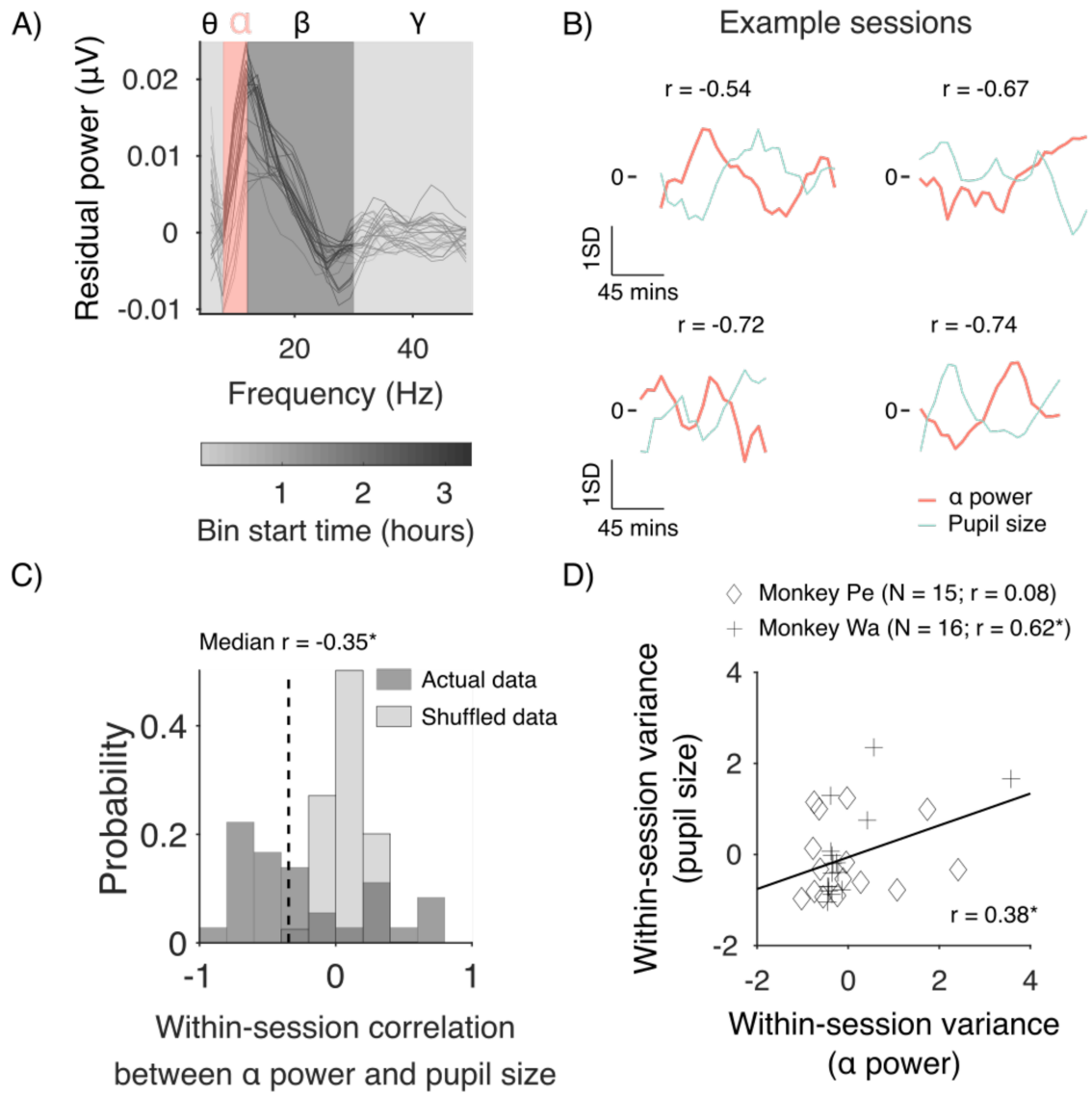


Figure 2. Correlation between pre-stimulus alpha power and raw pupil size. (A) Isolating slow fluctuations in pre-stimulus alpha power. A mean FFT was computed for each large 30-minute bin (represented by gray lines) by averaging across electrodes. Note that the aperiodic portion of the signal was removed prior to averaging across electrodes (see Methods), which explains why residual power, as opposed to raw power, is shown on the y-axis. (B) Four example sessions in which there was a moderate to strong correlation between pre-stimulus alpha power and raw pupil size. The top row contains two sessions for Monkey Pe, whereas the bottom row contains two sessions for Monkey Wa. Note that the data were z-scored for visualization purposes only (i.e., so that variables with different units could be shown on the same plot). (C) A histogram showing the distribution of correlation values across sessions between pre-stimulus alpha power and raw pupil size. We used a Wilcoxon signed rank test to test the null hypothesis that the median correlation across sessions was equal to zero (Monkey Pe: median $r = -0.41$, $p = 0.008$; Monkey Wa: median $r = -0.31$, $p = 0.301$). (D) A scatter plot showing how the magnitude of fluctuations in pre-stimulus alpha power (as measured by computing within-session variance) relate to the magnitude of fluctuations in raw pupil size. Note that the data were z-scored separately for each Monkey to control for potential differences in variance between subjects. Failing to control for this might have led to an artifactual correlation if the variance for one subject was greater than the other or vice versa. Individual correlations for each monkey have been reported in the figure legend along with the number of sessions included in the analysis. SD = standard deviation. θ = theta, α = alpha, β = beta, γ = gamma. $p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$.

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393 The example sessions in Figure 2B exhibit moderate to strong trends. However, it is difficult
394 to determine if two variables that fluctuate slowly over time are correlated over the course of a single
395 session. Standard correlation analyses assume that all samples are independent, but smoothed
396 variables can violate this assumption leading to “nonsense correlations” between variables that are
397 unrelated (Harris, 2020). An easy way to overcome this problem is to record data from multiple
398 sessions. Two approaches can then be adopted: 1) one can compute a correlation for each session, and
399 then perform a statistical test to investigate if the distribution of coefficients across sessions is
400 centered on zero; or 2) one can explore if the magnitude of fluctuations in one of the variables is
401 associated with the magnitude of fluctuations in the other variable. Both approaches were adopted in
402 the present study to investigate if there was a relationship between pre-stimulus alpha power and pupil
403 size across sessions (Monkey Pe = 15 sessions; Monkey Wa = 16 sessions). First, we investigated if
404 pre-stimulus power in the alpha band and raw pupil size were correlated over time. Within each
405 session, we computed a correlation (Pearson product-moment correlation coefficient) between pre-
406 stimulus alpha power and raw pupil size. As in our previous study (Johnston et al., 2021), we found
407 that null distributions (generated by computing correlations between sessions recorded on different
408 days) were centered on zero. Therefore, a Wilcoxon signed rank test was then used to test the null
409 hypothesis that the median correlation across sessions was equal to zero. Consistent with the pattern
410 of results observed in the four example sessions, we found that pre-stimulus alpha power was
411 significantly and negatively correlated with raw pupil size (Figure 2C, median $r = -0.35$, $p = 0.012$).
412 Next, we investigated if the magnitude of changes in EEG alpha power was correlated with the
413 magnitude of changes in raw pupil size. Within each session, we computed the variance of pre-
414 stimulus alpha power and raw pupil size. The data were then z-scored for each monkey separately to
415 control for potential differences in variance that might have led to an artifactual correlation when the
416 data were pooled across subjects. Finally, a correlation (Pearson product-moment correlation
417 coefficient) was performed to investigate if within-session variance in pre-stimulus alpha power was

significantly associated with within-session variance in raw pupil size. Results showed that the magnitude of changes in pre-stimulus alpha power was significantly correlated with the magnitude of changes in raw pupil size (Figure 2D, $r = 0.38$, $p = 0.035$). These findings support previous work in humans as they show that fluctuations in pre-stimulus alpha power were accompanied by global changes in the subjects' arousal levels (Hong et al., 2014; Van Kempen et al., 2019; Compton et al., 2021; Podvalny et al., 2021). This motivated us to ask if pre-stimulus alpha power is associated with other arousal-related metrics such as microsaccade rate.

Correlation between pre-stimulus alpha power and microsaccade rate

Recently, we found that microsaccade rate fluctuates over the course of a recording session in a manner that is consistent with slow changes in arousal over time (Johnston et al., 2021). More specifically, decreases in raw pupil size on a change detection task were accompanied by increases in microsaccade rate and vice versa. Hence, we were interested in whether pre-stimulus alpha power is correlated with microsaccade rate. Based on our previous research, we hypothesized that microsaccade rate would be positively correlated with pre-stimulus alpha power. To test this prediction, microsaccade rate measurements were binned using the same 30-minute sliding window stepped every 6 minutes. Example sessions for Monkey Pe and Monkey Wa are shown in Figure 3A (top and bottom rows, respectively). In support of our hypothesis, pre-stimulus alpha power was positively associated with microsaccade rate in each example session for both subjects.

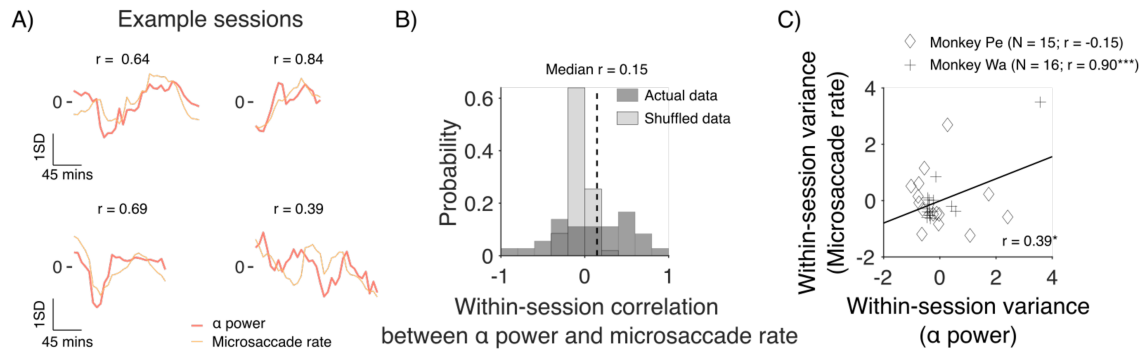


Figure 3. Correlation between pre-stimulus alpha power and microsaccade rate. (A) Four example sessions in which there was a moderate to strong correlation between pre-stimulus alpha power and microsaccade rate. The top row contains two sessions for Monkey Pe, whereas the bottom row contains two sessions for Monkey Wa. Note that the data were z-scored for visualization purposes only (i.e., so that variables with different units could be shown on the same plot). (B) A histogram showing the distribution of correlation values across sessions between pre-stimulus alpha power and microsaccade rate. A Wilcoxon signed rank test was used to test the null hypothesis that the median correlation across sessions was equal to zero (Monkey Pe: median $r = 0.23$, $p = 0.008$; Monkey Wa: median $r = -0.21$, $p = 0.44$). (C) A scatter plot showing how the magnitude of fluctuations in pre-stimulus alpha power (as measured by computing within-session variance) relate to the magnitude of fluctuations in microsaccade rate. Note that the data were z-scored separately for each Monkey to control for potential differences in variance that might have resulted in an artifactual correlation. Individual correlations for each monkey have been reported in the figure legend along with the number of sessions included in the analysis. SD = standard deviation. α = alpha. $p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$.

Next, we explored if a similar pattern was present across all sessions (Monkey Pe = 15 sessions; Monkey Wa = 16 sessions). As before, we first investigated if changes in pre-stimulus alpha power and microsaccade rate were correlated over time. Within each session, we computed the correlation (Pearson product-moment correlation coefficient) between pre-stimulus power in the alpha band and microsaccade rate. A Wilcoxon signed rank test was then used to test the null hypothesis that the median correlation across sessions was equal to zero. Despite the compelling trends on some example sessions (Figure 3A), there was no statistically significant correlation between pre-stimulus alpha power and microsaccade rate (Figure 3B, median $r = 0.15$, $p = 0.210$). Next, we investigated if the magnitude of changes in pre-stimulus alpha power was correlated with the magnitude of changes in microsaccade rate. Within each session, we computed the variance of pre-stimulus alpha power and microsaccade rate. A correlation (Pearson product-moment correlation coefficient) was then performed on z-scored data to investigate the relationship between within-

session variance in pre-stimulus alpha power and within-session variance in microsaccade rate. Results showed that the magnitude of changes in pre-stimulus alpha power was significantly correlated with the magnitude of changes in microsaccade rate (Figure 3C, $r = 0.39$, $p = 0.029$). Although we note that the median within-session correlation between slow drift and microsaccade rate was not significantly different from zero (Figure 3B), the compelling match in the time course of individual sessions (Figure 3A) and the significant session-by-session correlation in variance (Figure 3C) are important for at least two reasons. Firstly, they establish a novel link between pre-stimulus alpha power and fixational eye movements at long timescales. Secondly, they provide further evidence to suggest that fluctuations in pre-stimulus alpha power are associated with changes in arousal. If this is the case, one might expect alpha oscillations to be correlated with behavioral performance and other eye metrics that have been used to index changes in brain state such as saccadic reaction time and saccade velocity (Castellote et al., 2007; Di Stasi et al., 2013; DiGirolamo et al., 2016).

Correlation between pre-stimulus alpha power and other arousal-related metrics

Previously, we found that performance on a change detection task, as measured by computing hit rate and false alarm rate, fluctuates slowly over the course of a recording session (Cowley et al., 2020). The same is also true of other eye metrics including saccadic reaction time and saccade velocity (Johnston et al., 2021). To explore if pre-stimulus alpha power is associated with these additional arousal-related metrics, correlations (Pearson product-moment correlation coefficient) were computed within each session. Wilcoxon signed rank tests were then used to test the null hypothesis that the median correlation across sessions was equal to zero. Results showed that pre-stimulus alpha power was negatively correlated with false alarm rate (Figure 4, median $r = -0.28$, $p = 0.046$). However, it was not significantly correlated with hit rate (Figure 4, median $r = 0.03$, $p = 0.906$), reaction time (median $r = 0.12$, $p = 0.176$) or saccade velocity (Figure 4, median $r = -0.12$, $p = 0.389$). Note that pupil size and microsaccade rate have also been included in Figure 4 so that comparisons can be made across the different behavioral and eye metrics. This data is the same as

that reported in Figure 2C and Figure 3B, respectively. These findings are interesting because they demonstrate that pre-stimulus alpha power is associated with slow fluctuations in behavior over time. Previous research in humans has shown that pre-stimulus oscillations in the alpha band are associated with hit rate and false alarm rate (Iemi et al., 2017). However, it is difficult to make comparisons across studies due to task differences. In our paradigm, subjects had to make a saccade to the changed stimulus, whereas in Iemi et al. (2017) they had to make a yes/no decision about whether a near-threshold stimulus was presented. Either way, our results point to a link between alpha oscillations and global changes in arousal. Next, we asked if pre-stimulus alpha power, a non-invasive signal recorded on the scalp, can be used to index a neural measure of brain state acquired directly from the spiking activity of neural populations.

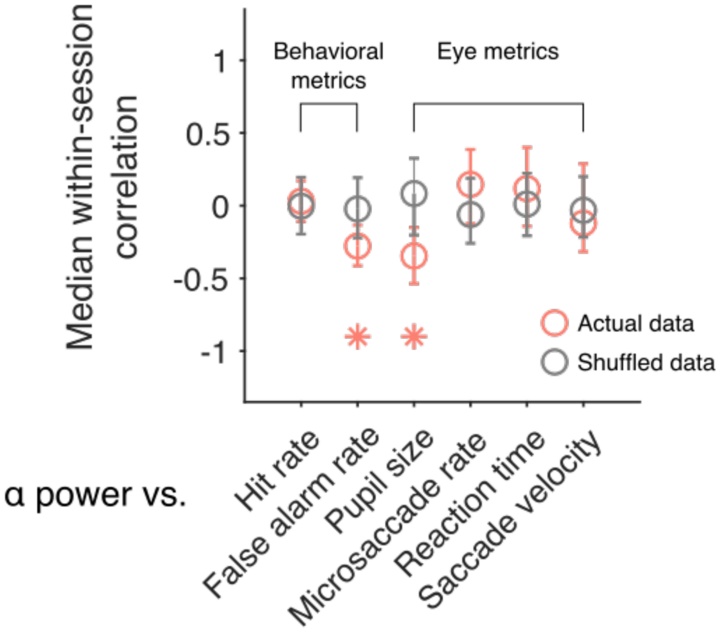


Figure 4. Correlation between slow drift and other arousal-related metrics. A scatter plot showing the median within-session correlation between pre-stimulus alpha power and a host of behavioral and eye metrics analyzed in our previous work (Cowley et al., 2020; Johnston et al., 2021). Note that pupil size and microsaccade rate have also been included so that comparisons can be made across the different behavioral and eye metrics. This data is the same as that reported in Figure 2C and Figure 3B, respectively. For Monkey Pe, the median correlation between α power and false alarm rate was -0.28 ($p = 0.083$), whereas the median correlation between α power and pupil size was -0.41 ($p = 0.008$). For Monkey Wa, the median correlation between α power and false alarm rate was -0.24 ($p = 0.326$), whereas the median correlation

515 between α power and pupil size was -0.31 ($p = 0.301$). Error bars represent bootstrapped 95% confidence intervals. $\alpha =$
516 alpha. $p < 0.05^*$.

518 Correlation between pre-stimulus alpha power and slow drift

519 As described above, we recently observed a pervasive signal in visual and prefrontal cortex
520 termed “slow drift” (Cowley et al., 2020). Interestingly, this neural signature was related to a subject’s
521 tendency to make impulsive decisions on a change detection task and a constellation of eye metrics
522 that are indicative of slow changes in arousal over time (Johnston et al., 2021). For example, we found
523 that slow drift was positively correlated with raw pupil size and negatively correlated with
524 microsaccade rate. This motivated us to ask if non-invasive EEG signals recorded on the scalp are
525 associated with slow drift. Based on our previous work, we hypothesized that pre-stimulus alpha
526 power would be negatively correlated with slow drift.

527 To calculate slow drift, residual spike counts were computed by subtracting the mean
528 response for a given orientation across the entire session from individual responses. This was an
529 important first step as it ensured that signals related to stimulus tuning were not present in the slow
530 drift. Residual spike counts were then binned using the same 30-minute sliding window that had been
531 used to bin the EEG, pupil and microsaccade rate data (Figure 5A, see *Methods*). We then applied
532 principal component analysis (PCA) to the neural data and estimated slow drift by projecting the
533 binned residual spike counts along the first principal component (i.e., the loading vector that
534 explained the most variance in the data). The sign of the weights in PCA is arbitrary meaning that the
535 correlation between slow drift and pre-stimulus alpha power in any session was equally likely to be
536 positive or negative (Jolliffe and Cadima, 2016). To overcome this issue, we flipped the sign of the
537 slow drift such that the majority of neurons had positive weights (Hennig et al., 2021). This
538 established a common reference frame in which an increase in the value of the drift was associated
539 with higher firing rates among the majority of neurons (see *Methods*).

540 We computed the slow drift of the neuronal population in each session using the above-
541 mentioned method, and then compared it to pre-stimulus alpha power. Example sessions for Monkey

Pe and Monkey Wa are shown in Figure 5B (top and bottom rows, respectively). In support of our hypothesis, pre-stimulus alpha power was negatively correlated with slow drift in each example session for both subjects.

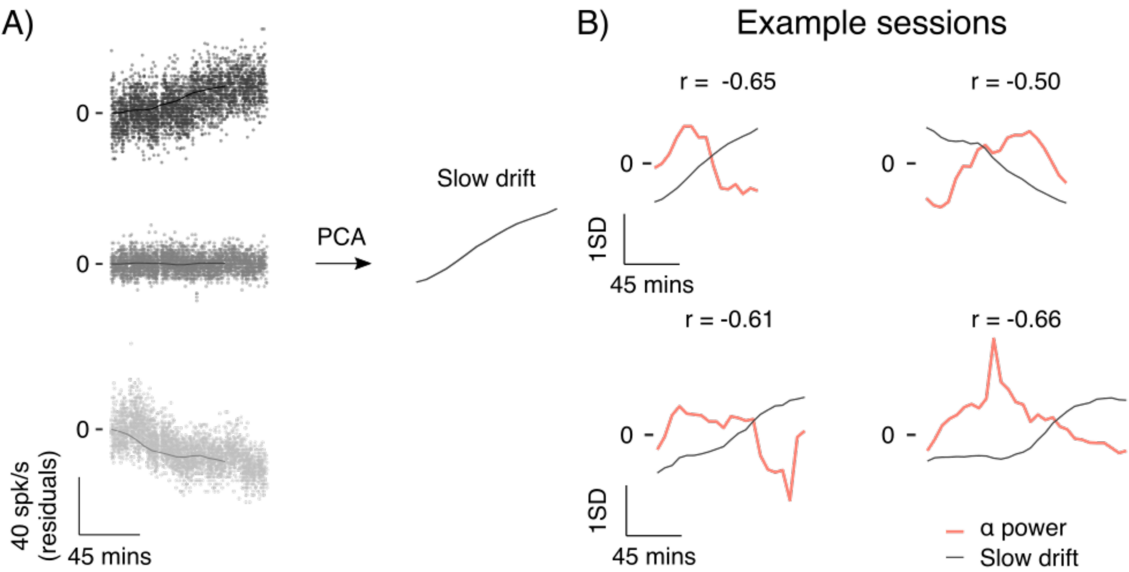
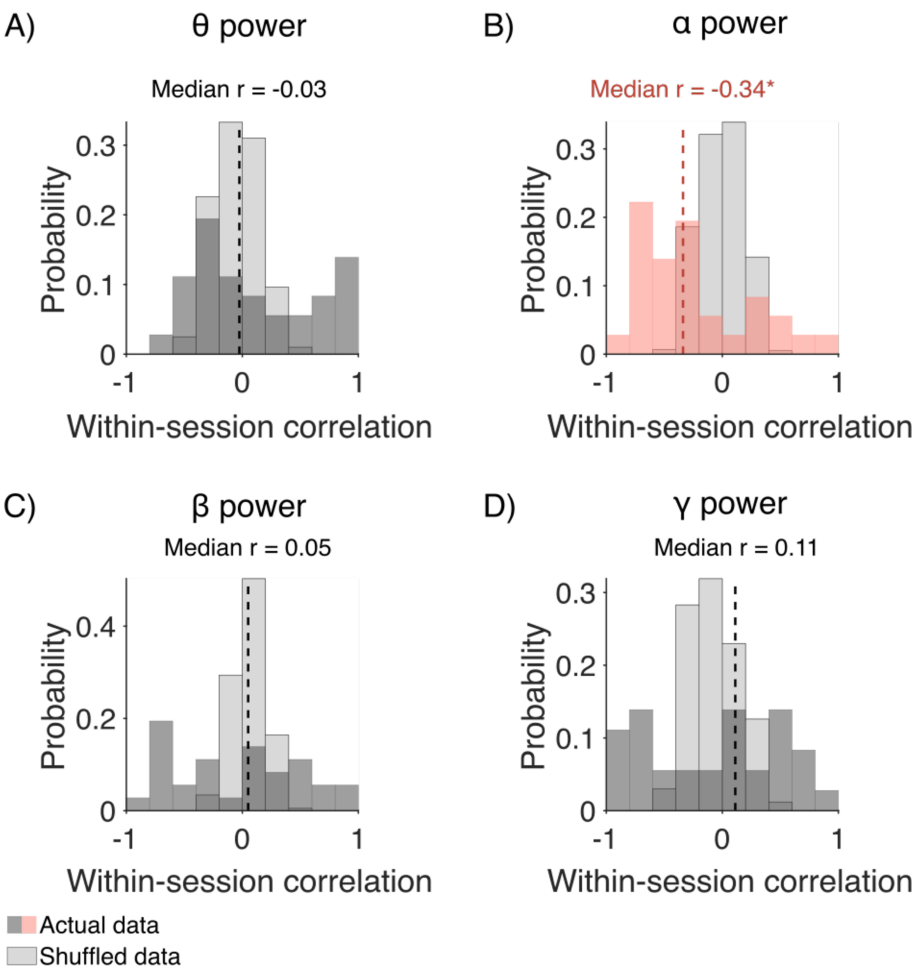


Figure 5. Computing slow drift. (A) Three example neurons recorded during the top left-hand session in (B). Each point represents the mean residual spike count during a 400ms stimulus period. The data were then binned using a 30-minute sliding window stepped every 6 minutes (solid line). PCA was used to reduce the dimensionality of the data and slow drift was computed by projecting binned residual spike counts along the first principal component. (B) Four example sessions in which there was a moderate to strong correlation between pre-stimulus alpha power and slow drift. The top row contains two sessions for Monkey Pe, whereas the bottom row contains two sessions for Monkey Wa. Note that the data were z-scored for visualization purposes only (i.e., so that variables with different units could be shown on the same plot). PCA = Principal Component Analysis. SD = standard deviation. α = alpha.

Next, we explored if a similar pattern was present across sessions (Monkey Pe = 15 sessions; Monkey Wa = 16 sessions). Within each session, a correlation (Pearson product-moment correlation coefficient) was computed between pre-stimulus alpha power and slow drift. Note that correlations were also performed to investigate the relationship between slow drift and pre-stimulus power in the theta, beta, and gamma bands. Wilcoxon signed rank tests were then used to test the null hypothesis that the median correlation across sessions was equal to zero. Consistent with the pattern observed in the example sessions, pre-stimulus power in the alpha band was negatively correlated with slow drift (Figure 6B, median $r = -0.34$, $p = 0.017$). No significant correlation was found between slow drift and

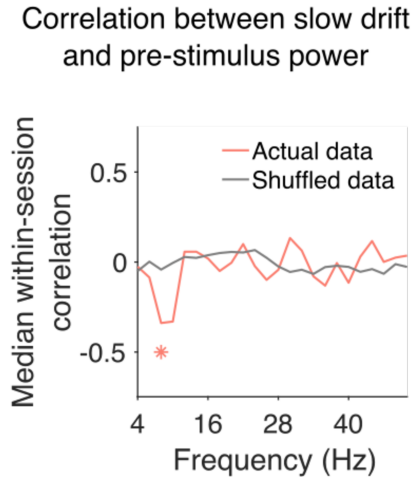
564 pre-stimulus power in the theta (Figure 6A, median $r = -0.03$, $p = 0.318$), beta (Figure 6C, median r
565 $= 0.05$, $p = 0.570$) and gamma bands (Figure 6D, median $r = 0.11$, $p = 0.531$). These findings suggest
566 that spontaneous components of the EEG signal, namely pre-stimulus alpha power, recorded non-
567 invasively on the scalp can be used to index low-dimensional patterns of neural activity acquired
568 directly in the brain.
569



570
571
572 Figure 6. Correlation between slow drift and pre-stimulus power in distinct frequency bands (A-D) Histograms showing
573 distributions of correlation values across sessions. Wilcoxon signed rank tests were used to test the null hypothesis that
574 the median correlation across sessions was equal to zero. The median correlation between slow drift and α power for
575 Monkey Pe was -0.47 ($p = 0.041$). For Monkey Wa, the median correlation between slow drift and α power was -0.24 (p
576 $= 0.215$). θ = theta, α = alpha, β = beta, γ = gamma. $p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$.
577

578 The frequency bands in the analysis described above (Figure 6) were chosen based on previous
579 research that has explored the relationship between EEG on the scalp and spiking responses recorded

580 directly in the brain (Musall et al., 2014; Snyder et al., 2015). However, there are disadvantages to
 581 assessing power in pre-defined regions of the power spectrum such as variability in the peak central
 582 frequency that is known to be associated with different task demands and/or cognitive states (Mierau
 583 et al., 2017). Given our interest in the link between pre-stimulus oscillations and arousal, we
 584 performed an additional analysis to investigate if slow drift was associated with power across a wide
 585 range of frequencies. To do this, we computed the median within-session correlation between slow
 586 drift and pre-stimulus alpha power using a 4Hz sliding window stepped every 2Hz. In support of the
 587 analysis described above (Figure 6), which was performed using pre-defined frequency bands, we
 588 found that slow drift was only significantly correlated with pre-stimulus power at 8-12Hz, the
 589 canonical alpha frequency band (Figure 7, median $r = -0.34$, $p = 0.017$).
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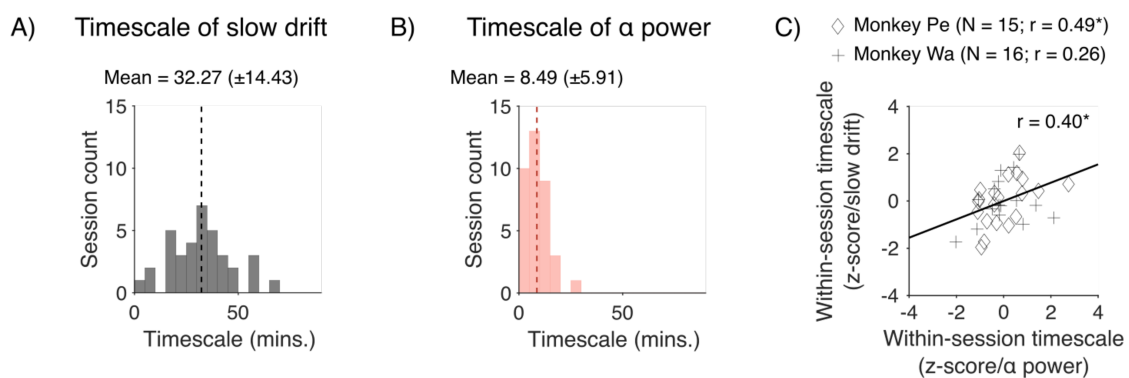


591
 592 Figure 7. Correlation between slow drift and pre-stimulus power across frequencies. The median within-session
 593 correlation was computed using a 4Hz sliding window stepped every 2Hz. Values on the x-axis represent the left edge of
 594 the window. The only significant correlation was between slow drift and pre-stimulus power at 8-12Hz i.e., the alpha
 595 frequency band ($p = 0.017$). Note that the p-value for the correlation between slow drift and pre-stimulus power at 10-
 596 14Hz was 0.06. $p < 0.05^*$.
 597
 598

599 Correlation between the timescale of slow drift and pre-stimulus alpha power

600 Finally, we investigated if the timescale of slow drift is correlated with the timescale of
 601 fluctuations in pre-stimulus alpha power. Note that these two variables are unlikely to have the same
 602 timescale because oscillations in the 8 to 12Hz frequency band are influenced by cognitive processes

603 such as attention that operate at a timescale of hundreds of milliseconds to seconds (Worden et al.,
 604 2000; Sauseng et al., 2005; Kelly et al., 2006; Snyder and Foxe, 2010). However, they may be
 605 modulated by a joint and continuously graded process (perhaps arising due to fluctuating levels of
 606 neuromodulators) that operates at a brain-wide level. If this is the case, one would expect a positive
 607 correlation between the timescale of slow drift and the timescale of fluctuations in pre-stimulus alpha
 608 power. To determine the optimal timescale at which a variable fluctuated over the course of a session,
 609 we used a cross-validated kernel regression method that applied Gaussian smoothing (with standard
 610 deviations ranging from 1 to 90 minutes) to the data and returned the time scale for smoothing that
 611 best fit held-out data (see *Methods*). We found that the timescale of slow drift (Figure 8A, $M = 32.27$,
 612 $SD = 14.43$) was significantly longer than the timescale of fluctuations in pre-stimulus alpha power
 613 (Figure 8B, $M = 9.32$, $SD = 5.89$) ($t(65) = 8.28$, $p < 0.001$). However, there was a significant
 614 correlation between the timescale of slow drift and pre-stimulus alpha power ($r = 0.40$, $p = 0.0255$)
 615 from session to session. This suggests that slow drift and pre-stimulus alpha power arise from distinct
 616 mechanisms on a moment-by-moment basis but may be linked to, or modulated by, a joint process
 617 that drives global changes in arousal over time.



620
 621 Figure 8. Correlation between the timescale of slow drift and pre-stimulus alpha power (A) A histogram showing the
 622 distribution of timescales computed for slow drift across sessions. (B) Same as (A) but for pre-stimulus alpha power. (C)
 623 A scatter plot showing how the timescale of slow drift relates to the timescale of fluctuations in pre-stimulus alpha power.
 624 Note that the data were z-scored separately for each monkey to control for potential timescale differences between
 625 subjects. Failing to control for this might have led to an artifactual correlation if timescales for one subject were greater
 626 than those for the other or vice versa. α = alpha. $p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$.

627

628 Discussion

629 In this study, we investigated if pre-stimulus oscillations in the alpha band could be utilized
630 as an external signature of an internal brain state, a recently discovered neural activity pattern called
631 “slow drift” (Cowley et al., 2020). We know from previous work that slow drift in macaque visual
632 and prefrontal cortex is correlated with a host of eye metrics across tasks with differing cognitive
633 demands (Johnston et al., 2021), suggesting that slow drift can be used to index brain-wide changes
634 in arousal. Since pre-stimulus alpha power is also related to arousal, we wondered if a link could be
635 established between a neural measure of an internal brain state acquired directly from the spiking
636 activity of populations of neurons (i.e., slow drift) and indirect signals recorded non-invasively from
637 the scalp using EEG. Results showed that slow drift was significantly associated with a pattern that
638 is indicative of changes in the subjects’ arousal levels over time: decreases in pre-stimulus alpha
639 power were accompanied by increases in raw pupil size and decreases in microsaccade rate.

640 Several studies in humans have found a relationship between pre-stimulus alpha power and
641 pupil size (Hong et al., 2014; Van Kempen et al., 2019; Podvalny et al., 2021). For example, on classic
642 Stroop tasks, trials with greater raw pupil size are associated with reduced alpha power and vice versa
643 (Compton et al., 2021). Our results support this finding as slow changes in pre-stimulus alpha power
644 were negatively correlated with raw pupil size. Furthermore, there was an association between the
645 magnitude of fluctuations in pre-stimulus alpha power (as measured by computing within-session
646 variance) and the magnitude of fluctuations in raw pupil size. These findings suggest that pre-stimulus
647 alpha power is associated with global changes in brain state that occur naturally over time, perhaps
648 due to fluctuating levels of neuromodulators in the brain. Testing this hypothesis would require the
649 simultaneous recording of EEG from the scalp and spiking activity in subcortical regions associated
650 with arousal such as the LC (Aston-Jones and Cohen, 2005; Sara, 2009; Chandler, 2016). Such studies
651 have been conducted in monkeys (Foote et al., 1980; Swick et al., 1994) but the relationship between
652 pre-stimulus alpha power and pupil size has not been elucidated in awake behaving animals

653 performing cognitively demanding tasks. Hence, an important question for future research would be
654 to determine how the spiking activity of subcortical regions associated with arousal relates to pre-
655 stimulus alpha power recorded on the scalp.

656 Another non-invasive metric that has been linked to oscillations in the alpha band is
657 microsaccade rate. We know from previous research that visual perception is altered up to 700ms
658 after a microsaccade has occurred, at a frequency of ~8 to 20Hz (Bellet et al., 2017). The results of
659 the present study show that a relationship also exists between alpha oscillations and microsaccade
660 rate at longer timescales. Recently, we found that slow fluctuations in raw pupil size were negatively
661 correlated with microsaccade rate (Johnston et al., 2021). That is, microsaccade rate decreased under
662 conditions of heightened arousal (as indexed by greater pupil size and increased saccade velocity)
663 and vice versa. Given this result, we hypothesized that there would be a positive correlation between
664 pre-stimulus alpha power and microsaccade rate at longer timescales, which are more likely to reflect
665 changes in a subject's internal cognitive state (Cowley et al., 2020). This is exactly what was found
666 in several example sessions for both monkeys. Furthermore, the magnitude of fluctuations in pre-
667 stimulus alpha power was significantly correlated with the magnitude of fluctuations in microsaccade
668 rate across sessions. A key goal for future research is to bridge the gap between microsaccade-related
669 EEG signals and neural activity in brain regions that have been implicated in eye movement control
670 such as the SC (Martinez-Conde et al., 2013). Research combining EEG and eye tracking has shown
671 that microsaccades are accompanied by: 1) a large potential over occipital electrodes ~100ms after
672 movement onset; and 2) changes in alpha/theta power (Dimigen et al., 2009). However, it is unclear
673 how these signals recorded on the scalp, at relatively short timescales, relate to the activity of SC
674 neurons. Similarly, we do not know how long timescale changes in pre-stimulus alpha power, which
675 we found to be correlated with microsaccade rate, link to firing rates in the SC. Future research
676 combining eye tracking, EEG and single unit/population recordings in the SC is needed to determine
677 the neural underpinnings of non-invasive scalp signals that are associated with fixational eye
678 movements.

679 Taken together, the results of the pupil size and microsaccade rate analysis suggest that
680 fluctuations in pre-stimulus alpha power are associated with global changes in arousal. This motivated
681 us to ask if non-invasive signals recorded on the scalp can be used to index a recently discovered
682 signature of an internal brain state called “slow drift” (Cowley et al., 2020). We know from previous
683 research that slow drift is positively correlated with raw pupil size and negatively correlated with
684 microsaccade rate across tasks with differing cognitive demands (Johnston et al., 2021). Therefore,
685 we predicted that there would be an inverse relationship between changes in pre-stimulus alpha power
686 and slow drift over time. In support of this hypothesis, we found that slow drift in visual cortex was
687 negatively correlated with pre-stimulus alpha power in several example sessions for both monkeys.
688 Furthermore, they were significantly and negatively correlated when the data were pooled across
689 sessions. It is important to note that this finding cannot be attributed to changes in 1/f noise that are
690 characteristic of several brain disorders (Peterson et al., 2017; Robertson et al., 2019) and healthy
691 ageing (Voytek et al., 2015). Firstly, aperiodic components of the FFT were estimated and subtracted
692 off prior to averaging across electrodes (Donoghue et al., 2020). Secondly, no significant correlation
693 was found between slow drift and pre-stimulus power in the theta, beta, and gamma bands. One might
694 have expected this to be the case if slow drift was associated with uniform shifts in power across
695 frequencies. Nonetheless, 1/f noise and other aperiodic fluctuations, might be related to global brain
696 modulations in ways that are not well captured by the slow drift we observe. A further interesting
697 question is whether slow drift is associated with other EEG signals such as the P1 component of the
698 visually evoked potential (VEP). There are at least two reasons why this might be the case. Firstly,
699 evidence suggests that early VEP components are negatively correlated with pre-stimulus alpha
700 power (Roberts et al., 2014; Iemi et al., 2019). Secondly, decades of research has shown that P1
701 amplitude is associated with global changes in brain state (Luck et al., 2000). For example, it is
702 significantly larger on trials in which a weak visual stimulus is detected (Ergenoglu et al., 2004;
703 Pourtois et al., 2006; Del Cul et al., 2007; Mathewson et al., 2009) and negatively correlated with
704 reaction time on spatial attention tasks (Mangun and Hillyard, 1991).

705 Another key finding from the present study is related to the timescale of slow drift and
706 fluctuations in pre-stimulus alpha power. We found that the timescale of these two variables was
707 significantly different: pre-stimulus alpha power had a shorter timescale than slow drift. This result
708 is unsurprising given that oscillations in the 8 to 12Hz frequency band are influenced by processes
709 such as attention that operate at a timescale of hundreds of milliseconds to seconds (Worden et al.,
710 2000; Sauseng et al., 2005; Kelly et al., 2006; Snyder and Foxe, 2010). However, we did find that the
711 timescale of slow drift and the timescale of fluctuations in pre-stimulus alpha power was significantly
712 correlated across sessions. This observation is important because it suggests that these two variables
713 are modulated by a common process such as arousal that operates at a brain-wide level. In the present
714 study, there was no experimental manipulation of the subjects' arousal levels meaning that the
715 timescale of slow drift and pre-stimulus alpha power varied naturally from session to session.
716 Evidence suggests that LC is a major source of fluctuations in arousal (Aston-Jones and Cohen, 2005;
717 Sara, 2009; Chandler, 2016). Therefore, activating neurons in this region directly via electrical
718 microstimulation, or indirectly via pharmacological manipulations, should lead to correlated changes
719 in the timescale of slow drift and pre-stimulus alpha power.

720 In summary, we found that a commonly used metric of cognitive state in human EEG studies,
721 pre-stimulus alpha power, is associated with gradual shifts in the underlying population structure of
722 neural activity throughout the brain. Together, these measures at the scalp, and in the cortex, were
723 predictive of changes in the monkeys' arousal levels over time. These findings show that indirect
724 measures of neural activity can be used to index a global signature of arousal. By linking a vast EEG
725 literature in humans with simultaneous scalp/microelectrode array recordings in macaques our results
726 bridge the gap between large-scale field potentials and the spiking responses of populations of cortical
727 neurons.

728

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