Mid-level arousal facilitates optimal behavioral state in humans and mice

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Abstract

Perceptual choice behavior alternates between discrete strategies, which can be identified through hidden Markov modeling. Peak performance occurs during mid-level pupil-linked arousal. Here, we (i) replicated the previously observed "inverted-U" relationship between baseline pupil-linked arousal in mice and engaged state occurrence (Hulsey et al., 2024), (ii) confirmed the model-based prediction that this relationship is mediated by GABAergic interneurons and (iii) established that this relationship generalizes to humans. We conclude that arousal dynamically modulates the cortical state of a sensory region to optimize perceptual decision-making.

Keywords: Perceptual decision making, hidden Markov modeling, pupil, arousal.

Introduction

Perceptual choice behavior is typically not stationary but instead evolves gradually (Roy et al., 2021) or alternates quickly between discrete strategies (Ashwood et al., 2022; Bolkan et al., 2022; Hulsey et al., 2024; Weilnhammer et al., 2023). For example, experimental trials can be clustered in states of engaged, disengaged, and biased decision-making strategies, and these behavioral states can be identified using generalized linear hidden Markov models (GLM-HMMs) (Ashwood et al., 2022; Hulsey et al., 2024).

Arousal, driven by the activity of globally projecting subcortical neuromodulatory systems, may be an important predictor of engaged states. By changing the functional properties of their target networks, neuromodulatory systems are in an ideal position to shape cortex-wide network activity underlying decision-making in a coordinated fashion (Aston-Jones & Cohen, 2005). Baseline pupil size, which reflects the tonic activity of multiple neuromodulatory systems (de Gee et al., 2017; Joshi & Gold, 2020) and the ensuing cortical arousal state (McGinley, Vinck, et al., 2015), indeed predicts optimal perceptual sensitivity during medium baseline pupil-linked arousal, and lower sensitivity during low and high arousal (Beerendonk et al., 2024; de Gee et al., 2024; McGinley, David, et al., 2015). The same “inverted-U” relationship was recently observed between the probability of being an engage state and baseline pupil-linked arousal (Hulsey et al., 2024).

Here, we aimed to (i) replicate the previously observed “inverted-U” relationship between baseline pupil-linked arousal in mice and engaged state occurrence (Hulsey et al., 2024), (ii) test the model-based prediction that this relationship is mediated by GABAergic interneurons (Beerendonk et al., 2024) and (iii) test if this relationship generalizes to humans.

Methods

The current study analyzed behavioral, pupil, and neural data from mice (N=9; audio-visual change detection task) and humans (N=69; auditory detection task; no neural data) (Fig. 1A). GLM-HMMs were fitted to choice behavior data to identify persistent behavioral states with distinct decision-making strategies. The relation between engaged state probability and baseline pupil-linked arousal was assessed with second-order polynomial regression models in mice and humans. For mice, spiking activity of V1 GABAergic interneurons and putative pyramidal neurons was recorded. A mediation analysis was used to investigate if the relation between baseline arousal and engaged state probability was governed by the baseline firing rate of these distinct neuron types.

Results

Mice and humans alternated between several discrete behavioral states (Fig 1B,C). Engaged behavioral state probability exhibited an inverted-U relationship with baseline pupil-linked arousal (Fig. 2). In mice, preliminary neural analyses further suggest that for visual change detection, this relationship was mediated by pre-change V1 firing rates of putative GABAergic interneurons but not putative pyramidal neurons.

Discussion

These findings imply a general mechanism by which arousal dynamically modulates the cortical state of a primary sensory region to optimize perceptual decision-making. This study furthermore highlights an important insight for consciousness research: conscious perception is governed by discrete and persistent states of altered sensory processing

Figures

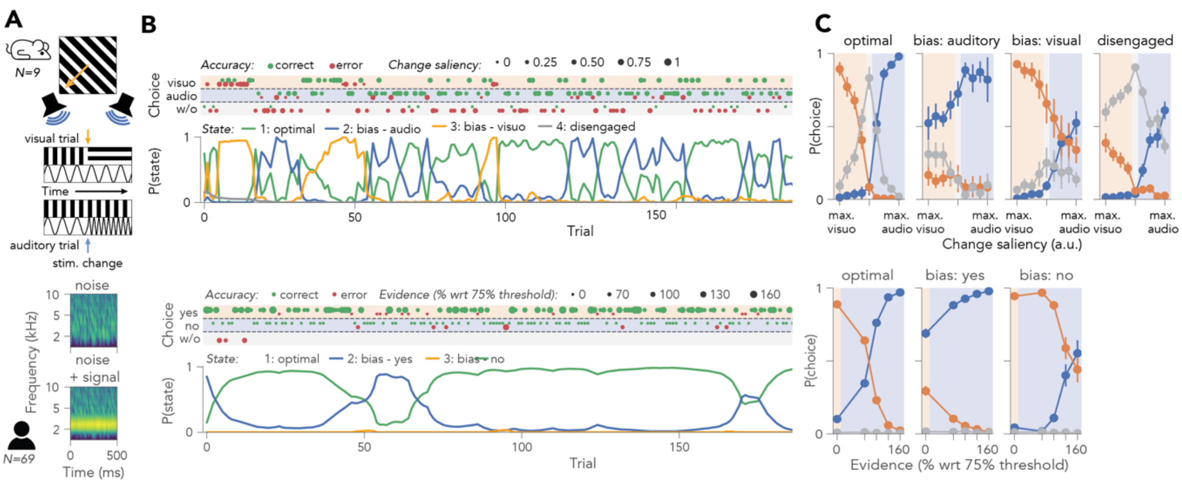

Figure 1. (A) Schematic of audio-visual change detection task performed by mice (N=9), and of yes/no auditory detection task performed by human subjects (N=69). **(B)** Example session showing alterations between discrete decision strategies. **(C)** Average psychometric fit across subjects for each behavioral state. Shading, S.E.M. across subjects.

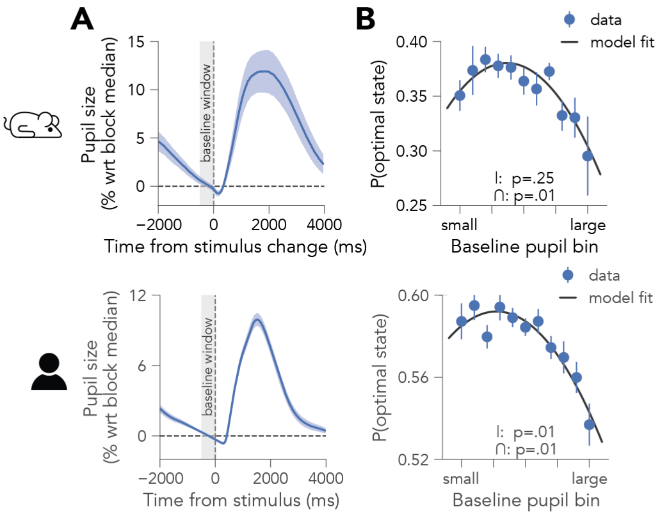

Figure 2. (A) Average pupil response around the time of a stimulus change. Grey window indicates the time window used for calculating baseline pupil. **(B)** Relation between baseline pupil size and optimal state probability. Optimal state probability is non-linearly predicted by baseline pupil size, with the highest probability occurring at intermediate levels of baseline pupil-linked arousal. All panels: shading or error bars, S.E.M. across subjects.

References

Ashwood, Z. C., Roy, N. A., Stone, I. R., Urai, A. E., Churchland, A. K., Pouget, A., & Pillow, J. W. (2022). Mice alternate between discrete strategies during perceptual decision-making. *Nature Neuroscience*, *25*(2).

Aston-Jones, G., & Cohen, J. D. (2005). An Integrative Theory of Locus Coeruleus-Norepinephrine Function: Adaptive Gain and Optimal Performance. *Annual Review of Neuroscience*, *28*(1), 403–450.

Beerendonk, L., Mejías, J. F., Nuiten, S. A., de Gee, J. W., Fahrenfort, J. J., & van Gaal, S. (2024). A disinhibitory circuit mechanism explains a general principle of peak performance during mid-level arousal. *Proceedings of the National Academy of Sciences*, *121*(5), e2312898121.

Bolkan, S. S., Stone, I. R., Pinto, L., Ashwood, Z. C., Iravedra Garcia, J. M., Herman, A. L., Singh, P., Bandi, A., Cox, J., Zimmerman, C. A., Cho, J. R., Engelhard, B., Pillow, J. W., & Witten, I. B. (2022). Opponent control of behavior by dorsomedial striatal pathways depends on task demands and internal state. *Nature Neuroscience*, *25*(3), 345–357.

de Gee, J. W., Colizoli, O., Kloosterman, N. A., Knapen, T., Nieuwenhuis, S., & Donner, T. H. (2017). Dynamic modulation of decision biases by brainstem arousal systems. *eLife*, *6*, 309.

de Gee, J. W., Mridha, Z., Hudson, M., Shi, Y., Ramsaywak, H., Smith, S., Karediya, N., Thompson, M., Jaspe, K., Jiang, H., Zhang, W., & McGinley, M. J. (2024). Strategic stabilization of arousal boosts sustained attention. *Current Biology*.

Hulsey, D., Zumwalt, K., Mazzucato, L., McCormick, D. A., & Jaramillo, S. (2024). Decision-making dynamics are predicted by arousal and uninstructed movements. *Cell Reports*, *43*(2).

Joshi, S., & Gold, J. I. (2020). Pupil Size as a Window on Neural Substrates of Cognition. *Trends in Cognitive Sciences*.

McGinley, M. J., David, S. V., & McCormick, D. A. (2015). Cortical Membrane Potential Signature of Optimal States for Sensory Signal Detection. *Neuron*, *87*(1), 179–192.

McGinley, M. J., Vinck, M., Reimer, J., Batista-Brito, R., Zagha, E., Cadwell, C. R., Tolias, A. S., Cardin, J. A., & McCormick, D. A. (2015). Waking State: Rapid Variations Modulate Neural and Behavioral Responses. *Neuron*, *87*(6), 1143–1161.

Roy, N. A., Bak, J. H., Akrami, A., Brody, C. D., & Pillow, J. W. (2021). Extracting the dynamics of behavior in sensory decision-making experiments. *Neuron*, *109*(4), 597-610.e6.

Weilnhammer, V., Stuke, H., Standvoss, K., & Sterzer, P. (2023). Sensory processing in humans and mice fluctuates between external and internal modes. *PLOS Biology*, *21*(12), e3002410.