Unraveling Neural Mechanisms of Insular Cortex in Empathic Decision-Making.

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Introduction

The anterior insular cortex (aIC) is a region implicated in interoceptive processing and is critical in facilitating prosocial behaviors. Previous fMRI studies in humans have demonstrated that activity in the insular cortex is modulated in response to others experiencing pain. Additionally, it has been associated with encoding retrospective valence to guide optimal decision-making in response to pleasant and unpleasant experiences. In this study, we propose the hypothesis that the insular cortex may encode empathic decisions. To investigate this hypothesis, we conducted in vivo high-density electrophysiological recordings in rats during a novel operant conditioning task, wherein the rats could choose whether or not to inflict distress on a conspecific in exchange for a reward. Gaining insights into the underlying mechanisms involved in decision-making associated with prosocial behaviors is of utmost importance for the development of future interventions targeting neuropsychiatric pathologies characterized by altered emotional perception, impaired empathy, or psychopathic-like behaviors.

Methods

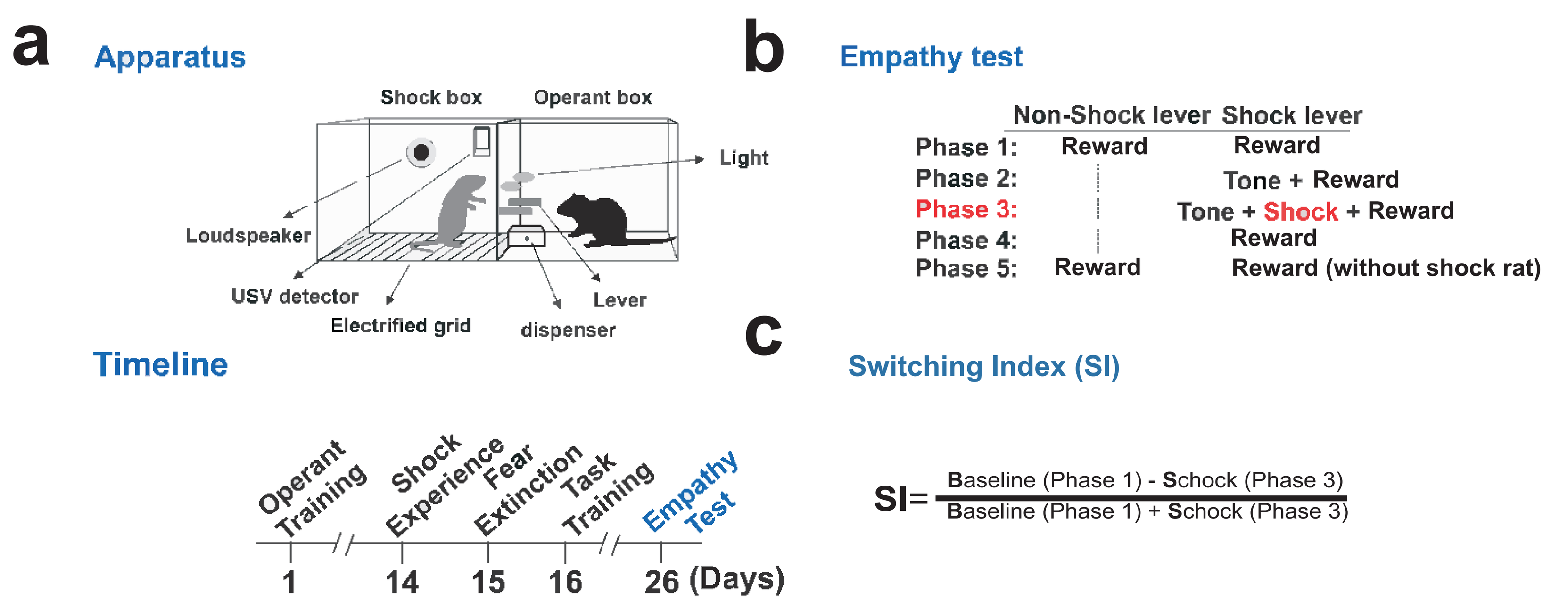

Figure 1: Behavior protocol and Empathy Test. a) Rats (N:5) were trained in an operant chamber with two levers. A drop of 20% sucrose was rewarded with each lever press according to the light instruction (randomized between right or left for forced choice or both for free choice). b) Then rats performed an Empathy test where they could choose to use a lever that would deliver a foot shock to a neighboring rat or change to another lever without a shock.
c) A switching index (SI) was calculated as the difference in the number of presses over the preference lever between the baseline (1st) and shock (3rd) phase during free choice trials . A bootstrapping was performed with SI values obtained from 23 rats. SI upper and lower confidence interval from the shock stage (phase 3) was used to classify Switcher's or empathic sessions (SI>0.15) and Non-Switchers or non-empathic sessions (SI<0.079).

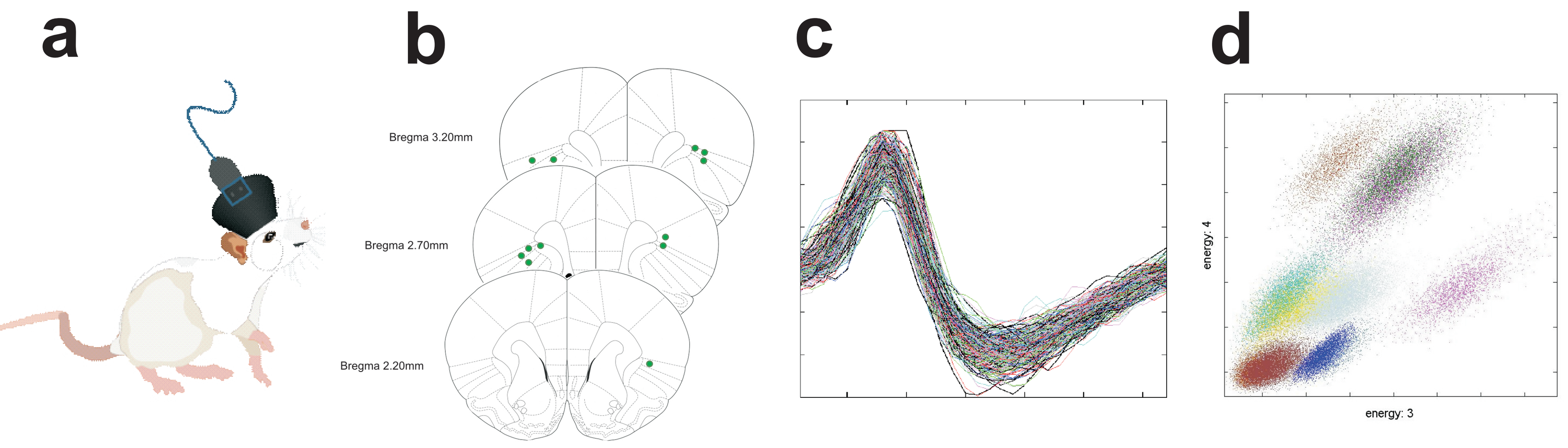

Figure 2: In vivo electrophysiology methods. a) Rats were implanted with tetrodes using a microdrive. The single-cell activity of the aIC was simultaneously recorded in behaving animals during the tasks previously described. b) Green points indicates tetrodes location. c) Spike waveform for a single cell from spike sorting. d) Examples of cluster-cutting analysis.

Results

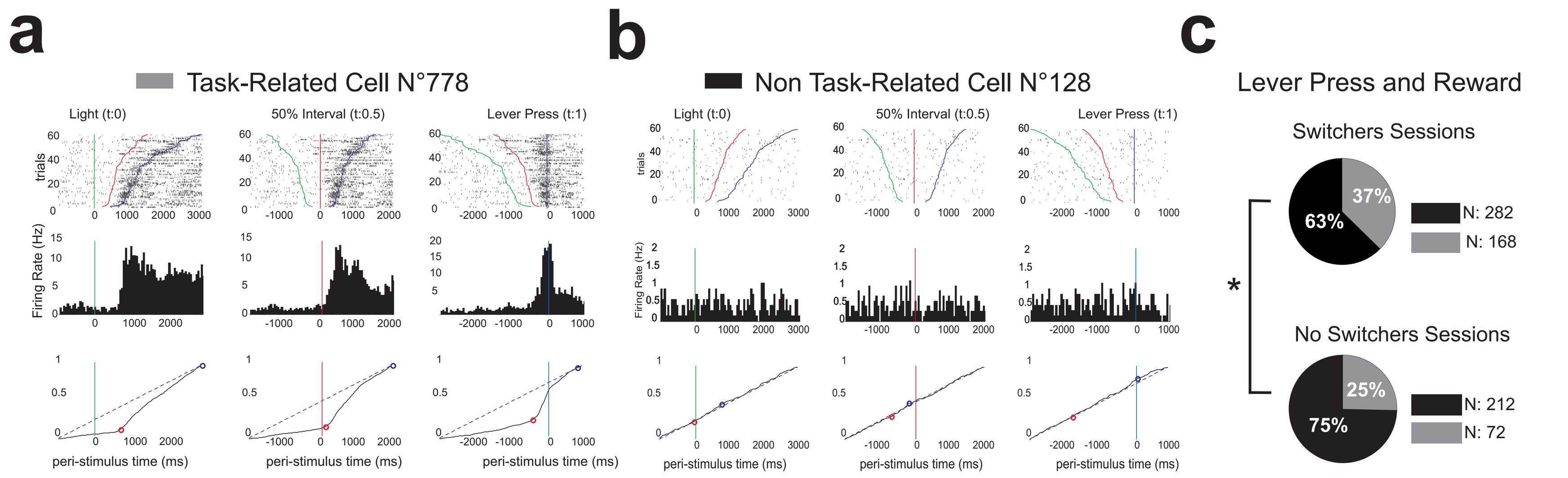

Figure 3. Cells classification of anterior insular cortex (aIC) during an empathic decision-making task. Spike analysis techniques, based on Kawabata et al., 2020, were used to characterize the neuronal response in relation to two consecutive events in the task: the light instruction and lever press, or lever press and reward delivery. A total of 1,015 neurons were recorded across 50 recording sessions involving 5 animals. A task relevance index was employed to identify neurons that exhibited significant changes in activity in response to task events. This index was accomplished comparing spike's cumulative distribution function (CDF) to a uniform distribution for each alignment and extracting TRp and TRd values (two-sample KS test). Neurons with TRp <10e-6, TRd >0.1, and more than 100 spikes were classified as task-relevant neurons. **Figures 3a and 3b** illustrate examples of a task-relevant neuron and a non-task-relevant neuron, highlighting the increase in firing rate around the lever press in the task-relevant neuron compared to the non-task-relevant neuron. **c)** A higher proportion of task-relevant neurons was observed in switcher sessions during lever press and reward delivery (Chi-Square test, *p-value< 0.05). Further analyses were conducted exclusively on task-relevant neurons.

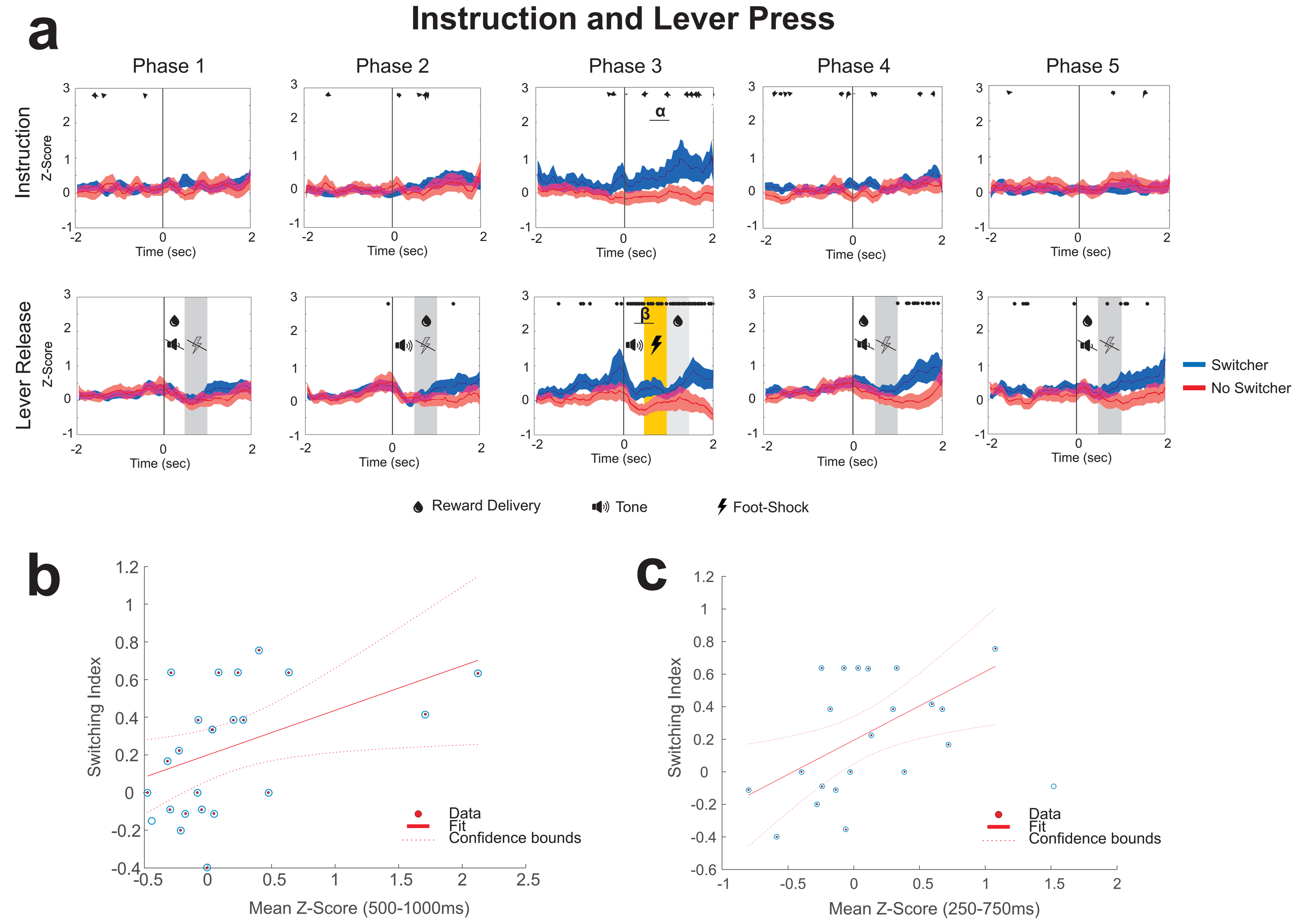

Figure 4: Average activity of the anterior insular cortex (aIC) during empathic decision-making. a) Neural activity in aIC was found to be significantly higher during empathic behaviour (Switcher sessions) compared to non-empathic behaviour (Non-switcher sessions), particularly in phase 3 when the rat must decide to harm or not harm his mates. This increase in aIC activity was observed after the instruction light and lever press. However, no substantial differences were detected in phases 1 and 2, with only partial distinctions found after phases 4 and 5 (*p<0.05).
b) Correlation analysis revealed a significant linear relationship between aIC neuronal activity after the light instruction and the switching index (p=0.035, r2=0.19; 23 sessions), **c)** and between the SI and aIC mean activity after lever release, suggesting a connection between aIC activity and the nature of decision-making (p=0.013, r2= 0.28; 21 sessions).

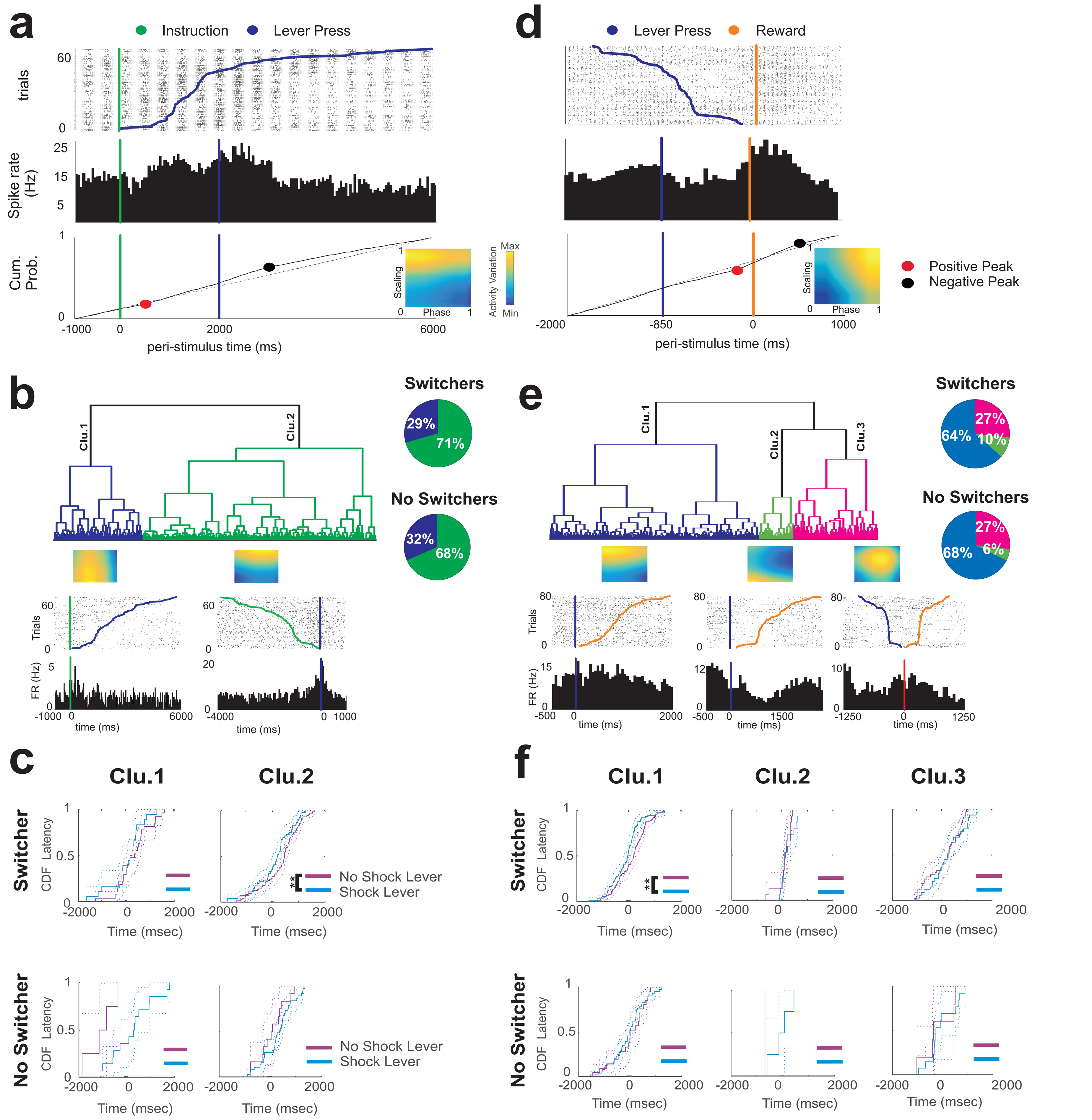

Figure 5: Selective modulation of aIC neuronal activity in response to shock-related choices during empathic sessions. Variation maps for each cell were created by calculating variation activity for different time alignments (phase) and gradually streching (scaling) of intervals times between events, representative examples in **Figure 5a and 5d**. **b)** Task-relevant neurons were categorized using hierarchical clustering based on variation maps. For the instruction to lever-press interval, we identified two primary clusters. The pie charts displaying the distribution of these clusters revealed no significant differences between Switcher and Non-Switcher behaviors, as confirmed by a Chi-Square test (*p-value < 0.05). **c)** In terms of the latency to activity change, Cluster 2 showed shorter latency in switcher sessions when animals chose to deliver a shock (*p<0.05; **p<0.01; Two-sample KS-test). **e)** Three clusters were found for the lever-press to reward-delivery interval, with no behavior differences. **f)** Only in Switcher sessions, Cluster 1 exhibited shorter latency during shock decisions .

Conclusions

• Our research unveils increased recruitment of aIC neurons during empathic sessions, and we also identified a positive correlation between aIC activity and empathic behavior. Notably, we observed selective modulation of scaled-activity neurons during empathic decisions, particularly involving mate foot-shock, highlighting their crucial role in empathic decision processes.
• These findings advance our understanding of how the brain encodes empathic and non-empathic decisions, illuminating the role of the aIC in these behaviors. This insight can also enhance our comprehension of its involvement in disorders characterized by a lack of empathy, such as psychopathy.

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