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Article in Cell

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Dear Cell

[1] Regarding the article:
Lin, Qian, Jason Manley, Magdalena Helmreich, Friederike Schlumm, Jennifer M Li, Drew N Robson, Florian Engert, Alexander Schier, Tobias Nöbauer, and Alipasha Vaziri. 2020. “Cerebellar Neurodynamics Predict Decision Timing and Outcome on the Single-Trial Level.” Cell 180 (3): 536–51.

[2] The Summary reads:
"...Goal-directed behavior requires the interaction of multiple brain regions. How these regions and their interactions with brain-wide activity drive action selection is less understood. We have investigated this question by combining whole-brain volumetric calcium imaging using light-field microscopy and an operant-conditioning task in larval zebrafish. We find global, recurring dynamics of brain states to exhibit pre-motor bifurcations toward mutually exclusive decision outcomes. These dynamics arise from a distributed network displaying trial-by-trial functional connectivity changes, especially between cerebellum and habenula, which correlate with decision outcome. Within this network the cerebellum shows particularly strong and predictive pre-motor activity (>10 s before movement initiation), mainly within the granule cells. Turn directions are determined by the difference neuroactivity between the ipsilateral and contralateral hemispheres, while the rate of bi-hemispheric population ramping quantitatively predicts decision time on the trial-by-trial level. Our results highlight a cognitive role of the cerebellum and its importance in motor planning..."

At this stage, my cerebellar cognition became head-fixed. I could not decide in time to remember which way I learned to turn for the agarose. I felt for my tail but it had not regenerated. These connectivity changes combined volumetrically to a global conditioned task. Finally, after >10 s, I reached out to deepAI.org (not Irelynn) to cluster Lin et al. (2020) in an operant trial-by-trial population dynamic outcome. The distributed network ramped arising exhibited functional brain state below.

[3] Translation of Lin et al. (2020) or Cerebellum is important for movement:

Summary
Researchers have found that the cerebellum, a region of the brain known for its role in motor coordination, may also play a critical role in decision-making and predicting outcomes. The study found that cerebellar activity could predict the timing of a decision on a single-trial level, and that its activity was predictive of whether that decision would be correct or incorrect. The results suggest a new understanding of the cerebellum's role in cognitive processing and decision-making, with potential implications for developing new therapies for neurological disorders.

Results
On a trial-by-trial level, we observed cyclic brain state dynamics in a t-SNE map, with correct and incorrect trials forming distinct loops. This indicates that during correct trials, specific brain states were consistently activated and that these differed from those during incorrect trials. This finding provides insight into the neural dynamics underlying performance on a memory task.

Our hypothesis is that effective decision making related to goal-oriented behavior is dependent upon the synchronized combination of information from various regions of the brain. Though this concept has been theorized, we have found no concrete evidence to support it yet.

The study looked for the neuroactivity within each cluster that caused the observed pre-motor bifurcation of brain states and was hence predictive of the motor response. However, some neurons had a mixed response, including decision-independent components, making it challenging to determine their contribution to the motor response.

In a study on individual learners, researchers found that there was a significantly higher level of preparatory activity on the same side as the hand used in correct trials, but a lower level of activity in incorrect trials. This was observed consistently across multiple participants and could have implications for understanding the neural mechanisms underlying motor learning and preparation. Further research is needed to fully understand these findings and their potential applications.

Discussion

The cerebellar neurodynamics for predicting turn direction and DT involve a competition-cooperation framework where turn directions are determined by the difference in activity between the ipsilateral and contralateral hemispheres. This bilateral relationship suggests that the cerebellum plays an essential role in predicting and controlling dynamic movements. Understanding the neurodynamics involved in turn direction and DT may lead to better insights into movement disorders and the development of more effective treatment methods.

Methods StarAstar

Zebrafish larvae, aged 7-9 days after fertilization, were immobilized in 2%-2.5% low-melting-temperature agarose in a custom-made chamber on a glass slide. The larvae were kept in fish water and incubated for 6 hours with the tail of the larvae freed from the agarose around the swim bladder. This procedure facilitates tail regeneration studies.

The LFM's image acquisition was controlled through Micro-Manager and custom MATLAB software, triggered by a dual-CPU workstation. The reconstructed LFM images were obtained offline, with a volume of approximately 700 μm × 700 μm.

The goal was to uncover a reliable behavioral task that would allow for the study of motor planning and decision-making during a delay period between sensory cue and motor response. We sought a paradigm that would involve learning and short-term memory, and would be robust enough to support research in these areas.

The neuronal signals were pre-processed by individually de-trending to correct for photo-bleaching and normalizing as $\Delta F/F0 = (F-F0)/F0$. This resulted in a fluorescence time series for each neuron with changes in fluorescence relative to its baseline.

To classify the tail movements of larval zebrafish as left turns, right turns, or struggles, offline behavioral classification was used along with online tracking. The method used was similar to the one previously described by Haesemeyer et al. in 2018. Larval zebrafish move in bouts rather than swim, making it essential to use a specialized classification method. This approach allowed for accurate and efficient classification of tail movements during experiments.

Decision time (DT) in a trial was measured as the time between heat onset and the initiation of the first turn, regardless of whether the outcome was correct or incorrect. Trials with DT longer than 5 seconds were selected because the temperature changes from the heat stimulus stabilized after this time. These criteria were used to ensure valid data for analysis.

The study analyzed the temporal evolution of brain states while making correct and incorrect decisions. The correlation between each brain state and a reference brain state was calculated using Pearson's r. The reference brain state was determined by averaging all brain states of the same type. The results showed that there was a clear difference in the temporal evolution of brain states for correct versus incorrect decisions. This suggests that analyzing brain states over time may be useful in understanding decision-making processes.

The partial correlation coefficient r of X and Y while controlling for the effect of Z was calculated using the formula rXY·Z=rXY−rXZrYZ(1−r2XZ)(1−r2YZ)√. The values of rXY, rXZ, and rYZ were obtained from pairwise correlation coefficients calculated using the formula rXY=cov(X,Y)σXσY. The computation was done using MATLAB (MathWorks) and the output contains the value of the partial correlation coefficient rXY·Z.

The t-Distributed Stochastic Neighbor Embedding (t-SNE) algorithm was utilized to analyze brain states by representing each state as an input vector encompassing the activity of every neuron at a specific time point. t-SNE is capable of transforming the complex structure in high-dimensional data into a compressed, two-dimensional visualization, facilitating the visualization of patterns and similarities between different states. Overall, this approach can be valuable for gaining insights into brain function and for studying how it may be altered in various neurological disorders.

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To identify task-relevant activity, we used "baits" in the form of regressors for behavior and heat
stimulus embedded in the neuronal space. These four regressors were created by convolving the actual time
series with temporal response k and included "Turn L," "Turn R," "Heat ON," and "Heat OFF." This approach
allowed us to highlight relevant activity during the task and better understand the neural mechanisms
underlying it.

Correlation was utilized to measure the level of coordination and integration in the brain. The brain
regions were identified using t-SNE, and functional clusters were derived from the neuronal space. The
mean pre-motor correlation was taken into account, and the absolute value was considered for analysis.Most
importantly, correlation was used as a quantitative metric to obtain a better understanding of the
relationship between different brain regions.
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[4] Lack of ethics:
Also, under "…Animal Subjects…Experiments were carried out in accordance with protocols approved by the Institutional Animal Care and Use Committee…"
Which one? The one in New York, Austria, or Cambridge MA? Or the one that does not exist in Singapore, the one Qian Lin published her other two (ahem) articles with?

[5] Cell Advisory Board:
Appears superfluous? What is being advised please?

Thank you,
Mohamed Helmy
MD, PhD

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