

Is there a tipping point in neuronal ensembles during learning?

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Abstract

Learning is important for humans and can be disrupted by disease. However, the essence of how learning may be represented within a neuronal network is still elusive. Spike trains generated by neurons have been demonstrated to carry information which is relevant for learning. The present study uses well-established mutual information (MI) analysis techniques to better understand learning within neuronal ensembles. Spike trains in tetrode recordings from the dorso-lateral striatum were used for computing MI as rats learnt a T-maze procedural task. We demonstrate that in in-vivo recordings the growth of MI is reflected in the behavioral response as learning proceeds. These changes in MI are seen to correspond to three phases, a low MI value, namely early learning, a rapid increase in MI value, task-acquisition and stabilization of MI, over-training. Over multiple training sessions, small changes in MI within the neuronal network suddenly produce a big change in ensemble MI during the task acquisition phase. This phase represents the “tipping point” in the neuronal network where the MI growth builds habits during motor learning in the striatum. © 2006 Elsevier Ireland Ltd. All rights reserved.

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The tipping point is a term borrowed from sociology to specify the moment when something unique becomes common. This term has been used to reveal the dynamic aspects of population response where multiple, small changes can result in a cascade phenomenon causing a profound change in the population behavior [7]. This effect has been described in epidemics, political elections and consumer economics. At the level of neuronal ensembles, a dynamical response may occur within the population of neurons in a very similar fashion, representing a “tipping point” during the learning process. In this scenario, information within a network of neurons is expected to reach a critical stage where a sudden and substantial change is seen in the network. This is a new way of understanding how, from an information point of view, learning occurs within neuronal ensembles. Learning is an important phenomenon that shapes all behavior. Learnt information is stored, retrieved and communicated between ensembles of neurons in the brain. Alteration in spiking of neurons individually and in ensembles is believed to be one indicator of population learning. The brain efficiently processes information in order to provide behaviorally relevant interactions with the environment. The ability to perform such

interactions easily by practice is well known and is regarded as learning in the behavioral sense [17,18,10,9,11,1]. The adaptation of the neuronal network to efficiently manage information flow within it may be the biological substrate for such behavioral learning. Adaptive changes in the neuronal network have been shown in the past [11,1,15,20,6]. Analyses of learning that quantifies the time varying relationship between neural activity and behavior also exist [19]. Additionally, a substantial literature on mutual information in single neurons and neural ensembles includes work on changes in activity due to adaptation to stimuli [5,2]. However, MI seems to be used exclusively to look at stimulus–response (SR) relationships. As an abstract quantity, there is no reason to restrict MI to SR applications alone.

Previously [13] an independent component analysis was used in order to understand information encoding within neurons. This experiment used 7–8 sessions of training. However, this may be an insufficient period of time to reveal any systematic changes in information during the learning process within the neuronal network. Indeed, studying longer periods of training could bring to light the essence of the learning process in neuronal ensembles. The application of mutual information analysis would be extremely valuable for neuronal ensembles that are observed over longer periods as learning progresses.

An information–theoretic approach such as MI analysis can be used to determine the association between spiking activities of

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neighboring neurons in close proximity of each other, recorded by the same electrode. Spike trains generated within neuronal ensembles can be seen as entities carrying information. In a network of neurons, the computed value of MI is an estimation of information shared by neurons in the recorded area. Additionally, MI measures the degree to which observations of one spike train in the ensemble allows us to make predictions about other spike trains from neurons within the same ensemble.

In order to study these relationships between neuronal activity and behavior during learning within ensembles, we used such an information-theoretic approach to analyze in-vivo tetrode recordings from dorso-lateral striatum in a rewarded T-maze learning task in awake, behaving rodents.

Chronic tetrode recordings from neuronal ensembles in the dorso-lateral striatum of freely behaving rodents were performed in a T-maze based rewarded task. A raised plexiglass T-maze with computer controlled gate and photobeam set-up was used for the behavioral recording. The test session began by opening of the start gate. This was followed by a randomized delivery of an audio tone that was linked to the side where reward was to be delivered, either left or right. This procedure is similar to prior work [11]. Recordings were carried out chronically from the dorso-lateral striatum [8,12]. Rats that achieved a correct learning criterion of 70% were felt to have completed the early learning phase [11]. Tetrode neurophysiological recordings were performed using accepted methods [8,12].

Using accepted sterile surgical techniques, a custom, head-stage holding tetrodes was implanted on the animals. Six tetrodes were in the striatum in all animals. Data were pre-amplified using a head stage mounted 26 channel 100× gain preamplifier and captured using a Neuralynx[®] 48 channel data acquisition system.

The average tetrode movement was 0.1 ± 0.05 mm throughout the entire recording period. We recorded an average of 9.2 ± 1.3 units per daily session per tetrode. The final positions of the tetrodes were histologically confirmed to be in the dorso-lateral striatum.

Spike sorting and unit classification was performed as previously described [12]. After sorting spikes into putative units, spike assignments to individual units needed to be confirmed to assess whether units were well separated from each other. Measures of unit isolation quality, L_{ratio} and isolation distance (ID), were used to evaluate the performance of the sorting technique [14]. Additionally, the quality of sorting was tested by analyzing unit auto-correlograms such that no spike in a unit fell within a 4 ms window after the previous or before the subsequent spike. Data from approximately 5.3 ± 0.6 well separated units per tetrode are used for computing MI.

A descriptive discussion of the method and steps of computing mutual information is provided here. The MI analysis is carried out once the data are sorted and the spike signals are separated into putative units. The spikes recorded per unit for the entirety of the day's session are used for the calculation of the entropy for every unit, individually.

Entropy for a series of neuronal spikes measures the degree of uncertainty in the occurrence of firing patterns. A probabilistic framework is required and spike trains within units are expressed

and analyzed in terms of uncertainty [3,16]. An important step in calculating the entropy or randomness of the time of occurrence of spikes is to compute the probability distribution P of the recorded spikes. If the obtained probability distribution P is spread across many states x_i , its information entropy is high and vice versa. Therefore, information as a quantity measures the compactness of the distribution of the spike firing pattern. For a random variable x represented by recorded spike trains, Shannon entropy $H_S(p) = -\sum p(x_i) \log p(x_i)$, $i \in N$ measures the uncertainty regarding the outcome of the variable spike train, and gives the number of bits required to encode the spike train.

Once the individual entropies are obtained, mutual information is computed between pairs of units recorded within every ensemble, for each tetrode. In order to do this, joint entropies are calculated. The joint entropy is computed from the distribution of aligned, co-occurring words in pairs of spike trains [16]. We follow this technique demonstrated by Strong [16] by sliding overlapping windows of length $T = n\Delta t$ where Δt is the discretized time step. The mutual information is the difference between the sum of individual entropies and the joint entropy.

The calculated pair-wise MI values are then summed to provide an MI value for the ensemble recorded, for each tetrode per session (see Fig. 2). The mean value for all tetrodes, on a per session basis generates a single MI value for all tetrodes, per session, termed mean EMI (ensemble mutual information). This is done for every animal (see Fig. 3).

Spike trains were discretized into words, using a range of bin sizes and word lengths. Bin sizes ranged from 5 ms to 30 ms, and word lengths ranged from 5–100 bins. Word frequency was histogrammed to obtain distributions for a given bin and word length. Extrapolation to asymptotic entropy values was computed using the methods described by [16]. The computation results in an estimate of entropy $H(X)$. For two neurons with variables X_1 and X_2 representing spike trains, their mutual information $MI_{12} = H_S(X_1) - H_S(X_1|X_2)$ measures the deviation from independence, where $H_S(X_1|X_2)$ is the conditional entropy. Conditional entropy can be written as $H_S(X_1|X_2) = H(X_1, X_2) - H(X_2)$, where $H(X_1, X_2)$ is the joint entropy of a pair of spike trains. This allows us to express MI as:

$$MI_{12} = H(X_1) + H(X_2) - H(X_1, X_2) \quad (1)$$

To compute joint entropy, a pair of spike trains is discretized as described above into pairs of words for each time interval, and a distribution is computed for each distinct co-occurring pair. Otherwise the estimation of entropy is the same.

For a given tetrode, the number of neurons recorded is a variable N . Since the values of mutual information are positive, then the mutual MI measured in tetrode k is:

$$MI^k = \sum_{\substack{i,j \\ i < j}}^N M_{ij} \quad (2)$$

where i and j define two neurons. For several tetrodes “ T ” per animal (there are six tetrodes in every animal) the mean ensemble

mutual information (EMI) is computed:

$$EMI = \frac{1}{T} \sum_{k=1}^T MI^k \quad (3)$$

The mutual information value computations are made under the assumption of stationarity. We assume that the processes in question are stationary over each session (that is, no drastic learning-related changes occur within a session), and computed

MI values only use histograms obtained within one session. In practice, a much weaker definition of stationarity called second-order stationarity or weak stationarity can be employed. If the mean of the $x(t)$ signal remains the same for all t and the covariance between $x(t)$ and $x(s)$ is a function of $t - s$ only, then the stochastic process is a second order stationarity. However, if the method of computing MI is adapted to the character of the spike signal, including nonstationarity and limited data samples, then the obtained results are fairly correct [4].

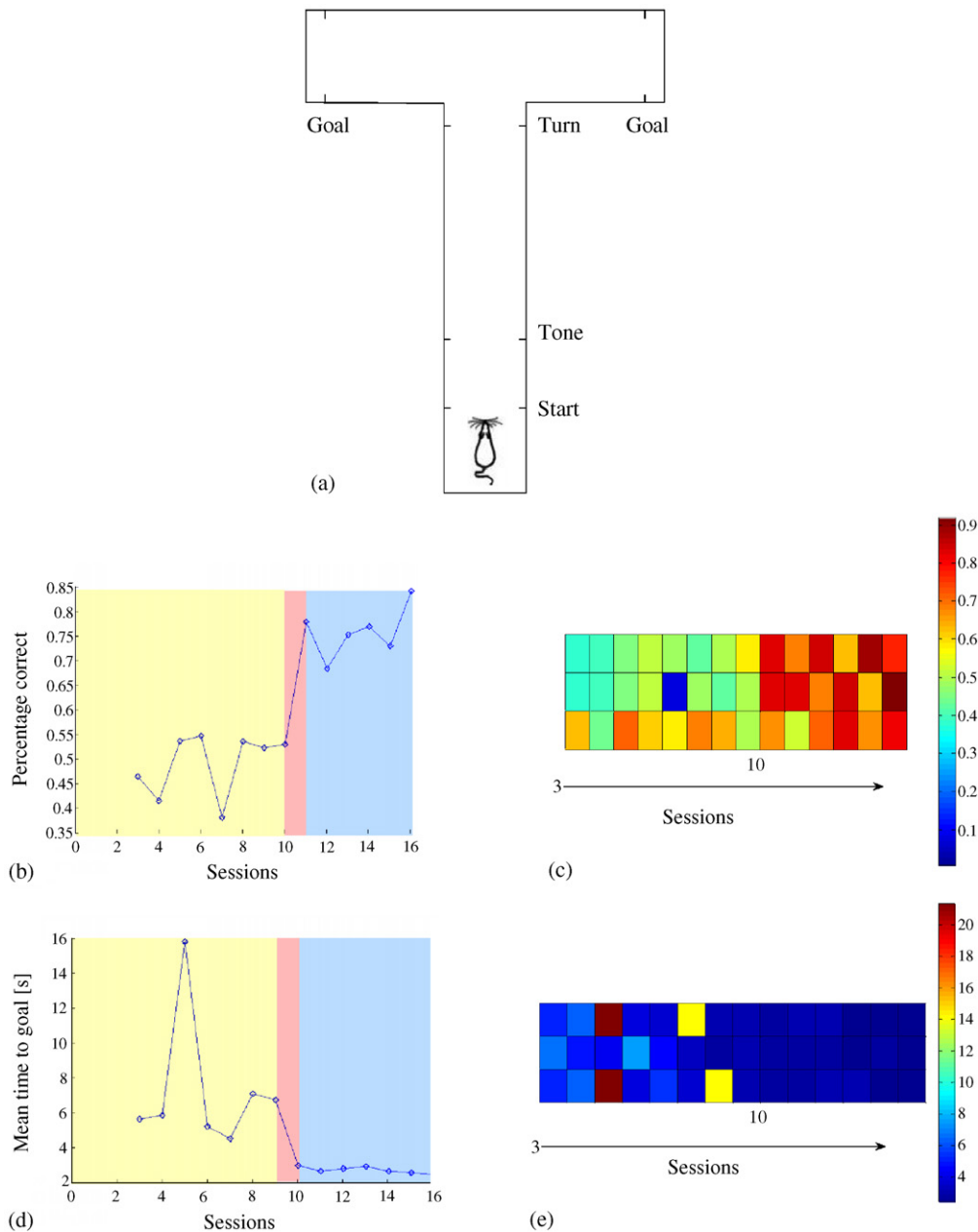


Fig. 1. Experimental data acquisition and behavioral analysis. (a) Schematic representation of the T maze experiment. (b) Mean percent correct responses for the three animals over the training sessions. The yellow column represents early learning, (mean percent correct, 48%) the red, task acquisition (rapid increase in percent correct well above the cutoff of 70%) and the blue, overtraining (75%, fluctuating well above the cutoff of 70%). (c) Color schematic of percent correct responses in the three different animals showing consistent learning. The blue color represents low, while the red high values for percent correct responses. All animals reached the dark brown/red color in a stable fashion. (d) Mean time from start to goal over the training sessions. The yellow column represents early learning, the red, task acquisition and the blue, overtraining. (e) Color schematic of time to goal in the three different animals showing consistent learning. The light blue or yellow color represents longer time to reach the goal, while the dark blue represents a decrease in time to reach the goal on average under 3 s in trained animals. All animals reached the dark blue color in a stable fashion.

All animals demonstrated the expected improvement of behavioral performance over time clearly showing learning on the T-maze task (Fig. 1a–c). A percent correct score of 70% was achieved by all animals by the tenth session. Recordings were continued after this period for an average of 4–14 days during the overtraining period. The behavioral data on the first two sessions was highly inconsistent and the animals did not perform better than 10% correct responses. This behavioral data is, therefore, not shown. The mean percentage correct before session 10 was 48%, while it was 76% after session 12. This is a 1.58-fold increase in the percentage correct behavioral responses between these two phases (Fig. 1b). As shown previously [12], the animals' time to goal also decreases as the task is learnt (Fig. 1d and e). After the tipping point has occurred, the time to goal also stabilizes. These results show that the time of running on the maze (motor speed) between start and goal is strongly correlated to percentage correct behavior and this is to be expected. Indeed animals became more regular and faster in how they run the maze around the time that they show the increasing percent correct. This also shows that there is a strong relationship between the transition in percent correct, information theory measures of neural activity and motor behavior. This analysis shows that it is likely that measures of task knowledge and motor variance cannot be dissociated during learning.

In the following analysis, MI measures the degree to which information about one neuron's spike firing pattern allows us to predict neighboring neuron's firing patterns within the same ensemble. Mutual information therefore provides us with a measure of the degree to which spike firing patterns across neurons co-occur, summarizing complex non-linear stochastic relationships between spike trains from neurons within the ensemble.

The color schematic representation of the mutual information (MI) values calculated in every tetraode for each of the three animals is shown in Fig. 2a–c. In this schematic, the dark blue represents low MI values implying that striatal neurons within the ensemble fire independently. The lighter and brighter (red) color represents high MI values implying increasing dependence of spike firing patterns of neurons recorded by each individual tetraode. A change from the dark to the lighter colors is seen in virtually all tetrodes in all three animals. Additionally, the color transition appears to be abrupt, occurring by approximately 10th–12th sessions and is represented by the dramatic rise in MI within the ensemble. Indeed these appear to be the precise behavioral sessions when the animals start making substantially correct decisions and are considered to have acquired the task. This trend towards a substantial increase in the MI values as the behavioral training progresses is a critical observation. An increase in the MI implies that individual neurons that contribute to the distribution of the spikes within each ensemble become increasingly dependent in their activity. This is the same phase where behavior appears to also become consistently highly correct. Finally, the values of MI also remain well above baseline suggesting dependent spike firing activity within units recorded by the same tetraode.

The mean ensemble mutual information (EMI) results are shown in Fig. 3a–c. Here, mean EMI values across all tetrodes are plotted per session, separately for every animal. Mean

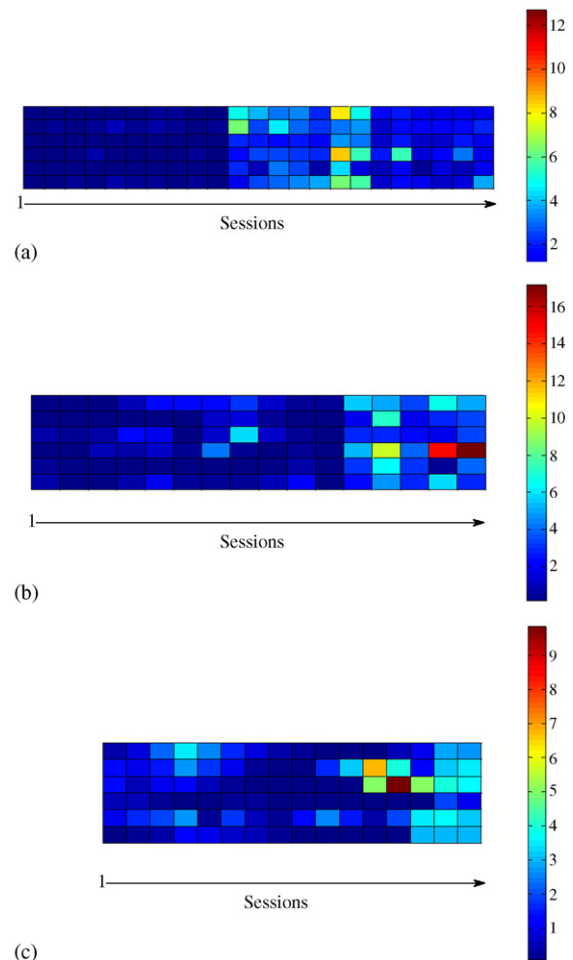


Fig. 2. Mutual information (MI) plots for three animals during training. Each column represents the training session number from beginning to end. Each row represents MI from separate tetrodes. (a–c) shows per session plots of mutual information for every tetraode k (MI^k , $k = 1, 6$) separately per animal. All animals show a trend in almost every tetraode for changing from low MI (dark blue) to higher MI (light blue–red) values over successive training sessions.

ensemble mutual information analysis for these data sets shows three clear phases that appear to reflect the behavioral learning pattern seen in Fig. 1b and c. In the initial phase (early learning), mean EMI either remains very low or has a low incremental–decremental pattern. During this stage, the animals are still acquiring the task. In the second phase between sessions 10 and 12 (task acquisition), mean EMI increases rapidly. Sometime around this same set of sessions (± 1 session) the animals begin to reach a stage of reasonable behavioral task accuracy, with this change also being quite abrupt (Fig. 1c). Animals now consistently exceed the minimum correct responses of 70%. Finally, during over-training when mean EMI has already increased to a maximum, the mean value remains at a high level compared with that in the early learning phase. Behaviorally, the animals are now performing the task consistently and reasonably accurately as per the criteria mentioned above. These three phases appear in all animals.

The average mean EMI values in the first phase for three animals are 0.1 ± 0.05 bits, 0.81 ± 0.5 bits and 0.82 ± 0.49 bits, respectively, while the average mean EMI values in the

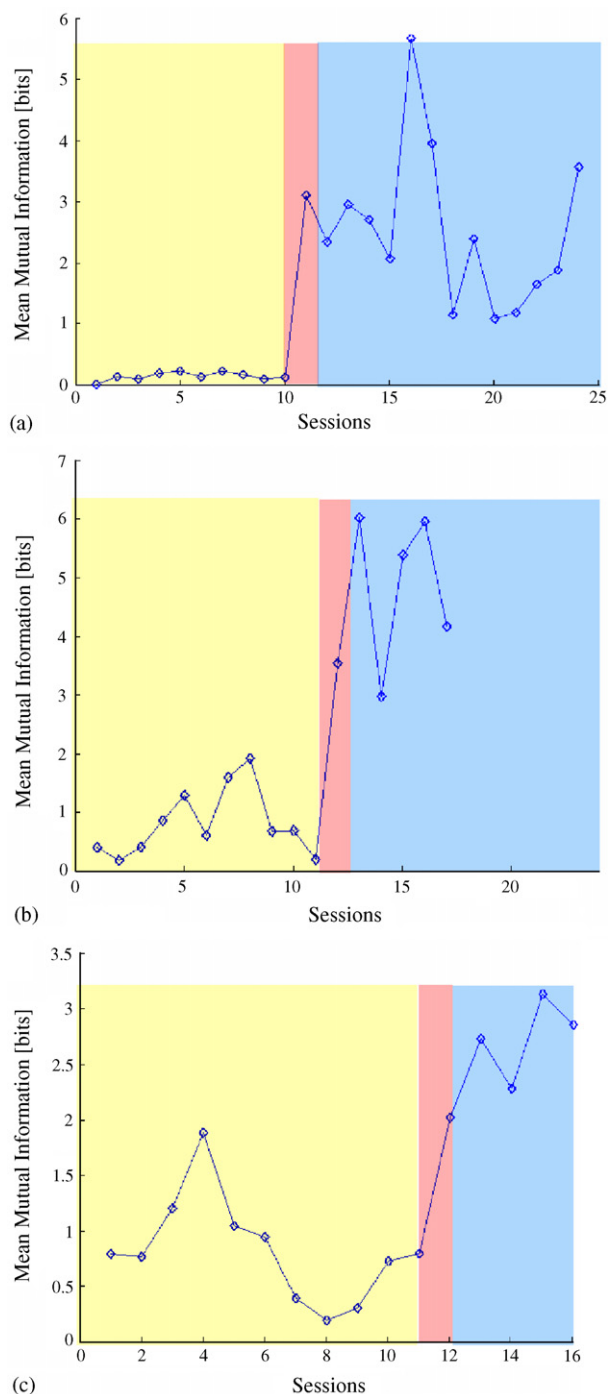


Fig. 3. Mean ensemble mutual information (EMI) plots for three animals during training. The X-axis shows training sessions while the Y-axis shows the mean EMI values. Similar to the color schema in Fig. 1, the yellow column is the early learning phase (low mean EMI value), the red, task acquisition (rapid increase in mean EMI) and the blue, overtraining (with high mean EMI value). All three animals show a clear point of inflection between session 10 and 12,—termed the “tipping point”. (a–c) show mean EMI values for every training session for each individual animal.

over-trained phase are 1.59 ± 0.81 bits, 4.89 ± 1.3 bits and 2.59 ± 0.44 bits. This change is highly significant and substantial, the ratios being about 15 times (1481%) in the first, 6 times (600%) in the second and 3 times (313%) in the third animal

(Fig. 3a–c). Importantly, the three phases seen in the mean EMI are mirrored in behavioral response at approximately the same sessions in all the animals. This matching is shown in the three colors yellow, red and blue used for the three phases shown in Figs. 1b and 3a–c. More specifically, the rapid increase in the mean EMI during the task acquisition phase is also clearly seen in the percent correct responses. Then, once increased from the baseline, this value of the mean EMI is mirrored in the reasonably stable behavioral response for each animal. Finally, fluctuations in the mean EMI in the overtraining phase appear to track similar fluctuations in the accuracy of the behavioral response, albeit both being at a significantly high level compared to baseline values.

We demonstrate that the representation of learning within a neuronal network is not gradual or linear from an informational point of view. Starting from a persistent low level, a point of abrupt change in mutual information in the neuronal network occurs as a task is acquired. This moment may be termed the “tipping point” in neuronal ensembles during learning. There are changes and fluctuations that occur during other periods in the graphs that show MI. However, if one looks closely at these other periods, the fluctuations are transient and all return to almost the baseline. In the sessions that we have specifically pointed out, i.e. sessions 10–12, the change is of a huge magnitude and is much more sustained, without returning to baseline. This is visible clearly in the graphs and is additionally clarified in the statistics above. This is why we have observed the periods of behavior and MI coincidence as the natural tipping point. The other fluctuation points do not correspond to the animal reaching behavioral accuracy.

It is important to stress that such a tipping point is a neuronal network property reflecting the pattern of information dynamics within the network. Once this tipping point is reached, the ensemble maintains a high level of mutual information reflected in visible, correct behavioral responses. From economics to political elections, the tipping point is reachable in a network where entities are communicating. Small changes in neuronal activity during several training sessions can make a sudden and big difference in learning motor habits.

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